DISCOVERY is not enough

how a new compliance agenda is changing the face of the industry

Safe and effective drug products for the 21st century can be developed if, and only if, firms understand the mechanism of action of their products, and they are able to successfully implement a holistic quality approach to the industrialisation of these products. The FDA and other regulators are changing the game by setting a new compliance agenda focused on reducing risk to the patient by the application of science to the design, development and manufacture of drug products. Much of the progress which is being made in understanding how drugs work will be subsequently eroded by the failure to evolve a quality-by-design approach in development.

By Dr Doug Dean and Frances Bruttin

In 2010, the pharmaceutical industry (Pharma) will sell a variety of targeted products and therapeutic healthcare packages that include diagnostic tests, drugs and monitoring devices, as well as a wide range of services to support patients. Companies that learn how to make these products will deliver greater shareholder returns than they have ever delivered before[1]. These new products will be more effective because they will be focused at a genetically-identifiable subset of the patient population. Researchers will eventually be able to differentiate diseases that currently get lumped together as if they were one, and treat them as different disease states. Genomics and proteomics will enable Pharma to define these diseases much more accurately and make commercially viable drugs for smaller patient populations.

The future of medicines – targeted treatment solutions

This redefinition of disease will culminate in 'targeted treatment solutions' – healthcare packages for treating specific disease pathologies. They will typically consist of biological rather than chemical molecules, based on clinically validated targets derived from a better understanding of particular disease mechanisms. They will measurably modify the diseases for which they are prescribed, with outcomes data and disease progression markers providing proof of efficacy. A network of services for diagnosing, treating, monitoring and supporting patients will support them (**Figure 1**). The development of targeted treatment solutions (TTS) for specific disease states will not only create new market spaces, but it will also benefit patients,

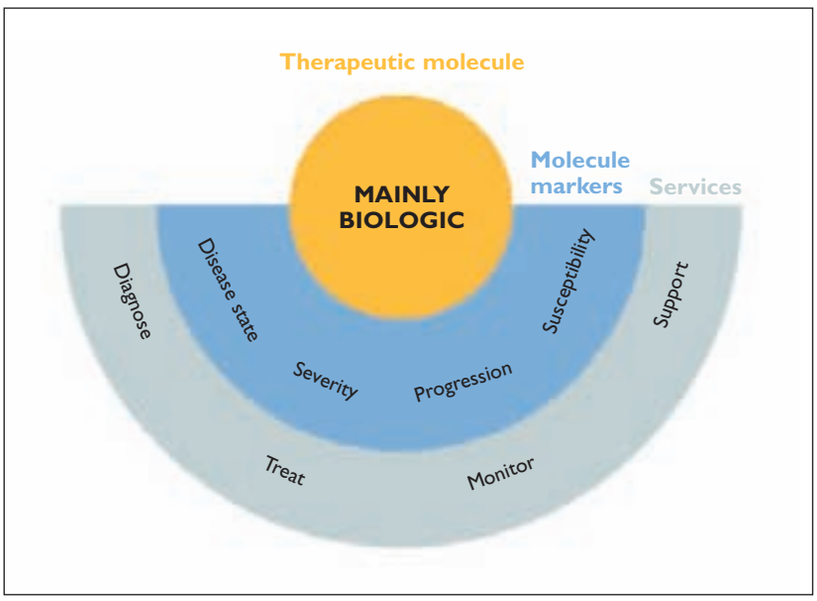


Figure 1
Targeted treatment solutions will be biologically-based and include diagnostics, drugs, devices and support services for patients with a specific disease pathology

healthcare professionals and payers, and the industry alike. Shareholders will also benefit since TTS will enable Pharma to charge premium prices for treatments that work demonstrably and significantly better for particular disease states. Given the forecasted shortfall of the compound annual growth rates required to meet established shareholder expectations, targeted treatment solutions are key for future success.

Getting there: discovery and development

For the targeted treatment solution business model to succeed, drug discovery and development have to be underpinned by an understanding of how different diseases function at a molecular level. The molecular sciences will enable the industry to define diseases much more accurately – and to create a collection of treatments and services for patients with specific disease subtypes, rather than making one-size-fits-all drugs for patients with similar symptoms but essentially different diseases. Most of these new medicines are likely to be biologically-based.

