Rewards and Regulations

Hedley Rees from Pharmaflow looks at the aspects of leveraging 21st Century Modernism through the effective management of production systems

Regulatory modernisation has been with us for some years now. Readers may speculate on reasons why this modernisation was conceived and translated into guidelines for the industry. There is little doubt that stakeholders were raising a red flag over issues related to development candidate attrition rates, patient access to innovative drugs and the quality and availability of products on the market. Some, charged with the responsibility of addressing these issues, may have found the regulators to be culpable, claiming that change approval was a time-consuming, costly and often precarious process. Whatever the motivation, there is now an impressive body of knowledge on the topic of modernisation, aimed at providing key players in the industry with a framework for meaningful change.

THE REGULATORY PROCESS

Early in this millennium, the FDA launched 'Pharmaceutical Quality for the 21st Century: A Risk Based Approach'. Roughly in parallel, the International Conference on Harmonisation (ICH) agreed guidelines under quality banners known as ICH Q8 – Pharmaceutical Development, ICH Q9 – Quality Risk Management, and ICH Q10 – Pharmaceutical Quality Systems. Industry, academia, regulators and other stakeholders have been working diligently to move the principles forward but there still seems to be a long way to go. This was confirmed by Janet Woodcock MD, current Director of CDER in a May 2007 update report (1):

"The journey has just begun. There is still much to learn and innovations to incorporate into all our processes. We, in the agency, will continue to emphasize the importance of the initiative and look forward to many more improvements in our regulatory processes for ensuring product quality."

It is common knowledge that regulators looked outside the pharma sector for ideas and are urging other key stakeholders to do the same. This article aims to discuss specific areas where innovation and improvement has occurred in sectors such as semiconductors, automotives, aerospace and electronics. This involves exploring the concept of a 'production system' and the evolving discipline of supply chain management (SCM).

NEW APPROACHES FOR PRODUCTION SYSTEMS

Drawing again on the words of Dr Woodcock at the commencement of the initiative, the stated aim of modernisation, as it related to the quality of pharmaceutical products, was to achieve (1):

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality products without extensive regulatory oversight."

There are a number of important points to note from this. Firstly, while the initiative is under the title of 'quality', the improvement target is the manufacturing sector. That is the end-to-end supply chain by another name, since the object of manufacture is to supply end customers (patients) and trial sites. When translated into the language of modern day business methods, this end-to-end supply chain is spawned by the 'production system'. This involves complete focus on the entire process of conceptualisation, design, development, full scale manufacture and final supply to the customer.

The second point is that the terms 'efficient', 'agile', 'flexible' and 'reliable' signal the regulators determination to move expectations beyond rote compliance. This is not to say that safety and efficacy should take a back seat, clearly that cannot happen. It does, however, introduce an obligation to seek new and better ways of doing things in the production system.

Thirdly, and probably most importantly, is the reference to high-quality product 'without extensive regulatory oversight'. This means that those conceiving, developing and making drugs under regulatory scrutiny and licenses must shoulder the major responsibility of improvement. In the same way quality cannot be inspected into a product, the regulators cannot inspect 'best practices' into our production systems and supply chains. The inevitable conclusion from this is that modernisation is about improving the way our production systems operate and perform.

The guidelines are a starting point, but the industry must own the implementation. One of the ways forward is to really understand production systems and leverage the potential of effective, end-to-end management processes, as other sectors have.

THE INDUSTRY IN RELATION TO PRODUCTION SYSTEMS

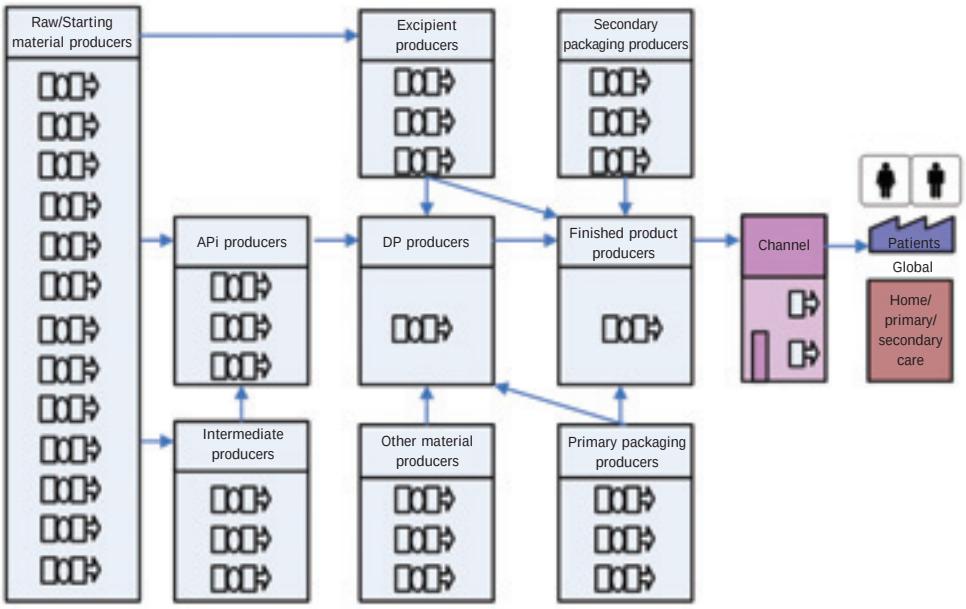
Every supplier, material, analytical method, contractor, logistics provider, process instruction and manufacturing formula selected by drug developers, and then encoded into Module 3 of the regulatory dossier (NDA/BLA/MAA), help define the supply chain.

