Risk: assessment, aversion and denial

Since its foundation the European Fine Chemicals Group (EFCG) has highlighted the risks and rewards globalisation brings to its members and to pharmaceutical fine chemical industry stakeholders. **Guy Villax** discusses the options faced by large pharma and regulators alike to meet the challenges of a fast changing industry

Over the past 20 years, the pharma industry has changed beyond recognition. Certain trends have accelerated, while others have inverted 180°. Europe, once the cradle of chemistry and pharmacy, is no longer at the forefront of R&D innovation. In 25 years, Europe has gone from the world's leading producer of APIs to an also-ran player supplying only a fraction of the ingredients that make up EU medicines today. Generic medicines, a non-existent industry before the 1980s, now fill the majority of prescriptions across the globe. Regulators are continuously elevating the bar and setting standards that just a decade ago would have been inconceivable, if not impossible to achieve, because the technology was not there.

Large pharma's investors are unhappy; total shareholder return has been negative at –2.4% a year between 2001 and 2007.[1] At the time of writing, performance can be expected to be even worse and the future outlook no better. Whatever your crystal ball tells you, the inescapable reality is that pharma's current business model is broken, and that its new strategy must, regardless of its shape, include low-cost manufacture, better returns on capital and new ways to create value. The big pharma industry also needs to re-invent itself if it is to take advantage of growth in emerging economies. Traditional markets may be where profits are made today, but they are experiencing sluggish growth. So what can be done to take advantage of fast-growing Brazil, India, Mexico, India, China and Turkey? These markets may not accept the high prices charged in the West, but they do have GDPs growing at triple the rate of traditional markets.

Andrew Witty, GlaxoSmithKline's CEO, has spoken about a branded generics plan for emerging markets – countries where enforcement of regulations is weak, and where a GSK brand on a generic blister pack may gain a patient's preference despite a mark-up.[2] David Brennan, CEO of AstraZeneca, is considering similar options.[3] Therefore, convergence of innovators and generics, with heavy emphasis on branding, may well be part of the new pharma model, especially in fast-growing markets.

lean and mean

Many believe the future business model will see big pharma companies retaining their development and marketing/distribution functions, but shedding both primary and secondary manufacturing. Eventually, big pharma may also shed its R&D, choosing instead to in-license aggressively compounds from innovative small pharma companies and biotechs. Merck & Co and AstraZeneca have made their exit from API manufacturing clear as a strategic option.[4-5] These companies have/will sell/close plants, while others, such as Roche and Pfizer, have gone the same way because of excess capacity. This is precisely what has happened in the automotive industry. Car makers today focus on design and marketing; only occasionally will they actually look into manufacturing or technology. Even at Porsche, the assembly of the Boxster model is outsourced. Furthermore, it is in industries under severe pressure that one finds best practices and where managers become the most aggressive at cutting fat and becoming "lean".

In relative terms, pharma is still very profitable, so it's no wonder that 6 Sigma and lean manufacture are still in their infancy in GMP operations. On the other hand, if we can drive very affordable, reliable, comfortable, good-looking and high-performance cars, it is because globally the automotives industry faced strong competition – pressures that led to restructuring, consolidation and specialisation, for example in component suppliers. A new car model today is first conceived, then actually put together, by parts suppliers under the baton of the car manufacturer. All

need to excel at "design for manufacturing" concepts and methods to ensure compatibility – in this respect pharma has a long way to go.

The US FDA has opened the door to a new paradigm of efficiency in terms of development and manufacturing, whether this is in the production of an API or of a tablet. "Quality by Design" (QbD) now makes 6 Sigma and lean manufacture a practical reality; process analytical technology (PAT) and parametric release allow trending, eliminating dead time from samplings and analysis, and avoiding rejections, deviations and reprocessings. So expect a step change in pharma manufacturing: far greater scientific understanding of the process, with significantly higher investment in process chemistry, data collection and sophisticated process automation. The introduction of car industry production techniques and great innovation in the fine chemicals industry itself, such as Britest,[6] will result in dramatic reductions in per kilo cost, in operating costs of plant, in costs to build and improvements in speed and flexibility and reduction of inventories.

This shift is contingent on pharma manufacturing ceasing to be captive and instead becoming mostly contracted out. It is the test of the market, and the demands of powerful customers, that will drive the API industry to consolidate, specialise and excel at compliant but low-cost manufacture. The savings large pharma is looking for are not related to lower labour costs or lower overheads driven by lower HSE standards.