New approaches to discovery – necessary but not sufficient

Exploration in fields such as genomics, proteomics and metabonomics is providing Pharma with plenty of new biological targets. As we discover which targets are relevant and which diseases they are associated with we will be in a position to develop the targeted treatment solutions which are vital to the future success of Pharma.

Although a different approach to drug discovery is a necessary factor for success, it is not sufficient. This is due to the fact that targeted treatment solutions will be more complex to develop and manufacture and will rely on 'quality-by-design' approaches in development. Quality-by-design will be a mandatory minimum not only because of the inherent nature of the new products, but also because of the requirements of FDA's new compliance agenda.

The new compliance agenda

In March 2004, the US Food and Drug Administration (FDA) acknowledged the extent of the difficulties facing the pharmaceutical industry when it launched an initiative to improve the product development process. "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"[2], the white paper published at the time of the launch, spells out the technological gulf between discovery and development. The initiative is a logical extension of the FDA's earlier efforts to modernise the regulation of pharmaceutical manufacturing and product quality[3].

Manufacturing is the culmination of a complex set of activities including physical design, the development of a manufacturing method and the shift from small-scale to full-scale production. The FDA has called this the 'industrialisation process' – and here Pharma is struggling as: "Problems in physical design, characterisation, manufacturing scale-up, and quality control routinely derail or delay development programs and keep needed treatments from patients."[4]

Greater product complexity

There is already some evidence of greater product complexity and the challenges it creates in industrialisation since the more complex products are more difficult to manufacture[5-7]. This will certainly be the case with targeted treatment solutions. Many of the new drug-device combinations amalgamate several different scientific disciplines and delivery technologies. Thus the industrialisation process will increasingly involve a network of technology suppliers and will be more likely to include contract developers and manufacturers. All this will compound the difficulty of managing the industrialisation process.

The current approach to product development

The FDA recognises that product development is now the weak link in what it calls the 'critical path' from scientific discovery to commercial product. The part of this which focuses on the development of robust processes for manufacturing on commercial scales is a recognised problem area since Pharma is not highly skilled at making the transition from the laboratory to the factory floor. The reasons are partly because very few people possess the hybrid

scientific and engineering skills required to bridge the gap, and also because there has been little traditional focus on technology transfer process so the skills and proven techniques just do not exist[8].

Scale-up is one of the biggest hurdles in development, particularly with biologics, where fermentation and the subsequent separation and purification steps can be even less predictable than the corresponding processes for traditional molecules. However, even when a product has successfully migrated into full production, problems frequently arise. One common issue is that different batches of excipients often vary slightly, causing significant variations in the end product. Sometimes it is simply a mixture of minor variations in different ingredients, machinery and unit operations that causes trouble – and when a problem is 'spread' across the process in this way, it can be very hard to detect and rectify[9].

The need for a new product development approach

In short, the existing model of product and process development is inefficient, and the trend toward more complex medicines is straining it further. It is estimated that as many as half of the factors causing attrition in drug development are related to chemistry, manufacturing and controls[10]. Problems with industrialisation are also responsible for a substantial number of the delays that occur in getting new drugs approved.

To help address this situation, over the past two years the FDA has actively encouraged the use of process analytical technologies (PAT) and other modern manufacturing techniques for improving production. In addition, it has promised to regulate companies that clearly understand the scientific foundations of what they are doing with a lighter hand than those persisting with traditional manufacturing methods. The agency has thus removed one of the greatest potential obstacles to the development of better manufacturing practices. This is significant since with compressed Phase III timelines there is less time to resolve problems and more pressure to have manufacturing methods stable much earlier in the development timeline.

Shorter clinical development times clearly increase the pressure to produce robust formulations and manufacturing processes much earlier in the product development cycle. Other changes in the nature of clinical testing could reinforce the need for faster, better industrialisation. The introduction of 'in-life testing' would provide a more comprehensive and more realistic means of testing drugs than conventional Phase III trials. Sir Tom McKillop, Chief Executive of AstraZeneca, recently proposed something similar when he called for a system of conditional approval, under which new drugs would be prescribed by medical specialists and closely monitored for side-effects before receiving a full marketing licence[11].

