

It will all end in multi-tiers!

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Nostrapharmus may be all about predicting the future, but let's begin by casting our minds back 30-40 years. Those of you who have held line management positions during those years can probably still remember what the Health and Safety regulatory environment was like, or not, as the case may be. The compulsory use of Personal Safety Equipment was creeping into the regulations. Managers spent many hours and disciplinary meetings with employees to convince, persuade, or force the use of safety shoes, glasses and noise protection. Moving forward a little in time; the Seveso disaster of 1976 was most tragic and left a never fading impression on the people that lived there, and survived this catastrophe. The impact on us, the pharma industry, was enormous. New legislation and regulations were introduced in response. Again, line managers often struggled to get their employees to adhere to the new rules. Other examples like the Thalidomide tragedy, and the Devonport Hospital disaster were pivotal in moulding today's regulatory environment. Each incident driving new legislation that bit further to defining the way in which pharmaceuticals should be both manufactured and released.

The regulators have always responded to trends or incidents by tightening the rules and introducing more stringent and far reaching laws. The pharma industry has responded by implementing the new legislations and, more often than not, creating even tighter self-imposed requirements in addition. The efforts to stay compliant have gone up over the years and so to have the costs.

Of course, stringent regulation is vital when it comes to protecting the health and safety of employees, the safety of the patients, and the environment that are all dependent on our products. Nevertheless, the burden is high.

Over the years, companies have begun to question the level of effort that they apply to ensure compliance. The concept of 'Lean Compliance' is now well established, and companies embarking on this path are able to demonstrate clear benefits without compromising the environment, employees, quality, or patient safety. The benefits are obvious; reductions in QC activities and bureaucracy quickly lead to big benefits in the form of lower cost or shorter cycle times. However, fundamental changes to the Safety Health and Environment (SHE) or Quality Management Systems (QMS) are a lot more difficult to achieve. Companies have created systems that have been tested in many audits and inspections. The systems are reflected in the manufacturing licenses that they have. Change becomes difficult and companies stay in the comfort zone that has been created over many years. In practice, this means that within a manufacturing plant the same rules are applied for all products and processes. This almost strict adherence to the 'don't rock the boat' principle is putting the shackles on the pharma industry; changes yes, but don't touch the Quality Management Systems or any of the other Management Systems!

The situation gets worse. The pharma industry is rapidly moving into outsourcing. The global market for CMOs is expected to continue growing at around 10% CAGR. At the end of 2008 the market was worth \$20.5bn, having expanded from \$12.8bn in 2002, a total increase of 60%. As large pharma continue to scale back on production and focus on core competencies, it is expected that by 2010 29% of all manufacturing output will be produced by third parties. The need to outsource is obvious; big pharma has surplus manufacturing capacity, R&D pipelines are drying up, regulatory barriers are delaying new approvals, and many of the blockbuster products are losing patent protection. As a result, companies are preparing to focus their internal resource on core activities they can add real

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value to, whilst outsourcing functions such as some manufacturing activities that can be performed, at least as well, externally. Companies are looking to CMOs to enable them to rapidly adjust production capacities to meet volume challenges and to provide access to new process technology that may not exist within internal manufacturing. However, expanding the number of CMOs brings inherent issues around the risks of non-compliance, in addition to quality and supply risks.

Naturally, the pharma industry has recognized these risks and has a reply at hand; the enforcement of the proven SHE and QMS on the CMOs. Looking at some of the more recent issues like the pet food problems in the US, and Heparin, one may wonder how effective this reply is.

The highest growth in CMOs is in Asia. Low cost competition from Asia will be a key influence on the CMO industry over the next five to ten years. Asia-based CMOs increased their contract service revenues by 44% during 2007. Countries like India, China, and Vietnam are leading countries for CMO activities. These countries are developing fast but, nevertheless, the regulations are in catch-up mode and still many years behind the standards of the western world. The regulations that these countries are developing are driven by our requirements. US and European Governments are demanding that developing countries put regulations in place to cope with some of the incidents that have happened over the last two years. The FDA has even opened an office in China.

What we forget though, is that the learning that we have been through has driven us to accept changes in regulations. Each incident or trend has led to a change for which the need was obvious. Step by step regulations have got tighter, and systems have adapted, and all employees have internalized the regulations so that we accept the importance of compliance without question.

Put yourself now in a position where you are the Manager of a department that oversees all supply chain outsourcing of a large Pharma company. It is the intention to outsource a portfolio of excipients to a company in China. After three days travel, you and a colleague from QA finally show up at the site carrying in your suitcase the company QA Manual. Can you imagine what the site will most likely look like? Cast your mind back again and think of your own plants 20, 30, or 40 years ago. Are you going to run an audit, impose the QA Manual, request a MAP to get the CMO compliant to your standards and start your three day journey home again believing that all will be okay? Hopefully not, but unfortunately this is the normal routine.

A more appropriate approach would be to perform a risk assessment based on an in-depth understanding of your product and your Supply Chain. The risk assessment will show you if the CMO contributes to an increase of Patient Safety or Supply Chain risks. An unacceptable increase in either one of these areas should indicate a clear 'no go' for the outsourcing decision. Based on the risk assessment you can then determine which elements of your QMS are critical to the CMOs operations. Those will be the ones that the CMO needs to get implemented before moving your product to the site. The regulations or standards back such an approach. For example, PS9100:2002 contains a risk based approach to determining the appropriate level of GMP.

First hurdle taken; the CMO will deliver a safe product. Your journey of developing the CMO has started. Time and effort invested in developing an all encompassing Supplier Development Program will, in a few years, bring the CMOs that you use up to the compliance levels that both you and the Regulators require. At the core of the Supplier Development Program sits Risk Management and an understanding that your CMOs need to go through the same learning curve as you've been going

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through for the last 20, 30 or 40 years. Only they will benefit from your experience and get up the curve a lot faster.

Have you ever thought of taking a similar approach within your own plants? Understanding the risks, the experience that has grown over many years can drive leaner compliance. Processes that were not fully capable when the product was introduced years ago could now be showing six sigma capability. Is the same QC test or in-process control regime still needed? Similarly, can we improve a process with low capability and then claim the benefits not only as higher yields but also as a reduction in effort to maintain compliance?

In the end, it means that you will be applying regulations and your QMS in a way that they support the manufacturing processes and ensure a safe product without the shackles of rigid bureaucracy.

Nostrapharmus predicts that in 10 years time the pharma industry will be running multi-tier Quality Management Systems, driven by a robust understanding of risks, and in a context where such an approach is embraced by all, including the regulators.

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