

Chief Executive Officer's review



Angus Russell—Chief Executive Officer

The Shire story

Past, present and future.

Like most CEOs, I get my fair share of invitations to speak at conferences. The focus is usually on new trends in our own industry but some look more broadly at business strategy, marketing, or change management. Whatever the banner, there's one single question I get asked more often than any other: how have we managed to take a small specialty pharmaceutical start-up, and turn it into one of the major world players in that field? It's true that when you look at where Shire is today, and compare it with where we were even five years ago, the scale of the change is pretty extraordinary, and those of us who have been part of that change can sometimes underestimate just how far we've come.

2009 was an important year for us—in many ways a watershed year—because the results we've achieved in the last twelve months are the direct result of a clear strategy that's been in place from the start, but has gained real momentum in the last five years. So it seems a good time to look again at the Shire story, because the sort of thinking that's producing strong results today is also shaping the way we're positioning the business for the next phase of our growth.

Phase I: Developing the model

Our business model has always been one of the most important keys to our success. The way we exploit that model is evolving over time, especially as we grow internationally, but our basic approach has remained unchanged for many years: a focus on specialist physicians, niche markets, unmet needs and symptomatic conditions where the impact of a successful treatment is immediate and tangible. This strategy started out as a positive response to a very practical business challenge—how do you build a successful pharmaceutical company when you have neither the resources to undertake large-scale high-risk research, nor the sales infrastructure to compete in mainstream therapy areas in primary care. Shire decided that the smart answer was to focus on lower-risk research and development, and make maximum use of the oral drug delivery know-how we already had in Pharmavene, a business we acquired in 1997 and renamed Shire Laboratories.

Shire Laboratories had the expertise to re-examine existing drugs and formulations like ADDERALL, and explore whether they could be delivered in a more efficient form. For example, if the required dosage could be reduced to once a day from three or four times,

the drug would be more convenient for the patient—this was the genesis of ADDERALL XR. This approach proved to be an extremely effective way of developing new drugs for a company at our stage of development, because the chemical formulations we were working on had already been through their safety trials, which meant we could get new versions to market quickly, and start generating the revenues we needed to re-invest in the business.

ADDERALL became the world's leading ADHD treatment in April 2000, with over 30% of the then \$1 billion US ADHD market. When ADDERALL XR was launched in 2001, it rapidly achieved a 26% share of a market that was worth around \$4 billion by the end of 2008. Shire was becoming a significant industry player; but by 2002 it was obvious to us—if not to the rest of the market—that the world was starting to change.

With hindsight, it seems obvious that generics were going to have an enormous and irreversible impact on the industry, but few people could have anticipated how wide that impact would be, or how quickly it would take effect. The pharmaceutical sector has always worked within the constraints of limited-life patents, and it was no secret that some of the world's big blockbuster drugs were going to come off patent in the late '90s. What did surprise people was the way the generic manufacturers used this opportunity to start challenging existing patents for the first time: the dynamics of the entire pharmaceutical market were about to change.

We soon saw exactly what this was going to mean in practice. We launched ADDERALL XR in 2001, but by 2003 we'd already attracted a generic filing challenging its patents. By 2004 approximately 60% of our product revenues came from our ADHD portfolio, and investors questioned how we would survive the loss of exclusivity. At the same time Shire was also facing the fact that reformulated drugs only attracted a price premium in the US. In the EU, reference pricing meant that health authorities would probably not pay more for a reformulated drug than they did for the older version. So it became evident that the strategy

US GAAP highlights

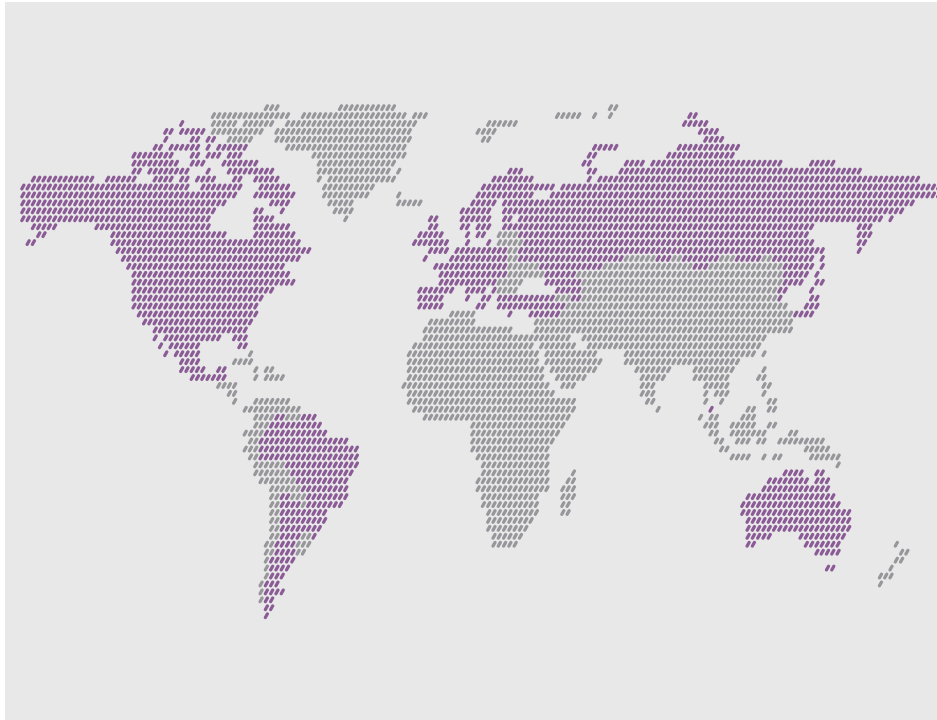
Revenues	\$3,008M
Operating income	\$620M
Net income	\$492M
Diluted earnings per ADS	\$2.69