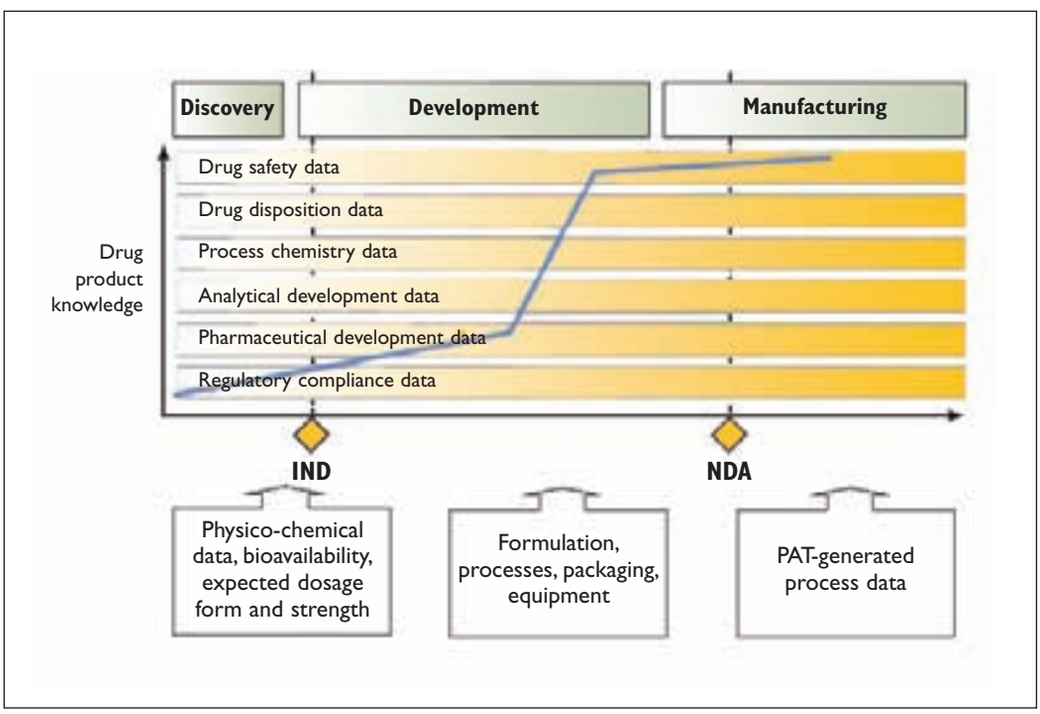
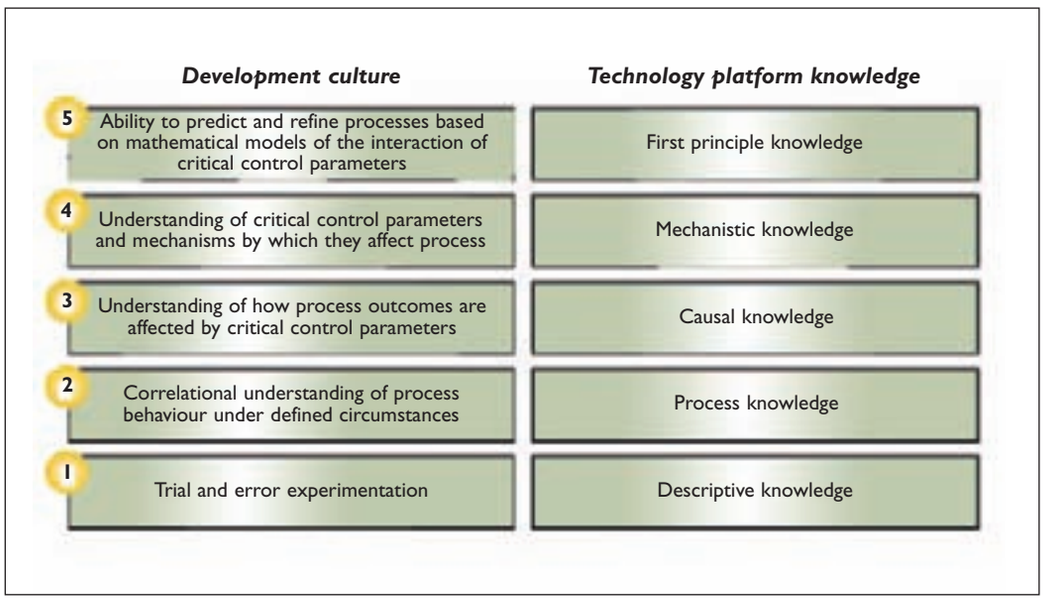


