Beyond the Blockbuster: What Can Big Pharma Learn from Mid-tier and Specialty Pharma?

Gerhard Symons, Pharmaceutical Executive Europe, May 2008

Mounting evidence suggests that the big pharmaceutical companies should change their R&D and business models if they are to compete with mid-tier and specialty companies in search of value. So what are the lessons Big Pharma can learn from the way its smaller rivals do business?
State of the industry
A glance at the structure of the global pharmaceutical industry shows that market share is highly concentrated. The leading 20 Big Pharma firms have annual revenues exceeding US$10bn, and dwarf the majority of biopharma firms by several orders of magnitude. These leading 20 firms, ranked by overall revenues, comprised just over 80% of the US$679bn total pharmaceutical sales in 2006.1 The remaining 18% of sales value was delivered by the long tail of mid-tier pharma, specialty biopharma and generic manufacturers. Traditionally, these 20 Big Pharma firms have been overly reliant on a relatively small number of blockbuster products hauling in more than US$1bn annually. Yet three trends threaten to shake up Big Pharma’s current business model: blockbuster patent expiries, rising R&D costs and the shifting emphasis to specialty care. What inferences can we make, and how will these trends shape the industry?

Big Pharma
Big Pharma firms are insulated with both annual revenues and total current assets typically between US$10-45bn. This ready cash allows them to use innovative development platforms, to explore novel drug classes and to operate across many therapeutic areas. All of which leads to multiple pharma projects — typically ranging from 50 to 200 per Big Pharma firm.2 Big Pharma has other advantages — sales and marketing operations deployed across all major markets, economies of scale for procurement, well-defined internal processes, established therapeutic franchises, brand equity and global networks of scouts to seek and evaluate the hottest technologies, the most promising of compounds.

But to support the commercialisation machine for a diversified portfolio and pipeline, Big Pharma pays a premium; on average, each firm spends over US$7bn a year to support the vast selling, general and administrative (SG&A) fiefdoms. What is more, over the period 1995–2006, SG&A expenditure increased from 28.7% to 34.5% as a share of total sales.3 The diversity of risk and strong fundamentals enable Big Pharma to cope with financial shocks such as voluntary withdrawal for commercialisation failures (e.g. Exubera [insulin)] or for safety concerns (e.g. Vioxx [rofecoxib]), and the inevitable pain of blockbuster patent expiry. Analysis from investors AXA Framlington shows that leading Big Pharma companies stand to lose US$74bn in sales due to blockbuster patent expiries from 2010 to 2012. Pfizer and AstraZeneca (AZ) will be worst hit, with respective revenue losses equating to 41% and 38% of total company sales over the next five years. Merck, sanofi-aventis, GlaxoSmithKline (GSK), and Bristol-Myers Squibb (BMS) all stand to expose between 22% and 34% of sales to generic competition.

To compensate for pipeline attrition, product withdrawal and patent expiry, and to sustain the bottom-line growth expected by shareholders, pharma spends ever-increasing sums on R&D. Within the top 400 firms in biopharma, worldwide total R&D expenditure increased 50% from US$66.6bn in 2002 to US$99.8bn in 2006 (CAGR4–6 10.5%); 75% of total R&D spend comes from just the top 20 Big Pharma companies. But can money alone buy effective innovation? The evidence is unconvincing — a Lehman Brothers’ 2007 analysis of pharma replacement power shows the differential ability of Big Pharma companies to replace the net present value (NPV) of existing products with pipeline products launched between 2008 and 2013. Among top companies, NPV replacement ranges from a relatively weak x0.16 for Schering-Plough to x0.55 for Merck, and an industry-leading NPV replacement power of x0.63 for GSK.4

Despite Big Pharma’s R&D investment to feed its dependence on primary care blockbusters, consider that in 2007 for the first time, the industry saw a reduction in primary care blockbusters from 33 in 2006 to 29, and an increase in specialty care blockbusters from 25 in 2006 to 30.5 Moreover, US consultancy Easton Associates estimates that specialty products will drive new dollar growth from 2004 to 2012 by 67%, compared to 33% by primary care blockbusters. As Big Pharma reduces overheads, reorganises monolithic R&D structures, and suffers loss of market share after blockbuster patent expiry, it is time, perhaps, to take some lessons from mid-tier and specialty pharma.

