Are Regulatory Agencies on the Defense?

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Imports of pharmaceuticals to the U.S. are on the rise, as well as criticism of the U.S. Food and Drug Administration (FDA) that it has not inspected foreign plants with any regularity. The FDA is clearly on the defensive. Likewise in Europe, member states inspectorates are facing similar pressures of greater regulatory oversight with fewer resources. A hiring freeze on inspectors in the Medicines and Healthcare Products Regulatory Agency (MHRA) is one example.

What are the implications for regulated life science companies — less frequent communications, longer periods for approving drug applications?

One may expect fewer chances of inspection or a slower response by the FDA and the European Medicines Agency (EMA). With both agencies under fire to protect the public from new threats with only incremental increases in resources, one could assume this to be the case — but not necessarily.

Agencies are retrenching on a number of fronts to address criticisms and increased demands to ensure product quality, safety and efficacy. There has been a steady consolidation of inspection resources among the EMA in Europe, Therapeutic Goods Administration (TGA) in Australia and the FDA in the U.S. This includes the FDA-TGA sharing of inspectional findings [1], joint programs between U.S. and European Union authorities for parallel assessment on quality by design (QbD) applications [2], and a Good Clinical Practice (GCP) Initiative [3] to remove the duplication of submitting clinical results separately to each agency.

The Medicines Regulation: Transatlantic Simplification Plan [4] is an ongoing initiative between the FDA and EMA to simplify administrative practices and guidelines, including areas such as joint inspections, access to each other's databases, and harmonization on such things as common electronic technical document and safety update reports. Collaborative work also extends to the World Health Organization impact initiative for information exchange on counterfeit cases detected in the supply chain.

Initiatives to create greater efficiency of agency resources have three primary objectives:

1. Meet growing demands and threats from global expansion;
2. Reduce compliance costs for new drug authorizations; and
3. Better assurance that manufacturers are compliant with good

manufacturing practices (GMPs).

The effects of agency consolidation and resource utilization are demonstrating offensive regulatory oversight, rather than a defensive one. More recently, FDA Form 483s, warning letters and legal action have focused on accountability of corporate individuals and suppliers.

For example, supplier deficiencies noted in Form 483s found in a recent review that a biotech service contractor “lacks adequate documented evidence to support the integrity of the service provider’s work.” In another violation for a medical device maker’s materials supplier, “temperature storage controls have not been established … [resulting from unobtainable] storage temperature range recommendations” … from your supplier.” In 2012, new European Commission Guidelines on good distribution practice of medicinal products will hold suppliers accountable for GMP compliance during storage and transportation as well.

The FDA enforcement actions and plans have also highlighted serious efforts to target corporate and personal accountability:

1. $8 billion in fines paid by U.S. drug companies from 2009 to 2010 for marketing unapproved drugs;
2. Notice of the FDA’s strategy, working with the justice department, to file criminal charges against pharmaceutical executives;
3. Import alerts issued on pharmaceutical company active pharmaceutical ingredients (APIs) and dietary supplements from India and Mexico, respectively; and
4. U.S. Congress hearings on the FDA’s request for statutory changes in authority to secure the pharmaceutical supply chain.

The FDA’s membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S) organization signals the agency’s dedication to harmonizing inspection criteria with 38 other participating regulatory authorities. In the other direction, one of expansion, the FDA opened and staffed foreign offices to be closer to regulating off-shore manufacturing. Additionally, the agency created and staffed a super office of compliance to focus on supply chain safety.

No doubt the EMA and FDA are being subjected to the crushing pressure of increased government legislation, outsourced manufacturing, new biologics and a complex supply chain. However, these agencies have shown strong leadership and progressive thinking that demonstrates anything but paralysis.

With advancing harmonization, mutual agreements to share data and a focus on risk-based approaches, regulators may in fact be on the offense. These changes will

place greater responsibility on industry's corporate management to take an active role in improving their quality management systems. The operational efficiencies gained by agency actions should put industry on notice to brace for more targeted inspections, not fewer.

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