Figure 2
Sharing data between clinical development, pharmaceutical development and manufacturing facilitates the creation of more robust manufacturing processes

Figure 3
A company's development culture determines the extent of its knowledge about its technology platforms. Traditional three-batch validation has the industry stuck at level 2



Building a better industrialisation process

Pharma needs a new paradigm for industrialising products. If it is to capitalise on the progress that has been made in biomedical research and accommodate emerging trends that are pressurising traditional approaches, it must move from an empirical to a more mechanistic and predictive mode of working. Pharma needs to manufacture products that are increasingly complex; it needs to develop the processes for manufacturing them increasingly rapidly; and it needs to verify the processes are stable prior to launch. Three elements are especially important in achieving these changes: cross-functional 'data-sharing'; 'quality-by-design'; and systematic building of 'process capability'.

Cross-functional data-sharing

A lot of the basic data required by a pharmaceutical development team are ascertained in discovery and early clinical studies. However, at present very few development teams have the tools to collaborate closely. The discovery, clinical development, pharmaceutical development and manufacturing teams meet regularly, but they do not necessarily share crucial data on a day-to-day basis (**Figure 2**). The ability to share such data throughout the industrialisation process would allow the pharmaceutical development team plenty of time to solve any problems with the drug candidate. Collaboration with the manufacturing function is also essential to confirm that the team does not design a product which cannot ultimately be manufactured.

Quality-by-design

If cross-functional data sharing is vital, so is scientific development of a manufacturing process that reduces or mitigates the risk of making products which lack the features that are critical to quality. Experience in other industries shows that the key to quality-by-design is the preferred technology platform.

Although most pharmaceutical companies repeatedly use the same technologies, this is usually an ad hoc exercise relying on individual expertise that is often poorly aligned with manufacturing. If Pharma is to make increasingly complex products and make them in a scientific manner, it needs to adopt a much more formal approach. Creating preferred technology platforms that are implemented throughout the entire company has several advantages. It enables companies to standardise the equipment, materials and processes they employ, thereby optimising the use of those resources. It also facilitates the development of a knowledge base that can be used to predict how technologies will perform at commercial scale.

Preferred technology platforms are equally important in designing an enterprise pharmaceutical development plan. Again, most companies are halfway there. They have development manuals which document their preferred modes of working, but these do not generally incorporate interactive templates that can be tailored to a given project and automatically updated to accommodate the latest experimental results – features necessary to facilitate the transition to fully scientific development and manufacturing.

Systematic building of process capability

Using preferred technology platforms and development plans only produces a basic manufacturing equation. The ultimate aim is to design 'right first time' in more than 99% of cases – which means building robust pharmaceutical development and manufacturing processes to consistently deliver quality output (**Figure 3**).

For each step involved in a particular technology platform, a determination of process capability (Cpk) shows how reliable the process is. Process measurement can also be used to acquire a better understanding of technology platforms. Suppose, for example, that the pharmaceutical development team wants to learn more about dry blending. It might employ manufacturing data generated through the application of PAT to correlate variations in materials, environmental factors and equipment with variations in the finished product. It could then use the data to refine the performance of the processes prior to the transfer to manufacturing. As its level of understanding increases, a company can eventually create a set of mathematical models to predict and continuously refine the performance of its technology platforms and manufacturing processes (**Figure 4**).

However, building process capability and understanding at the levels of mechanistic and first-principle knowledge is almost impossible without ready access to historical process data, primarily data generated in manufacturing. The ability to predict the most likely sources of variation and what changes might reduce them is arguably one of the greatest benefits of using PAT[12].

