

Putting the Teeth into Risk-Based Regulation

As technology advances and regulation becomes ever more globalised, *Warren Perry* asks whether the US FDA will be able to deliver on its promise of a risk-based approach to compliance.

Regulation in the pharmaceutical industry has changed significantly over the past several years as a result of advances in technology, industry globalisation and the increase in the number of pharmaceutical products on the market. This in turn has led to pressure on resources at the US Food and Drug Administration (FDA), reducing the agency's ability to oversee all aspects of pharmaceutical products and production. The explosion in biologics has only added to the strain on the agency.

In 2002, the FDA decided to take a more risk-based approach to inspections, trying to match its efforts to enforce compliance with the magnitude of risk. Now, five years later, it is time to ask how the FDA is progressing with this initiative.

The quick answer is "not so good across the board". While the FDA is doing a satisfactory job in taking a risk-based approach when it comes to addressing issues in the pharmaceutical, biotech and device industries, troubling red flags are popping up as the industry becomes increasingly global. In addition, the agency has fallen down when dealing with two other major industries that come under its authority: the food and cosmetics industries.

To really understand why the FDA is not doing an adequate job in regulating these two industries, why it moved to a risk-based approach to regulation, and the inevitable trouble that lies ahead in the life sciences sector, one first needs to look back at the origins of the agency.

It is widely accepted that the FDA was created as a direct result of Upton Sinclair's 1906 novel *The Jungle*. In this infamous book, Sinclair described the deplorable working conditions that an immigrant Lithuanian family faced while working in Chicago's meatpacking district and called into question the quality and safety of US meat products. Meat sales quickly fell, and panicking meatpackers extensively lobbied the US government to pass legislation that required detailed inspections and certification for meat packaging companies. This eventually led to the Meat Inspection Act and Pure Food Drug Act, which then created the FDA.

The agency closely regulated the food industry, and as a result there were no major issues or scandals for several decades. However, as pharmaceuticals began to rise in prominence and become big business, regulation of the food industry, while still important, was no longer the FDA's major focus. The same can be said for the cosmetics industry. It did not come under a great deal of scrutiny like the food industry because it did not have a chequered past. Also, FDA inspectors were less concerned with products applied to the exterior of the body than with food and drugs that are ingested and are much more likely to be able to cause harm.

Focusing primarily on the US market and its manufacturers, and only concerned with the quality of exported products as opposed to the quality of products coming in from other countries, the FDA did a relatively solid job of overseeing the industries under its purview. However, with the growing globalisation of all these industries – food, drug and cosmetics – the agency began to struggle and increasingly found itself faced with the same issues as the industries it regulated: a lack of resources and budget constraints that caused it to be spread too thinly.

Moving to a risk-based approach

As mentioned earlier, in 2002 the FDA decided to take more of a risk-based approach to its inspections and regulatory efforts relating to current good manufacturing practices (cGMP) in the pharmaceutical industry. This effort, which took place 25 years after the last major revision to drug cGMP regulations, resulted in the FDA publishing a document called *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*.

The changes were intended to make sure that:

- the FDA incorporated the most up-to-date concepts of risk management and quality systems approaches while continuing to ensure product quality;
- the FDA encouraged the latest scientific advances in pharmaceutical manufacturing and technology;

In 2002, the FDA decided to take a more risk-based approach to inspections

Historically, pharmaceuticals became the FDA's major focus, to the detriment of regulation of the food and cosmetics industries

Among other things, the risk-based approach was intended to incorporate the most up-to-date concepts of risk management and quality systems approaches...

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...and consistently apply regulation and manufacturing standards

- the submission review programme and the inspection programme operated in a co-ordinated and synergistic manner;
- the FDA consistently applied regulation and manufacturing standards;
- management of the programme encouraged innovation in the pharmaceutical manufacturing sector; and
- the FDA used its resources to address the most significant health risks most effectively and efficiently.