In the world of new product introductions, large pharma will be facing an acid-test. Will big pharma look to have its cake and eat it too? For new product introductions, companies will not compromise on standards. They will expect to speak at their usual scientific level with contractors, and they will seek to verify compliance with high standards of quality, GMP, HSE and ethics. Yet they will also want to avoid capital investments and expect a low (and constantly lowering) cost-of-goods-sold. They will want someone else to keep their inventories and they will want just-in-time delivery. And yes, they will still want to be able to take advantage of the tax strategies manufacturing has traditionally afforded them.

new partnerships

Today not many contractors can offer this value proposition and, similarly, big pharma companies do not realise how much they will need to change to be able to capture these benefits. Focusing on small-molecule new product introductions, going forward there will have to be significant consolidation of the API industry because few such firms currently have sufficient production capacity to truly serve the API needs of any large pharma player.

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Contractors and pharma companies are still discovering QbD,[7] and few have supported QbD filings. But to do this, and to capture all the possible value, large pharma must become a more creative purchaser and it needs to establish true partnerships with API suppliers. Relationships need to be long in term and wide in scope, starting at the process development stage, with IP captured in ways that contribute to a tax-favourable structure when it comes to manufacture, that will have to take place in the usual places. Forging such relationships requires major changes in mindset. We are talking about very close and long-term collaboration, data integration and a level of transparency that is currently unknown within big pharma itself – creative solutions require a high degree of trust.

Small pharma companies have shown how this can be done. Almost 10 years ago, Agouron saw the FDA approve its HIV protease inhibitor NDA in a few months, and a 20-ton API forecast became a 100-ton per year manufacturing challenge. Within 12 months of approval, API plants in Japan, Italy and Portugal were on line. Together with building block manufacturers this product mobilised 1,000m^3 of reactor capacity. Within four years, continuous improvement and competition had reduced the API's price per kilo to levels generic firms would balk at. Agouron was later taken over by large pharma and API production was brought in-house.

looking east or west?

A current trend in pharmaceutical fine chemical manufacturing seems to be a geographical shift eastwards – even Lonza is building small molecule manufacturing in China. Yet if Merck & Co and AstraZeneca are going to entrust their next launch to anyone they will prefer the API to be made in a familiar setting. Irish facilities have not received a warning letter since the mid-1990s. Cork has the highest density of API producers anywhere in the world (mostly tax-driven captive manufacturing for US and Japanese large pharma), but even after stripping out the tax effects (about two-thirds of the export value) and the manufacturing inefficiencies of captive manufacture (about 50%), Ireland is still as big as China or India (see Table 1).

Today there are virtually no contract manufacturers in Ireland, mostly the result of big pharma buying up their plants in the heyday of the 1990s. Ireland, unfortunately, has allowed its cost base to spin out of control, probably in part because the magnitude of tax-savings dwarfed plant operating costs. The reality is the current cost base is tough for contractors.

Although Ireland has a talent pool that cannot be ignored, what remains to be seen is whether its stakeholders, from Ireland's Industrial Development Agency (IDA) to the trade unions, will confront the cost issues, working with contract manufacturers to provide their industry with a new lease of life. Buyers will be asking whether custom synthesis producers in Ireland can offer APIs to the usual Cork standards at Indian prices. Yet the telling factor will be, for instance, what David Smith, AstraZeneca's executive vice-president of operations, expects the right price to be.

Table 1: Geographical shift in manufacturing

For 2007 ($ billion)	Actual pharma exports	Tax effect netted out	Manufacturing inefficiencies netted out	API in %	Finished form in %
Ireland	34	11	6.5	–	–
Singapore	11.5	5.5	2.8	–	–
China	6.5	6.5	6.5	90	10
India	6.5	6.6	6.5	30	70

Source: Ireland's Industrial Development Agency (IDA)[8], Singapore's Economic Development Board (EDB)[9], PricewaterhouseCoopers[10]

Will Ireland remain the number one place for validating and launching NDAs? Nowhere else comes close in terms of compliance with GMPs and HSE. And will other places in Europe be producing intermediates for the first generation process? Will India and China be limited to providing the building blocks for the second generation process? As for the generics sector, the answer is simple: the generic drug is already a mostly Asian product, and only effective enforcement of regulations can stop a worrying trend towards a level of risk that is becoming unacceptable. Absent the imposition of quality standards by a regulator through deterrence and effective inspections of primary and secondary manufacturing (and across the distribution chain) competition will make sure the purchasing department will win every time over the quality unit.