A pharmaceutical development process that aspires to quality-by-design starts with the features that are critical to quality from the perspective of patients; translates them into the features that are critical to quality in the manufacturing process; and then defines the critical control parameters for producing a drug with the right specification. The end result is a design space that shows how each step in the manufacturing process must be performed. It also shows how the critical control parameters can be varied to consistently produce a drug with the right specification.

The benefits of process understanding

Process understanding through the collection and manipulation of vast quantities of development and manufacturing data has real business value. The FDA has already promised that it will lessen the regulatory burden for those companies that can show they have a firm scientific grasp of the processes they are using. In addition to attaining improvements in operational efficiency, better process understanding can also mitigate the risks of product recalls with all their attendant damage to a company's bottom line. Research suggests that improving pharmaceutical development and creating a manufacturing method that is stable from the moment a drug reaches the market could help to accelerate the point at which sales peak by up to five years, thereby increasing the revenues a billion-dollar drug generates over its lifetime by as much as $1.6 billion[13] (**Figure 5**).

Conclusion

Pharma has traditionally treated pharmaceutical development and manufacturing as poor relations to discovery and clinical development. However, as the drugs made and the processes used to manufacture them become increasingly complex, so the status of the chemistry, manufacturing and controls function is being slowly elevated. The FDA has reinforced this trend with its drive to protect patients more effectively – for example, through its two-year programme to improve the regulation of

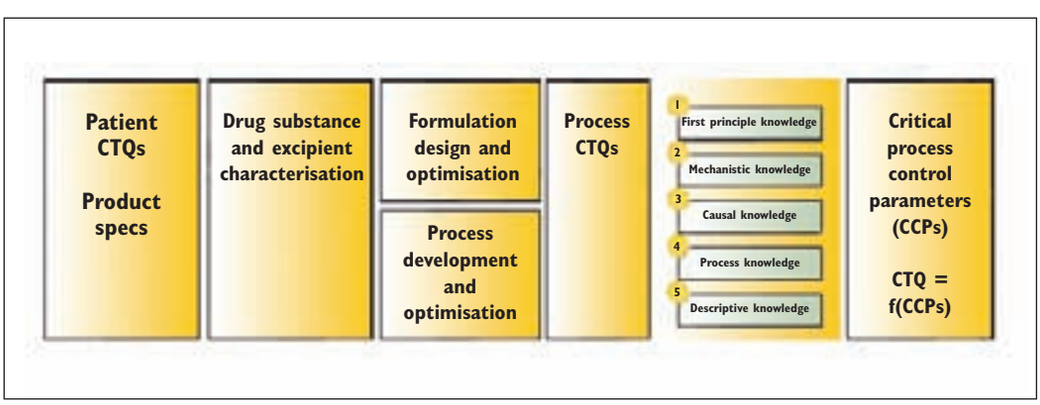


Figure 4: The aim of quality-by-design in pharmaceutical development is to build a mechanistic understanding of process capability and variability

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References

1 Arlington, S, Barnett, S, Davies, N and Palo, J. Pharma 2010: The Threshold of Innovation. IBM Institute for Business Value, Publication G510-3976-02, IBM Corp. Somers, NY, USA, October, 2004. http://www-1.ibm.com/services/us/index/wss/xs/imc/a1001099

2 US Food and Drug Administration. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medicinal Products. March, 2004. http://www.fda.gov/cdrh/ocd/criticalpath.html

3 US Food and Drug Administration. A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (CGMP's) for the 21st Century. August, 2004. http://www.fda.gov/oc/guidance/gmp.html

4 US Food and Drug Administration. Innovation or Stagnation. p.8.

5 Ortho-McNeil website, http://www.orthomcneil.com/news/article111504.html

6 SkyePharma website, http://www.skyepharma.com/approved_depocyt.html

7 Nektar Therapeutics website, http://www.nektar.com/content/pr_1078414166

8 Gilchrist, M and Van Dyck, W. Transforming Industrialization, a New Paradigm for Pharmaceutical Development. IBM Institute for Business Value, Publication G510-3997-00, IBM Corp. Somers, NY, USA, January, 2005. http://www-1.ibm.com/services/us/imc/pdf/ge510-3997-transforming-industrialization.pdf