that had initially worked well enough for Shire in the US was going to prove more challenging in building a platform for growth in other international markets. This was a pivotal moment: if Shire could no longer benefit from reasonable exclusivity periods for drugs like ADDERALL XR, or sell them at a price that would recover the investment, we would need a new approach. And we found it.

Phase II: New technologies, new markets

In 2003, the Board took a long hard look at where we were and how we were going to grow the business going forward. Shire sold a range of reformulated drugs in the US, and a number of other small-scale treatments on a market-by-market basis in the EU. There were no global drugs, which meant no international economies of scale. So we went back and re-evaluated the feasibility of high-risk early-stage research, and dismissed it again for the same reasons we had before. We then re-examined our basic 'specialty pharma' business model and decided that the rationale behind it was still sound—but we needed another way of delivering it. The challenge now was to sell our products on a global basis, at a price that made them economically viable. We also realized that reformulated products are vulnerable to generic challenges, and that new chemical entities have the benefit of longer periods of US regulatory exclusivity. True innovation and foresight in new therapies was the way forward. Around this time our work on developing anagrelide (AGRYLIN in the US and XAGRID in the EU) gave us our first experience of the 'orphan' drugs sector. Historically this has been less attractive to very big competitors, because the numbers of patients affected is very small, which is the main reason why regulatory exclusivity can be as much as seven years in the US, and 10 years in Europe and some other parts of the world.

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Argentina	Japan*
Austria*	Mexico
Australia	Netherlands
Belgium	Norway*
Brazil	Poland
Canada	Portugal
Czech Republic*	Russia*
Denmark*	Singapore*
Finland*	Spain
France	Sweden
Germany	Switzerland*
Greece	Turkey
Ireland	United Kingdom
Italy	United States

*representative office

Our Business Development team started to look for opportunities in this area that matched our existing focus on specialist physicians, symptomatic diseases, niche markets and unmet needs. What they found was Transkaryotic Therapies, Inc. ('TKT'), the business now known as Shire Human Genetic Therapies. TKT's focus on rare genetic diseases was a version of our own business model, and was built on expertise in a leading-edge proprietary technology. The difference was TKT dealt with large molecules, proteins, whereas Shire's business up to that point had been based on small molecules. Also, TKT's ability to produce enzymes from human cell lines was an exciting new area, but very few drugs had actually been commercialized at that stage, making it something of a calculated risk. But the closer we looked at the TKT opportunity, the more attractive it became. They'd already started to sell REPLAGAL, and there were two or three more drugs in the pipeline that we knew could be sold internationally.

Biologics are now attracting serious attention from many of the larger pharma companies, but we had the foresight to see the opportunity early, and the courage to translate that insight into effective action. This acquisition initially surprised the investment community, but our shareholders quickly realized how much of a great opportunity it was for Shire and the results now speak for themselves. The success of REPLAGAL and ELAPRASE has allowed Shire to establish operations in 28 countries, compared with nine in 2005. This new international infrastructure has given us a very powerful platform from which to exploit the growth that's going to come from the so-called 'pharmerging' markets.

Shire's international expansion comes at a time when the US government is putting more and more emphasis on reducing the cost of US healthcare. Most pharmaceutical companies derive at least a third of their revenue from the US; at Shire this percentage was once as high as 80-85%. We've been working to reduce this dependence on the US market over the last few years, and by the end of 2009 it was down to 70%. Our aim is to be making half our

revenues outside the US by 2015, and to have 25% of that revenue generated outside the top five European markets. This is an aggressive target and it will take a lot of hard work to get there, but we believe we've built a product range that can help us achieve it.