Figure 1 shows a typical end-to-end supply chain and how the stages build up, from raw materials to eventual delivery of the product to patients. It can be (and almost invariably is) a long and convoluted journey. Is this a forgone conclusion, or is it an avoidable outcome? In my opinion, much of it is avoidable, but there is a hurdle to overcome; those involved across the scientific and technical disciplines of drug development rarely understand that they are involved in production systems building end-to-end supply chains. Their focus is on getting to the next clinical end-point and generating data for the regulatory filing, with little thought given to the design and construction work

necessary for longer-term supply needs. This is not their fault of course, because the industry has operated this way historically to avoid putting work in if the compound eventually fails; and with attrition rates as they are, this is highly likely.

This does, however, leave us with a dilemma. For those drugs that get to market, their supply chains will have received scant attention as to their fitness for purpose. They may have issues such as suboptimal process yields, inappropriate sourcing, complex logistics, capacity constraints and locked-in compliance risks, for example.

Figure 1: Schematic of end-to-end supply chain



Once launched, there has been little historical appetite to risk changing anything unless it is an absolute show stopper. Sadly, this change inertia often exists similarly from the IND/CTX stage, where the initial application to run a clinical trial is approved. At this point, the regulators are informed of the chemistry, manufacturing and controls (CMC) information for clinical trial scale manufacture. Companies can be reluctant to 'rock the boat' once the regulator is involved. The net result is that our supply chains in commercial launch are often based on early stage suppliers and processes that are inappropriate for the rigours of commercial supply.

Should we now be asking ourselves 'does it have to be this way'? Is drug development so different to any other product development process that we cannot improve the status quo? The answer is no, as we shall see from reviewing how other sectors manage their production systems.

THE ESSENCE OF MODERNISATION

Readers should suspend judgment for the moment to counter the urge to say we do not have the time in our sector. Remember the hare and the tortoise? The Japanese manufacturing sector proved that by taking time and effort at the earliest stage of product concept, the results could be startling. Modernisation is about doing a similar thing in pharmaceuticals. Many think it can't be done, some think it can, others are not sure one way or the other. In order to help decide, we should look at what other sectors have done in their production systems.

At an early stage, the exemplars recognised that the designer throwing his or her proposals 'over the wall' for others to manufacture, was a major problem for quality. To counter this, they involved all relevant parties at the design stage. This included, for example, marketing, manufacturing, procurement and key suppliers. If there were issues with a design, ways would be explored cross-functionally and inter-company to gain the same or similar effect in a workable way. The focus of attention was on relentlessly meeting customer expectations for value as delivered by the end-to-end supply chain. The logic to this being that no matter how impressive the idea, if it cannot be delivered to a customer, the value is not realised in terms of cash receipts.

Along with this, they moved towards programme management. The programme head (often the Chief Engineer in Japan) held responsibility for taking the product to market, not just to an initial phase, proof of concept or prototype stage. There was consequently no handover of responsibility as with discovery research to development and with development to commercial manufacture. Accountability was transformed and essential knowledge was retained for optimum learning. It became possible to institutionalise risk management into everyday working, with a focus on identifying and implementing mitigations within the programme management process.

With this integrated, process-orientated approach in place, the platform was there to drive improvements in quality of output from the production system. The following account of these improvements is brief by necessity, but is well-documented for those who wish to research further (2-5).

