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Is it Time to Revamp cGMPs?

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Just within the past few days, news headlines have screamed that the drug industry is not in control of its processes or products. There was bad news from literally every corner of the world.

We saw the final chapter in Ranbaxy's consent decree and whistleblower lawsuit, which sparked boycotts of the company's drugs in India (more on this soon). Johnson & Johnson executives in South Korea were threatened with legal liability over errors in API loading in Tylenol. India's Wockhardt faces an export ban on products from its Aurangabad facility to the US.

What do we do to change things? How much is our fault as developers and manufacturers of medicines? How have the world's regulatory agencies contributed to the problem?

Current good manufacturing practices (cGMPs), established decades ago in the US, provide the lowest possible level of protection for the public, and even they are being skirted, ignored, or followed very hesitantly. Surely we haven't reached the point where anyone can set up a shingle and claim to be manufacturing drugs.
Complicating the picture is the fact that 80 percent of the APIs and 40 percent of the generics sold in the US come from overseas. Can our current regulations and inspection practices prevent another drug safety catastrophe like the heparin scandal? All it takes is an incident that's serious enough to affect 0.1 percent of patients taking a drug.

India has just required its API manufacturers to follow European cGMPs. That's all well and good, but are cGMPs enough today?

To answer this question, I reviewed 2012 US FDA drug citations. The FDA issued 3,278 citations to drug manufacturers for compliance problems. Being a manufacturing/technology person, I figured that many or most of the citations would be related to poor manufacturing practices. But only 28 (0.85 percent) featured the word "yield." Does that mean most companies don't have manufacturing issues, or does it mean the inspectors don't know how to find them? In each of these cases, the FDA said, "Actual yield and percentages of theoretical yield are not determined at the conclusion of each appropriate phase of manufacturing of the drug product." This made me question how well these companies function on a day-to-day basis.

Forget about pharma's three-letter acronyms (PAT and QbD, both of which I wholeheartedly support). I come from the old school, where chemists, chemical engineers, and even financial types were taught to have a clear understanding of theoretical versus actual yield when they developed, commercialized, and set a price for any product. Standard accounting methods should uncover material overage or underage problems regularly. Either some business systems are out of control, or some companies are engaging in financial engineering.
As has been noted in a previous post, most of the 2012 citations pointed to a failure to follow proper procedures, rather than manufacturing problems. But was any research done to show whether these procedural problems had an impact on quality?

Lack of training was cited in 153 (4.7 percent) of the cases. This could be due to a combination of high staff turnover and too many products being run through the same facility.

There were also failures to validate material testing results. In many citations, the FDA said, "Reports of analysis from component suppliers are accepted in lieu of testing each component… without testing to establish… the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."

Trust but verify is a good approach, but this means pharma cannot have just-in-time procedures in place with ironclad assurances from third parties that suppliers have properly tested the materials. Some citations said,

"The quality control unit lacks authority to review production records to assure that no errors have occurred" or, even worse, "The facility does not have a quality control unit."

The 21 CFR regulations are the most minimal regulations one can have, especially for pharmaceutical products. Rampant noncompliance with even this baseline has raised questions and caused some soul searching at the FDA, most recently by CDER head Janet Woodcock, as Pharmaceutical Online reported recently. Is the system in need of a total revamp? If companies can ship off-spec and contaminated products, are our regulations stringent enough?

The problems lie much deeper than procedures and paperwork. Recent pharma quality incidents point to flaws in the regulations and regulatory systems and raise some questions.

1. Why can't companies complete their minimal obligations to comply with the regulations?
2. Why are regulatory bodies directing product quality requirements? Shouldn't the companies be setting and meeting them themselves?
3. Why can't the companies have command of their own processes and make sure that they are reproducible?
4. Are regulatory inspectors trained to catch noncompliance? Are staff members trained to find manufacturing flaws before product is shipped?
5. Do we have the right regulations in place?
6. What is the purpose of these regulations if companies cannot or do not want to comply, or if they comply hesitantly?
7. Are companies so focused on completing the paperwork that they aren't being careful about manufacturing processes and practices?
8. Is it time to establish regulations that hold company officers accountable for violating quality regulations?
9. What measures can be incorporated into 21CFR 210 and 211 and other sections of the federal code to ensure that adulterated drugs cannot be imported or sold?
10. Pharmaceutical manufacturing has expanded multifold in the last 20 years. Have regulations kept pace? How about operations? How do we resolve this as an industry? Please write in with your thoughts.