A key component of that portfolio is VYVANSE, for the treatment of ADHD. At the time we were working through the TKT acquisition, we were also looking at our important ADHD portfolio. ADDERALL XR, our most significant product in terms of sales, was being challenged by generic companies, and clearly wasn't the answer. The solution to this challenge was very similar to the one we found in TKT: having investigated the market we discovered that a company called New River was developing a new way to deliver amphetamine using a proprietary technology platform called 'Carrierwave'. This made the effect of the treatment much smoother and longer-lasting for the patient—it had a potential duration of effect of at least 13 hours, meaning only one dose would cover the whole day from start at school to bedtime. No ADHD treatment had been able to do this before, but it seemed that New River's new compound just might. This ultimately led to our acquisition of New River in 2007 bringing us global rights to VYVANSE and ownership of the Carrierwave technology.

As things stand now, we can see real signs that international awareness and understanding of ADHD is growing as is the need to treat adults, and there's an increasing need for an effective once-a-day medication. This will give us the potential to take VYVANSE into a number of markets outside the US. VYVANSE is already covered by US patents out to 2023, and pending patents in the EU out to 2024.

Phase III:**The pharma company of the future**

The success of Shire's last ten years is the result of a combination of foresight, good planning, and excellent execution. Shire's basic business model remains the same (specialty biopharmaceuticals, symptomatic disease, unmet need, niche markets, robust intellectual property protection); but we'll be adapting and growing that model in response to new opportunities and new market trends. Over the next few years we'll also need to carefully manage the internal impact of our international expansion. Traditionally we've been a very Anglo-American company, but as we expand in markets like Eastern Europe, Latin America and the Pacific Rim, we'll need to adapt to new cultures, new languages and new ways of collaborating internally. A business with a presence in nine countries is very different from one that covers 28: we need to understand how these new markets work, and adapt our own operations to fit local needs. A lot of this is about having the right people, but it's also about the right systems, and the right infrastructure, so that we can cope with a much higher volume of international sales.

Another challenge is to grow the business without losing the special culture that's made Shire what it is today, and we want to keep our agile and entrepreneurial way of working. We're aiming to do this through a 'hub-and-spoke' model, with regional centers across the world and semi-autonomous business units taking responsibility for decision-making on the ground. It's important for us to have a 'personalized' structure that allows us to develop a clear understanding of the needs of the specialist physicians and patient populations that we serve.

On the manufacturing side we'll continue to make our own drugs only if there is a strategic reason to do so. For example, most of the treatments in the Specialty Pharmaceutical portfolio are derived from small molecule chemicals, where out-sourced manufacturers have the experience and the capabilities to produce the product themselves. This is why we're in the process

CARRIERWAVE TECHNOLOGY

Carrierwave is a technology acquired as part of the acquisition of New River Pharmaceuticals ('NRP') and is used in VYVANSE. Since its acquisition, Shire scientists have significantly improved the understanding and breadth of this technology. It potentially allows Shire to develop New Chemical Entities ('NCE's), but with less risk, as the products will be based on the understanding of known products which we seek to improve.

Carrierwave NCEs are thus designed to have improved safety/tolerability, efficacy and/or pharmacokinetic profiles when compared to the original/existing product—significantly enhancing their potential medical utility and value.

The first successful application of Carrierwave technology is VYVANSE for ADHD (launched in the US in 2007). Shire has a number of Carrierwave NCEs presently in development across several key therapeutic areas (including ADHD) and sees applicability of this technology in supplementing the pipelines of both Shire businesses (Specialty and HGT).

Carrierwave™

of transferring manufacturing from our site at Owings Mills to one of our contractors. On the other hand, many of our HGT products are made using complex techniques and proprietary technology, and there are currently almost no contractors in the market who can do this better, more cheaply, or more reliably than we can.

Looking more widely, everyone in our industry knows that the world of healthcare is changing. Populations are ageing, which changes the balance of needs, while at the same time there's a constant stream of new and more sophisticated treatments that offer the hope of new cures. The net result is that an ever-larger proportion of GDP is being consumed by healthcare, which translates into more pressure on pricing, and an increasingly competitive market. The successful pharmaceutical company of the 21st century will need to be more cost-effective, more productive, and more proficient at demonstrating the value of its treatments to the authorities who pay for them. Technology will become more and more important, as will new ways of working, not only inside the business, but with partners, academic scientists, and suppliers. We still believe passionately that we have the right model, but we're very much aware that it will need to continue to evolve over the next decade, just as it has already done over the last one. So the new Shire will be 'more of the same' in the best possible sense, but better, more efficient, more agile with faster return on investments.



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