



Accessing the U.S. Pharmaceutical Market: Resources for Risk Reduction

Although demand for pharmaceutical products is growing around the globe, the largest consumers remain the United States and Western Europe. Together, they represent nearly 75 percent of the world market in terms of revenue. It is widely known that the standard of care for drug manufacturers is significantly higher in the United States and Western Europe than it is for countries outside these regions. The regulatory bodies in the United States (US) and European Union (EU)—the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively—are responsible for ensuring the efficacy and safety of all drugs supplied within their jurisdictions. In theory, any drug manufacturer supplying pharmaceutical products in these regions must meet these bodies' high quality and regulatory standards and expectations.

Recent globalization has taxed these regulatory bodies. Non-U.S. and non-European sources provide these regions with an increasing volume of active pharmaceutical ingredients (APIs) and contract manufacturing of finished drug products. In addition, there has been an increase in the supply of generic drugs from manufacturers outside the region. Together, increased outsourcing and generic supply from outside the U.S. and western Europe have tested the agencies' ability to monitor and maintain the desired standard of drug products. However, recent events involving heparin and melamine have heightened their sensitivity toward drug products supplied from other countries. Consequently, the U.S. Food and Drug Administration (FDA) has become increasingly vigilant in its oversight, particularly of pharmaceutical products manufactured outside the United States and Europe.

The current environment in the United States

Fueled by events such as the deaths of patients from contaminated heparin manufactured offshore and melamine food contamination, as well as by public sentiments against outsourcing, the U.S. Senate is pressuring the FDA to ensure that companies that supply active pharmaceutical ingredients (APIs), prescription and over-the-counter drug products to the United States market achieve full compliance. As a result, FDA has intensified and increased the number of inspections it conducts of offshore facilities in India, China and other countries. Recently, the agency has found a number of facilities to be out of compliance with cGMP regulations and statutory requirements and has issued both warning letters and import alerts, even banning entry of products until the violations are adequately addressed. These bans immediately prevent any released inventory from being shipped and put planned manufacturing to fulfill orders for the U.S and European markets on hold. The financial impact of these actions can be measured in tens to hundreds of thousands of dollars per day.

Potential pitfalls and challenges

Interpreting the real expectations underlying the FDA and EMA requirements is a complex process. It is one thing to read and interpret a governmental regulatory document. It is quite another to understand unwritten requirements, to recognize the expectations of the regulatory body half a world away and to then adequately implement those requirements in practice. It is challenging to design facilities and establish processes that comply with current regulations. It is additionally challenging to keep facilities and processes in compliance while products and personnel are changed and facilities are expanded or renovated. The regulations, especially the expectations, are also changing rapidly, which creates more pressures on the manufacturers to stay in compliance. It is very difficult for in-house resources in a different country to stay current with the agencies' changing regulations and expectations. An *experienced* third party practicing in the drug compliance field can often provide valuable insights and an objective and current perspective on compliance and risk management.

With respect to regulatory issues, one recurring theme is the ability of manufacturing organizations to implement an effective and efficient change management program. This issue has arisen frequently in both U.S. and overseas manufacturing facilities. An offshore location adds extra layers of difficulty. Communication may be a problem, and the facility doesn't have the advantage of being "in the community," i.e. able to exchange ideas and solutions with other local companies. Finally, that facility potentially is exposed to a higher level of scrutiny by visiting regulators.



Some of the key issues that can lead to compliance failure include:

- Inadequate reduction of risk to product
 - Inconsistent procedures and protocols in various facilities within the same campus, e.g., applying a higher degree of risk management in newer facilities than in older buildings
 - Misaligned concepts in facility and facility systems design - e.g., concepts surrounding potent compounds
 - Improperly implemented design concepts - e.g., inconsistent application of clean room, zoning or operations concepts
 - Improper qualification activities - e.g., either over-qualifying systems with low impact on the product, which can result in an unnecessarily complex change control and compliance system, or not qualifying a system against properly defined user and functional requirements
 - Improper process validation practices and related ongoing process monitoring - e.g., ill-defined Critical Quality Attributes and Critical Process Parameters (i.e., no application of *Quality by Design* concepts)
- Inappropriate documentation practices
 - Incomplete/inadequate production records
 - Over-documentation of non-impactful items and lack of proper documentation for impactful items
- Inadequate change management practices
 - Inadequate evaluation of engineering changes for risk to drug product and employees - Compliant facilities often fall out of compliance due to inadequate evaluation of risks associated with proposed facility changes. On the other hand, a lack of focus on where the risk actually lies can lead to over-qualification of changes.
 - Inconsistent approaches to assessing the impact of changes to facilities and operations - Regulators are particularly sensitive to inconsistencies, such as misalignment of business and compliance practices

Reducing risks for offshore facilities

The challenge for any manufacturer is to determine how to achieve and maintain compliance at the right cost. Since 1989, IPS has delivered technical and business risk management services to clients in regulated industries around the world. With extensive operations and facility management experience relevant to the development and implementation of facility, operations and quality designs, IPS is closely aligned with FDA's new risk-based and lean approaches. The IPS staff of professionals includes former pharmaceutical operations managers and facilities operations personnel—all of whom are committed to helping clients meet their business and compliance goals.

For programming new facilities, IPS offers a comprehensive range of project services, including planning, concept development, full design, construction management, and commissioning and validation/qualification. The IPS design review and design qualification processes can help ensure that the facility design is consistent with compliance requirements. IPS professionals can also help organizations integrate the concepts of Quality by Design into their facility and processes in order to achieve a cost-effective risk-reduction strategy. Finally, IPS can develop and train management staff in concepts and practices for ongoing facility and operations life-cycle management.

For reprogramming existing facilities, IPS offers expert consulting on compliance and commissioning. IPS professionals can conduct site assessments, review related facility and operations documentation and quality systems, advise clients on how to enhance facility and change management and suggest cost-effective modifications in order to achieve and maintain compliance with applicable regulations while maintaining business goals. IPS not only advises clients on solutions but also helps clients implement them.

IPS can help

With more than 700 pharmaceutical and biotechnology industry clients around the world, IPS is already working to help manufacturers in India, China, Europe and Israel address issues related to implementation of and compliance with FDA regulations. IPS's experience is helping these companies access the largest pharmaceutical market in the world.

To learn more about how IPS can help your company, please contact:

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