Specialty and mid-tier pharma
Specialty and mid-tier pharma have operated in a space hitherto ignored by Big Pharma. Speaking to Pharmaceutical Executive Europe, Jo Pisano, Director, Market & Value Advisory at PriceWaterhouseCoopers (PwC) said “mid-tier pharma tends to occupy niche specialist areas particularly by focusing on diseases with significant unmet needs, such as in CNS or orphan diseases’ (see sidebar, ’Pharmion: The renaissance of thalidomide’). By focusing on therapeutic areas that typically require a specialist to prescribe, and with annual treatment costs between US$8,000 to US$250,000, mid-tier pharma has been able to structure a business model to generate profit from annual product sales greater than US$200m by having a smaller, highly-trained sales force.6

“Marketing specialty products requires a different mindset from the Big Pharma model,” comments Claude Allary, Managing Partner at Bionest Partners. Since specialists are generally up-to-date with the clinical literature, and have received extensive training in the disease, they are more exacting in their critique of new products and will often require first-hand experience with the drug and in

1 p.26, Scrip Company League Table August 2007
2 Pharmaprojects v5.1, March 2007, p.26, Scrip Company League Table August 2007
3 PriceWaterhouseCoopers, Pharma 20:20, and p. 84, Scrip Company League Table, August 2007.
5 In Vivo blog, 12 February 2008, Windhover.
6 Health Strategies Group, Specialty Pharmacy Management, 2005.

Ibid.

Although currently unlicensed in Europe, it is prescribed for MM on an oncology focus, to estimate thalidomide usage for the treatment of multiple myeloma (MM) in the EU. For obvious reasons, thalidomide is strictly regulated. Although currently unlicensed in Europe, it is prescribed for MM on compassionate use basis only. PwC estimated thalidomide use by prevalence data, publicly-available data on incidence and survival, and by analysing treatment parameters. In addition, they conducted semi-structured interviews with haemotologists in several markets, to compensate for a scarcity of reliable sales data, and to account for the diversity in prescribing practice by treatment stage and market.

Says Jo Pisano: “This engagement was the first time that thalidomide had been quantified in Europe and it formed the foundation for Pharmion’s European market entry strategy. Part of Pharmion’s ongoing success was to engage with regulators and establish a rigorous risk management programme.” Since Pharmion’s entry into the market, the firm has sold 11 million thalidomide capsules in the EU — approximately 40% of all thalidomide sold. With three products due for EU approval in 2008, Pharmion estimates revenues between US$600m and US$750m by 2010.

**PHARMION: THE RENAISSANCE OF THALIDOMIDE**

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Pharmaceutical Executive Europe, Dr. Ken Seamon, Senior Associate at the Institute of Biotechnology, University of Cambridge, said that understanding clinical connections between leading physicians and centres of expertise was vital: “A specialty pharma might not have huge research grants to disburse, but they can certainly interest opinion leaders with good science and the treatment potential.” By engaging leading PAH physicians in clinical development across Europe, Actelion has acquainted the prescribing community with the drug, and reduced the crucial adoption time lag after marketing authorisation. Furthermore, Actelion has raised the barriers to entry for competitor follow-on products; with GSK due to re-enter the PAH therapy area with an innovative therapy, Volibris (ambrisentan), due for 2008 EU approval, it will have its work cut out training its sales force to understand customers’ needs, the clinical literature and the complexities of the disease.

**CELGENE: PUNCHING ABOVE ITS WEIGHT**

For Claude Allary at Bionest Partners, the US specialist oncology firm Celgene is a paragon of how best to compete against Big Pharma: “Normally specialty biopharma only has the resources to work in one or two areas, but Celgene has been pretty good, making an incredible success of developing difficult drugs.” The facts bear this out; ranked 68th in terms of overall global sales, Celgene is 10th in the global oncology market by sales (US$0.8bn), and the top independent biotech firm by value in oncology. Not only does Celgene have 19 oncology clinical programmes, beating Big Pharma companies with oncology programmes such as Abbott, Baxter, Schering-Plough and Wyeth, it also has the potential to be on equal terms with AZ, J&J, and sanofi-aventis in oncology by 2012.

Part of Celgene’s success has been their ‘blitz’ strategy — conducting on average, 6.3 clinical programmes per compound to enhance chances of success. This ‘learn and confirm’ model, which is being slowly adopted by Big Pharma, is critical to filing a high quality submission with regulators. The end goal is to build, what Andrew Witty, CEO Designate of GSK, called the ‘progressive blockbuster’ by slicing target populations. Acknowledging Roche/Genentech’s incontestable leadership in oncology as the clear exception, Claude Allary adds that Celgene’s commercialisation strategy is “evidence to suggest that Big Pharma should change their approach — but they haven’t so far.”


* Ibid.
In terms of complexity, oncology lays claim to being unique in therapy areas by the number of tumour types and tumour grades with numerous therapeutic options all with varying demonstrable efficacies. According to a recent report from Bionest Partners, oncology will be the leading therapy area by value in 2012 with US$92bn sales, which merits closer scrutiny. Specialty biopharma has been nimble in capturing the value through meeting unmet need in therapeutics, supportive care and *in vitro* diagnostics; of the 650 oncology compounds in Phase II, Phase III and pre-registration at the end of 2006, ~75% are of biotech origin. One specialty player in particular has capitalised on its technical expertise to "segment the market into smaller chunks," according to Claude Allary (see sidebar "Celgene: Punching above its Weight").