8 York, P. Molecules, Materials Science and Medicines. The Pharmaceutical Journal, vol. 267, p.438, 29 September, 2001. http://www.pharmj.com/pdf/society/pj_20010929_bpcscience.pdf

Continued from page 13

10 Wechsler, J. FDA Eyes Manufacturing Innovation to Boost Drug Development. Pharmaceutical Technology, May, 2004, p.28.
11 Durman, P. AstraZeneca Chief: We Need Safer Medicine. The Sunday Times, 21 November, 2004. http://www.timesonline.co.uk/article/0,,2095-1367455,00.html
12 Bruttin, F and Dean, D. The Metamorphosis of Manufacturing – From Art to Science. IBM Institute for Business Value, Publication G510-4034-01, IBM Corp. Somers, NY, USA, May, 2005. http://www-1.ibm.com/services/us/imc/pdf/ge510-4034.pdf
13 Gilchrist, M. Transforming Industrialization. p.15.

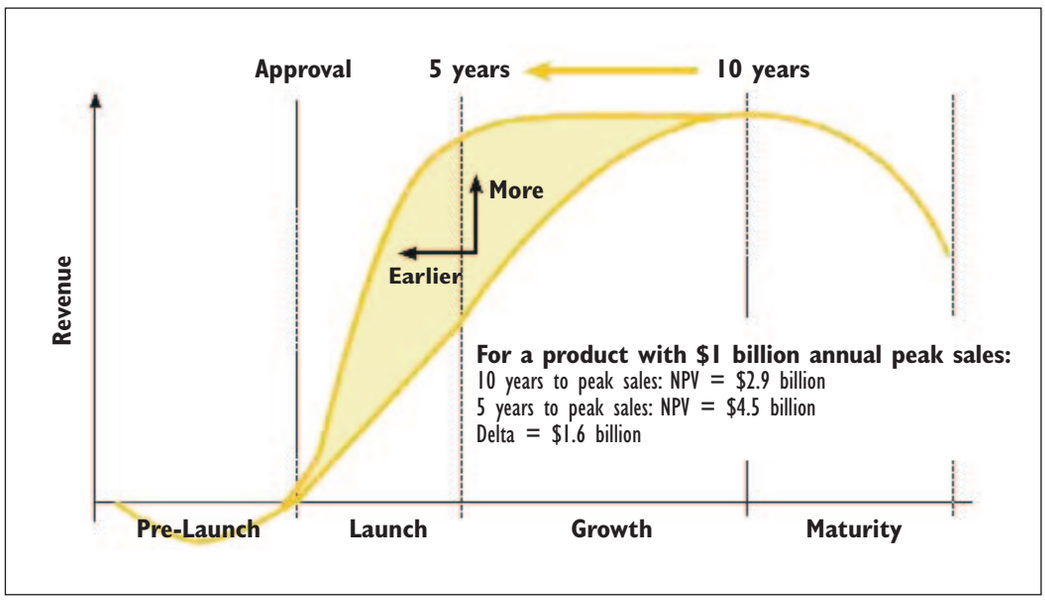

Figure 5: Bringing the point at which sales peak forward by five years could add $1.6 billion to the lifetime value of a product with $1 billion annual peak sales

pharmaceutical manufacturing and its more recent initiative to transform the industrialisation process.

As a growing number of industry executives are beginning to realise, manufacturing is no longer a standalone activity to be conducted in isolation from what happens in the laboratory. It is, rather, part of a continuous research and development loop. Transformation of the industrialisation process from art to science will remove some of the roadblocks in getting new drugs already in the pipeline to market and enable companies to develop better products in future. This transformation can also help to unlock far more value from the products companies make.

Without a new approach to the process of industrialisation, companies are likely to lose the benefit of emerging targeted treatment solutions that are resulting from new approaches to drug discovery. In an era where the regulatory focus is on risk reduction via quality-by-design, new discovery capabilities cannot stand alone and must be linked to dramatically different approaches to development. Absent this, even the most sophisticated discovery advances will fail to deliver the business value required. DDW

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