This new approach was also created partly to address major shifts in the environment of pharmaceutical regulation, such as the higher number of pharmaceutical products and the greater role of medicines in healthcare; the decreased frequency of FDA manufacturing inspections resulting from fewer resources being available for pharmaceutical manufacturing inspections; the FDA's accumulation of experience with, and lessons learned from, various approaches to the regulation of product quality; advances in the pharmaceutical sciences and manufacturing technologies; the application of biotechnology in drug discovery and manufacturing; advances in the science and management of quality; and the globalisation of the pharmaceutical industry. The FDA additionally implemented principles focused on science-based policies and standards, integrated quality systems orientation, international co-operation and strong public health protection. The agency then decided that immediate steps – which are still ongoing – needed to be taken. They included:

- holding scientific workshops with key stakeholders;
- enhancing expertise in pharmaceutical technologies (eg pharmaceutical engineering and industrial pharmacy) through additional training and hiring, and by leveraging external expertise;
- encouraging innovation within the existing framework of statutory provisions and regulations by allowing certain changes in the manufacturing process without prior review/approval (eg comparability protocols);
- evaluating the best mechanisms for effectively and efficiently communicating deficiencies to industry, including content, consistency, disclosure and education;
- shifting the agency's lead on the implementation of requiring electronic signatures as a component of 21 CFR Part 11 to the Center for Drug Evaluation and Research (CDER), with continued involvement of the other centres and the Office of Regulatory Affairs (ORA);
- including product specialists, as needed, as a part of inspection teams;
- having centres provide a scientific and technical review of all drug cGMP warning letters;
- developing a technical dispute resolution process that integrates technical experts from the centres and addresses perceived inconsistencies between centres;
- emphasising a risk-based approach in the work planning process; and
- improving the operations of team biologics.

The FDA decided that additional measures were needed

Limited resources

Since 2003, just one year after the FDA announced that it would undertake its risk-based initiatives, the number of investigators and inspectors at the agency has actually decreased. At the same time, however, the amount of food being imported from other countries has almost doubled. Clearly, faced with limited resources and a growing demand for its services, the FDA cannot achieve wide success with its risk-based approach.

China proving to be a problem

At this point, China is the biggest thorn in the FDA's side. There have been several product recalls in the US involving products made in China, although these have not been in the human pharmaceutical area. Earlier this year, for example, there were major recalls of pet food products in the US, with more than 100 brand names being recalled, after several pet deaths were linked to foods containing melamine, a prohibited chemical that is used to make plastic. It was determined that the melamine was in rice protein concentrate imported from China and used in the manufacturing of the dog and cat foods. The FDA estimated that more than 6,000 pigs in eight US states could have been fed pet food with products containing the melamine-laced rice protein. As a result, several hundred pigs may have entered the food distribution system for human consumption. So far, no related human illnesses or deaths have been reported as a result, but it demonstrates how this issue could have caused a great deal more harm than it did.

Several product recalls have involved products made in China

Right on the heels of the pet food recalls, toothpaste manufactured in China came under scrutiny after tests on products sold in Australia, the Dominican Republic and Panama showed the toothpaste contained high amounts of the lethal chemical diethylene glycol, an ingredient often found in antifreeze. Chinese manufacturers used the chemical, also known as DEG, as a low-cost sweetener and thickening agent to help keep the toothpaste moist. The FDA took immediate steps to make sure that no contaminated toothpaste crossed into the US market. Tainted toothpaste did show up in a few retail stores in Miami, Puerto Rico and other locations, and several people became slightly ill, but no significant illnesses or deaths were reported.

Chinese and American food experts agree that China's large and mostly fragmented food-processing industry makes inspection extremely challenging. Currently, many Asian countries lack the supply chain infrastructure to support a risk-based system (although of course, countries like Japan, South Korea and Singapore are notable exceptions). As a result, the potential for similar problems occurring in these and other industries in the future is very high.

China's large and fragmented food-processing industry makes inspection extremely challenging

Risk-based challenges: what is working and what is not

Clearly, the FDA is having major issues with protecting the integrity of food and cosmetic products entering the US. A risk-based approach does not appear to be working, because of the lack of compliance-based infrastructure in some of these countries, and dwindling resources at the agency.