Yet, there is more value in oncology than therapeutics alone — consider chemotherapy-induced nausea and vomiting (CINV), or breakthrough cancer pain, both of which significantly reduce patients’ quality of life, and comprise an attractive market. According to Bionest Partners, the global supportive care market in 2006 for anti-emetics was worth US$2.4bn, and for opioid drugs, US$2.6bn. It is by launching innovative products for these therapeutic areas in 2008 and 2009 that ProStrakan — a publicly-listed UK specialty pharma — intends to accelerate its commercial goals to break-even in 2009, and achieve profitability by 2010, according to Abid Karim, Head of European Commercial Operations at ProStrakan (see sidebar, right).

**Mid-tier pharma: risk and reward**

Specialty and mid-tier pharma are not the natural constituency to be enthused by ever more onerous regulatory hoops. Yet, the genie is out of the bottle; post-Vioxx, the industry needs to instil confidence with regulators, payers, the medical profession and patients. In the EU, a risk management plan (RMP), legally mandated for marketing authorisation, outlines how risk will be detected, assessed and minimised.\(^9\) RMP can be a strong point of differentiation for specialty and mid-tier pharma, according to Dr. Swapu Banerjee, Head of Risk Management and Regulatory Practice, Pope Woodhead & Associates. "Big Pharma might have better resources for practical implementation, but mid-tier pharma is often better placed to create alignment between internal stakeholder groups with the external market place," he says. In Big Pharma, internal ownership of RMP may change hands from the safety department pre-launch, to medical marketing post-launch; however, in specialty pharma one key individual may have responsibility for the entire process, often with the assistance of external consultancy. Dr. Banerjee concludes, "For high-value products commercialised by mid-tier pharma, RMPs also convey a good message to payers for reimbursement, in that they may control diffusion of the product."

Risk management is a highly specialised area, and specialty and mid-tier pharma will not always have the relevant expertise in-

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However, regulators are often open to innovative approaches. Dr. Seamon encourages firms to engage with regulators early in development and view them as a co-development partner in discussing, for example, what is acceptable evidence. He adds: “I’ve always seen successful development projects when companies see regulators as partners — when it works in practice it is fantastic.” Although Dr. Seamon concedes that there are more opportunities to meet with the FDA, mid-tier companies operating in Europe can often take informal approaches, such as meeting regulators at scientific meetings: “as with most things in life, developing a relationship with regulators is critically important.”

**Big Pharma strategies**

In reaction to the business challenges in the market place, Big Pharma’s response has been to overhaul R&D structures that serve the existing business model. In broad terms, one can categorise the response into two different strategies — although some firms will display elements of both: (1) by adopting leading-edge technologies to produce incremental benefits throughout the R&D process; and (2) by fundamentally reassessing R&D’s role in the business and radically changing the structure:

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**INNOVATIVE INITIATIVES**

A few years ago, the FDA noticed a discrepancy between the large steps made in basic sciences in the late 1990s and the decrease in new molecular entities (NME) submitted for approval. This gave rise to the publication of the Critical Path Initiative (CPI) paper in March 2004 to identify how the path in biomedical R&D could be streamlined. Exactly two years later the FDA published a detailed opportunities list — listing 76 specific areas in which the critical path to submission could be made more efficient, and to eliminate the uncertainty as to what the FDA deems acceptable evidence. Examples include defining the role of biomarkers in progressing innovative medicines for new therapeutic indications, or how best to file electronic submissions. In 2007, the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA) launched an analogous ‘Innovative Medicines Initiative’ (IMI) funded by industry and the EU, to make drug development more competitive in Europe, and to develop and validate new methods in predictive efficacy and safety. Dr. Ken Seamon considers that “IMI may aim to achieve the same goals as the critical path programme, but it will take quite a few years before we see a significant impact.”

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**Incremental change**

Companies such as Merck, which want to reclaim leadership in the industry, are taking advantage of advances in the critical path initiative to develop ‘disease and proof-of-concept (POC) tools’ by providing researchers with predictive biomarkers in early-phase clinical trials [see sidebar: “Innovative initiatives”]. By looking at plaques from patients with peripheral artery disease, Merck is hoping to assess the drug effects on plaque biomarkers, such as lipids and RNA expression. Coupled with research in biomarkers, Merck played a particularly heavy bet on RNAi as a next generation macromolecule platform with its US$1.1bn acquisition of Sirna in October 2006. By industrialising its research efforts in this area such as automated, genome-scale, high throughput RNAi screening to identify novel drug targets, the company is looking for substantial returns. Part of this preclinical effort is to learn as much as possible about the biology and the drug candidate before late stage clinical development. In this new paradigm, the traditional three-staged clinical approach of development is replaced by a two-phase approach ‘learn’ and ‘confirm.’ Wyeth has restructured its clinical development teams to develop deeper insights in, for example, the dose-response relationship, to improve Phase III outcomes. Although the learn phase may be longer than traditional Phase I and II, it is expected that the confirm phase, involving the more costly Phase III trial will be quicker. Indeed, Wyeth has a global patient recruitment strategy to improve enrolment, reduce costs by using centres in emerging markets, and to give these centres 24/7 access to highly-trained call-centre staff in the US, France, and Australia.