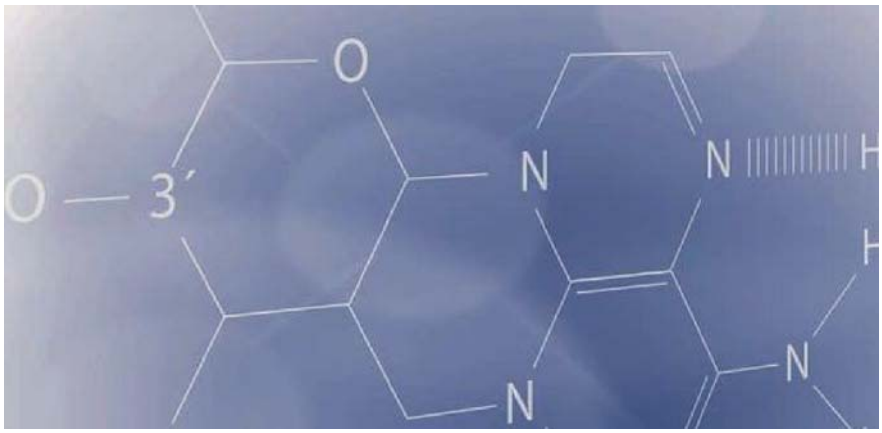
patient safety

For the regulators, 2008 was a turning point, even before the heparin disaster broke out. On both sides of the Atlantic, politicians and lawmakers had started to point out that the regulatory infrastructures, insofar as supervision of generics was concerned, were woefully obsolete and unable to maintain effective oversight over this globalised industry. Built to keep an eye on a national industry, Europe's medicines agencies today stare impotently over billions of parallel imports within the EU and over a flood of APIs pouring into Europe after DMFs are approved on a "paper-only" review. When inspections to plants identify non-compliant situations, a "rapid alert" is raised and we have seen recalls, but there is still no system in place to ensure that EU customs block the entry of APIs coming from producers known to be non-compliant.

After around 150 inspections worldwide (>65% in Asia, most others in Europe) conducted over a period of under 10 years, the European Directorate for the Quality of Medicines & Healthcare (EDQM) has in total suspended or withdrawn almost 40 CEPs (Certificate of Suitability). This means that large quantities of 40 very unsafe APIs have for years been administered to patients in the EU.

From a patient safety perspective those CEPs should never have been granted in the first place. All the CEP suspensions and withdrawals by the EDQM related to API manufacture in Asia, compared with zero in Europe. But the EFCG has always applauded the EDQM because until recently it was the only European entity that arranged for API inspections outside of Europe.

In April 2008, we saw for the first time the European Commission aiming for "mandatory inspections in third countries without equivalent GMP and inspection standards".[11] Over in the US, one of the bills being discussed in Washington right now contemplates mandatory disclosure of the country of origin of the API in the drug product packaging. The EDQM has recently altered its policy,[12] and its DMF database will disclose for each API all the sites used, not just the one involved in the final step. Is it not time for the EU to have a foreign inspection service?



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Another statistic likely to raise some question marks relates to how, whenever there is a major quality issue with an API (which is global, by the very nature of the supply chain), it only seems to affect Americans – Europeans appear to be immune to such events. If we look at the disasters caused by sub-standard APIs (for instance, L-tryptophan, gentamycin sulfate and heparin/oversulphated chondroitin sulphate (OSCS)) deaths were only reported in the US. What are we supposed to conclude? That Europe has safer generics? That European data gathering has flaws? Or is it something else?

At present, and for the foreseeable future, large pharma will remain the major driver, and valuable contributor, to the pharmaceutical standard-setting process. The consultation process over regulations, guidelines, monographs, ICH standards, etc, has limited generic involvement. However, the big pharma industry is no longer the major player: generics now fill more than half of all prescriptions worldwide. Is this not likely to lead to an increasing disconnect between standards and the fastest growing part of the pharma reality? Could this disconnect cause the credibility of our drug system to erode?

Companies and regulators are short of much needed expertise to understand the new shape and forces that are accelerating pharma's globalisation. The correct options are not the most obvious – yet it is clear that deliberate and decisive actions are urgently required to meet challenges and discharge responsibilities. SCRIP

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