- The exemplars developed the concept of a 'value stream', rather than the functional approach to manufacture that had been taken by the ways of mass production. The value stream was aligned to the specific needs of the product family being manufactured, so that the people, and the development of the facilities and equipment, displayed had a deep understanding of the market and the processes by which the customers were supplied. The key element was to join equipment and processes together to shorten the time between taking a customer's order and receiving the cash. This meant they had to solve problems that arose across the value stream, such as supply defects, process variability, operator error and so on. They did not allow themselves the

luxury of being able to continue producing to bulk while a downstream process was stopped due to unplanned maintenance. Everything stopped while the problem was solved. It took a tremendous amount of determination and discipline, but delivered phenomenal results. There was no room for defects to lay hidden in the system.

- In achieving the above, the responsibility for 'quality' was re-defined. Edwards Deming proved in the 1950s that if operators were given simple statistical tools that they understood and applied for themselves, they could vastly improve the defect levels from their work. The massive quality functions were redirected away from inspection into more value adding areas such as quality engineering, where they worked on the integrity of the quality system.
- These improved quality systems were directed at reducing opportunities for error across the value stream. They recognised that that complex, ill-defined systems work strongly against the best efforts of committed employees.
- The concept of a value stream manager was established, a role with accountability for creating and maintaining the flow of value to the relevant customer markets.
- They accepted that in some areas, their suppliers were critical to their competitive advantage and so deep and long-term relationships were developed where risks and rewards were shared. This also allowed them to put in place agreed cross-company processes with less potential for us-and-them finger pointing.

This account goes on and on, as some sectors have sought to continuously improve.

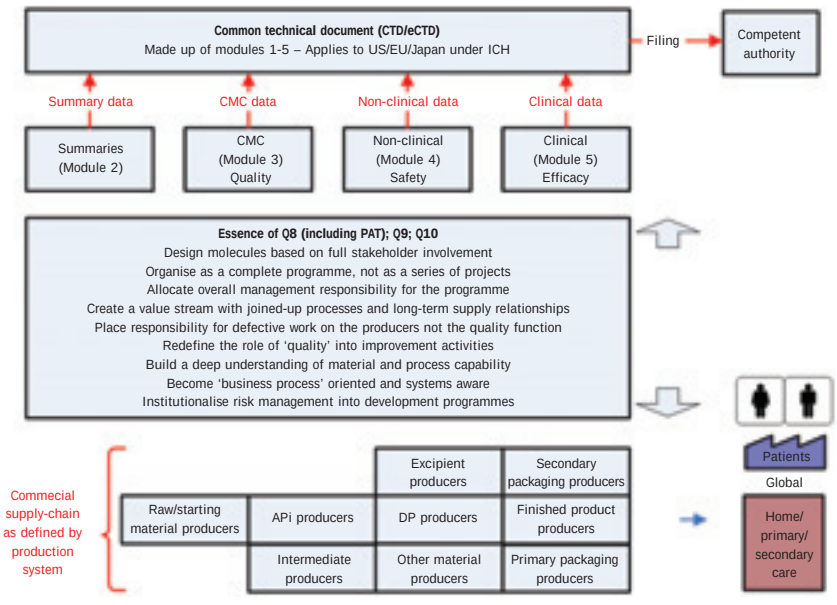
CONCLUSION

The modernisation guidelines appear to be the regulators' attempt to 'kick-start' the process of moving in the direction taken in other sectors. There is, however, limited evidence that the intended transformation posed by Dr Woodcock's intention is taking place. Our supply-chains are receiving unprecedented attention from regulators as compliance, integrity and cost issues remain.

These guidelines will remain impotent, however, unless issues of organisational and cultural change are addressed at the core of the industry. While we ask a 'quality' function to shoulder the responsibility for output from our production systems, we will never be able to emulate these other sectors, because they shifted that responsibility to where it should have been, onto those making the products.

If we do not involve commercial manufacturing, procurement, suppliers and market development in the initial stages of molecule design and prototyping, we will never be able to emulate these other sectors, because they did just that and proved it worked.

Figure 2: Modernisation in drug development



About the author

Hedley Rees is a practicing consultant, coach and trainer, operating through his company biotech Pharmaflow. Previously he held senior supply chain management positions at Bayer, British Biotech, Vernalis, Johnson & Johnson and OSI Pharmaceuticals. His specific interest is in helping drive industry improvements through the regulatory 21st Century Modernisation frameworks of FDAs Critical Path Initiative and ICH Q8 to Q10. He holds an Executive MBA from Cranfield University School of Management, is a corporate member of the UK's Chartered Institute of Purchasing and Supply (MCIPS) and of UK BIAs Manufacturing Advisory Committee. He regularly speaks at international conferences and he has publications in US and EU pharmaceutical journals, as well as being a published author on supply chain management.
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