Novartis continues its 2005 reorganization to improve target identification and to accelerate compounds through POC, which have been discussed previously. Using elements employed by Merck, such as the use of biomarkers, Novartis is going one step further in working closely with regulators to build and test disease models. This ‘build and confirm’ model mirrors Wyeth’s, although Novartis would seek provisional approval in a highly-limited population, before monitored release and subsequent full approval.

**Radical change**

Following the GSK merger in 2000, six centres, focused on drug discovery, were formed around core therapeutic areas. These centres of excellence in drug discovery (CEDDs) have expanded by five to include centres for biopharmaceutical development, and more importantly, a centre for excellence in external drug discovery (CEEDD). Through this CEEDD, GSK has been able to access 15 pipelines within various companies. The CEDD model has been the template for Roche’s new R&D restructuring along therapeutic lines...
which took place in 2007; with five disease biology area leadership teams (DBALTs), Roche expects that these DBALTs will be managed with a venture capital (VC) philosophy embodied by a Strategic Portfolio Committee, particularly when products move past POC stage (Phase II)."17

Despite these radical restructurings, there is talk that Big Pharma might have to disaggregate to realise the value that mergers were supposed to deliver. At a recent conference in London a senior R&D figure within GSK discussed the possibility of separately-listed therapy areas — effectively spinning out the R&D function to allow programmes to compete for resources under a VC-style management. In February 2008 AZ took the radical step to spin out its Sweden-based gastrointestinal R&D organisation to allow private equity to fund early-stage candidates, whilst retaining large commercial assets; Actelion is a good example of a successful Big Pharma spin-out, having left the Roche fold in 1998 with a strong management team and late-stage assets. Within two years Actelion launched its IPO on the Swiss Bourse at the height of the 2000 biotech boom with a US$800m valuation, delivering a healthy x26.2 return for lead investors, Atlas Venture.18,19

It is not inconceivable, then, to envisage a future where forward-looking Big Pharma companies allow proprietary programmes to compete for resources from investors without the financial security of a parent company — which is precisely how many specialty pharma companies operate today.

Conclusion
In the last twenty-five years, the primary care blockbuster paradigm served Big Pharma admirably. It served as a driver for the industry consolidation seen in the 1990s, as companies struggled to meet double-digit returns to satisfy shareholder demands. However, since 2005, shareholder returns from the pharmaceutical industry have not kept pace with the Standard and Poor’s (S&P) 500 index, according to data from The Economist.20 Specialty and mid-tier biopharma are the fastest growing firms in the industry; of the 50 leading companies ranked by growth of total revenue from 2005 to 2006, only five are Big Pharma, with Roche, GSK, sanofi-aventis, Boehringer-Ingelheim, and Bayer occupying positions 35, 38, 39, 45 and 50 respectively.21 Furthermore, 2007 data from Tuft’s Center for the Study of Drug Development, Boston, MA, shows that FDA drug approvals of NMEs and biologics for specialty care products increased from below 25% of all approvals in 1998–99, to 45% of all approvals in 2004–05. These trends suggest opportunities, both for mid-tier and Big Pharma and one may envisage the pre-eminence of one of two dominant strategies: (1) on the back of specialty care ‘progressive blockbusters,’ mid-tier pharma/specialty integrate forward, expanding geographical and therapeutic borders at the expense of Big Pharma in order to sustain growth; (2) more radical disaggregation within Big Pharma as greater shareholder value can be realised by owning controlling stakes in entrepreneurial spin-outs, which have tighter correlations between effort and reward. Despite locked in mutual co-operation and competition (‘co-optition’), both Big Pharma and mid-tier pharma share similar dilemmas: (a) constantly balancing the interests of shareholders with long-term R&D requirements; (b) squaring the circle of increased bureaucracy and reduced agility as firm grows beyond a certain size; and (c) the judicious placement of strategic R&D bets, the outcomes of which are only apparent many years hence.

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18 Wager, J. et al, “Unlocking the value of life science innovation through corporate spinouts Apeiron Advisors,” LLP.
21 p.16, Table 3.1: Leading companies ranked by growth in total revenue, Scrip Company League Tables 2007.