However, where the pharmaceutical industry is concerned, regulation with a risk-based component has largely succeeded. In fact, the drug industry in comparison has embraced a risk-based approach, mostly because the FDA has done a good job of fostering a high level of co-operation with drug manufacturers. Typically, the FDA is willing to work with companies if they have problems and will not fine them if they are transparent and proactively report problems they encounter. This is because it is in everyone's best interests to keep a company viable, since it is providing potentially life-saving products to consumers and quite frankly can be worth billions of dollars to both investors and the economy. However, if a manufacturer attempts to cover up any issues in its manufacturing processes and the FDA discovers problems, the agency will severely fine the company and even its officers, depending on the severity of the transgression. It is this "we'll work with you" environment in conjunction with a secure supply chain that has allowed a risk-based approach to regulation to work so well in all areas of the life sciences industry.

Risk-based regulation has largely succeeded in the pharmaceutical industry

Trouble from halfway around the world

Nonetheless, the ever-increasing globalisation of the industry means that the potential for serious problems is growing in the pharmaceutical area as well. So why have Asian countries like China proven to be a major problem with the FDA in general and its risk-based initiatives in particular?

One of the main reasons is that in 2002, the FDA could not possibly have envisaged the large quantities of ingredients for food, drugs and cosmetics coming from Asia, and from China in particular. The sheer volume has quickly overburdened the system. To add to this, it is unrealistic to expect Chinese manufacturers that employ millions of illiterate workers to educate them on policies and procedures, and then track their performance.

Even given the problems with China – and they are big problems – the FDA's aim of applying risk-based compliance on a global level is flawed. One of its main points is to consistently apply the latest in scientific and technological advances. But this is not going to work in today's global world, especially in certain parts of the world such as China and Eastern Europe, which do not have the infrastructure in place to participate. Even parts of Western Europe are to some extent resistant to adopting risk-based compliance because of privacy issues and the fact that it is a US initiative.

The problem is that if a drug manufacturer can't sell in the US, it will struggle to be successful, because about 50% of drugs consumed worldwide are sold in the US. It is inevitable, therefore, that these countries will continue to do whatever they can to sell in the US. Recognising this, the FDA should realise it has leverage to institute more of a risk-based approach to compliance for these companies.

The FDA's aim of applying risk-based compliance on a global level is flawed

What is the solution?

Unfortunately, there really is no easy solution. The FDA is essentially building a house of cards by relying on programmes that are based heavily on technology.

In theory, and for parts of the world such as the US and Canada, this is a good approach. But for countries like China and India, it will not work because their manufacturers and factories do not have the necessary technological infrastructure and risk-based manufacturing principles in place. It is also important to point out that embarking on risk-based approaches based on technological

solutions incurs a significant cost that many businesses just are not willing to absorb. It is akin to being environmentally friendly – it's a good idea in principle, but you need to be able to afford it.

If the FDA is to get serious about putting some teeth into risk-based enforcement of its regulations across all the industries it oversees, both in the US and abroad, several things need to happen. A two-tiered system should be introduced, inspection processes must improve and there has to be political buy-in.

The solution is a two-tier system, with a certification programme for drug manufacturers that meet certain requirements...

In terms of a two-tiered solution, the FDA should institute some type of certification programme for drug manufacturers that contain certain requirements based on technology, workflow processes and sound GMP. Companies meeting these requirements would fall into one tier that, for lack of a better term, would receive less scrutiny, be looked upon more favourably and perhaps receive some type of financial incentive, as opposed to a second tier of companies that did not meet these requirements.

With regard to better inspection processes, the FDA needs to find a way to set up arrangements so that it can regularly inspect foreign manufacturers before problems arise. This type of arrangement already exists with countries such as the UK, France and Germany, where US inspectors can visit factories and issue warnings if there are problems. The US also has reciprocal agreements with these countries so they can do the same to US factories. Obviously, this is not currently the case in countries such as China and Russia, as the political implications are much too high.

...together with better inspection processes, and political buy-in, with countries working together in a truly global fashion

In consideration of political buy-in, until countries start working together in a truly global fashion, consistently enforceable regulation will not be possible. Funding and financial incentives must be put in place. This, of course, will require transparency on all levels, which some countries may be unwilling to agree to.

Conclusion

These are three seemingly simple parts of a bigger solution, but they could potentially have far-reaching effects. If the FDA and the US Congress do not seek to seriously address some or all of these ideas, it is more than likely that we will at some point in the future be looking at drug-related recalls and related incidents far worse than those resulting from pet food and toothpaste recalls.



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