

Marketing case

The rise and fall of Baycol/ Lipobay

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Abstract This case study describes the history of Bayer's anti-cholesterol medicine Baycol/Lipobay from its early development to its withdrawal from the market. Initially available only in low doses, sales of the aggressively priced Baycol/Lipobay picked up when the product was marketed at higher doses, especially in the large US market. On course for €1 billion sales, the product was suddenly withdrawn worldwide in response to reports of a number of deaths associated with its use. The withdrawal resulted in public criticism of the pharmaceutical industry and the company, multiple lawsuits against Bayer and a decline in the sales and profitability and strategic repositioning of its pharmaceutical division.

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BAYER PHARMACEUTICALS

Ranked number two worldwide in 1980, Bayer's pharmaceutical business had fallen down the league table to 16th place in 1999. It was perceived as having a 'stodgy long-term performance, punctuated by occasional flashes of growth',¹ poor profitability and lacking critical mass in R&D and marketing, especially in the US market. Although analysts concluded (and Bayer management concurred) that its pharmaceutical business needed a merger, the combination of management's insistence on holding at least a 50 per cent stake in any partnership and Bayer's low stock market valuation eliminated all such opportunities. Management therefore focused on cost reductions, product lifecycle extensions and putting resources

behind the development and marketing of new products.

STATINS

Statins are the drugs of choice for lowering the bad LDL-cholesterol. Launched in 1987, Merck & Co's Mevacor (lovastatin) was the first statin to reach the market, followed by its second statin brand Zocor (simvastatin) (1988; 1992 in the US). Bristol-Myers Squibb's Pravachol (pravastatin) entered next (1991), followed by Lescol (fluvastatin) from Novartis (1994). Lipitor, developed by Warner-Lambert and co-promoted by Pfizer, was launched in February 1997, only two months ahead of Bayer's Baycol (cerivastatin)² in April 1997. Statins were one of the largest and fastest growing drug categories.

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Statins rarely induce adverse effects but rhabdomyolysis is one of the more serious observed adverse effects. Rhabdomyolysis refers to muscle ache or weakness (myopathy) combined with creatine kinase (CK) levels usually greater than ten times the upper limit of normal (CK>10×ULN), with decreased renal function or acute renal failure. If untreated, rhabdomyolysis may be fatal.

Rhabdomyolysis is dose-related, that is, it occurs more frequently with higher statin doses; the risk of rhabdomyolysis also increases when statins are used together with certain other drugs, especially the fibrate gemfibrozil.^{3,4}

In pre-approval clinical trials of statins prior to Baycol, between 0 and 0.5 per cent of patients experienced muscle symptoms combined with elevated CK levels (CK>10×ULN). Rhabdomyolysis requiring hospitalisation was encountered in only one trial in the mid-1990s, leading to discontinuation of the project, namely Zocor's 160mg sustained-release formulation.⁵

Because of their relatively small size (less than 2,500 subjects) and restrictive inclusion criteria for subjects, pre-approval clinical trials for statins were, however, unable to detect rare, serious adverse events. Cases of severe statin-associated rhabdomyolysis, therefore, had only emerged post-marketing as statins began to be used by a growing and diverse patient population.

The common view was that 'Statins cannot be differentiated based on their propensity for adverse effects'.⁶ Therefore, the US prescribing information for all statins included a similar, bolded statement in the 'Warnings' section indicating the risk of rhabdomyolysis.

BAYCOL'S DEVELOPMENT

Baycol was the most potent statin. Baycol 0.4mg had a similar cholesterol-lowering

efficacy as 10mg Lipitor, 20mg Zocor, 40mg Mevacor and Pravachol and 80mg Lescol.

In 1991, during internal discussions about the clinical development plan for the IND (Investigational New Drug Application) submission to the FDA, Bayer's toxicologists stipulated that 'The highest daily dose which can be used in our clinical development programme is 0.4mg'. They emphasised that they 'felt very strongly not to allow a step up to higher daily doses because the slope of the dose response curve (of Baycol) is much steeper than that of (Mevacor). The safety margin for our compound from the no-effect level to non-tolerable dose is less than three-fold, whereas for (Mevacor) it is at least 12-fold'.⁷ In 1995 they expressed 'strong concerns' about a clinical development plan with high doses, 'which cannot be supported by toxicology'.⁸

Baycol was first approved by the UK Medicines Control Agency under the EU's decentralised mutual recognition procedure. The initial approved maximum dosage worldwide was ≤0.3mg.⁹ The clinical trial data from 2,815 patients showed no case of elevated CK levels (>10×ULN). Furthermore, Baycol's dual elimination mechanism was thought to impart a safety benefit relative to other statins, which were metabolised via a single pathway.¹⁰

Still, as the post-marketing reports of the other statins had identified rhabdomyolysis cases for both monotherapy and co-medication, Baycol's initial US labelling included a warning that rhabdomyolysis had been reported with statins, and that the combined use of statins and fibrates should be avoided. Baycol's EU labelling included similar warnings.

While the ≤0.3mg approved dosage allowed Baycol to remain below the maximum 0.4mg dosage stipulated by

Bayer's toxicologists, it also limited Baycol's LDL-C-lowering efficacy. Yet the rapid market penetration achieved by Lipitor, the statin with the greatest LDL-C-lowering efficacy, demonstrated that this was becoming the most important statin attribute for the majority of physicians. Bayer was therefore conducting clinical trials with 0.4 mg, 0.8 mg and 1.6 mg dosage levels. J.P. Garnier, CEO of Bayer's US co-promotion partner GlaxoSmithKline, commented: 'We know we have a linear dose relationship in efficacy. That is excellent news ... that means that if you push the dose you get more efficacy. The question is, do you also get more side effects?'¹¹

Other statins were also under investigation in clinical trials with higher dosage strengths. For example, Merck filed for an increase in Zocor's starting dose from 10 mg to 20 mg, and a new 80 mg dosage strength. Lipitor, the market leader, was available in 10 mg, 20 mg, 40 mg and 80 mg dosage strengths.

BAYCOL'S LAUNCH

Bayer engaged in co-promotion and co-marketing partnerships in many markets, notably the US, France, Italy, Spain and Japan. The UK was the first launch country in April 1997.

In the key US market, which accounted for over 60 per cent of worldwide statin sales, Baycol was launched in February 1998 with the 0.2 mg and 0.3 mg dosages, 0.3 mg being the starting dose. Like all other statins, it was indicated for the reduction of elevated total cholesterol and LDL-C cholesterol. Baycol, however, lacked Lipitor's and Zocor's indication for triglyceride reduction, as well as the indication for heart disease benefits which Zocor, Pravachol and Mevacor had obtained.

Priced below other statins for comparable LDL-C reductions, Baycol's

promotion emphasised safety and price. The launch effort for Baycol was significant, with Baycol's 1998 share of anti-cholesterol details estimated at 16 per cent.¹² But one year after launch (Q1/1999), Baycol had obtained only a disappointing 3 per cent statin prescription share (0.9 per cent value share).

Post-marketing spontaneous reports rapidly showed that Baycol, like the other statins, was associated with rhabdomyolysis. In the majority of cases, patients were taking Baycol and gemfibrozil at the same time. As a result, on 12th May, 1999 Bayer filed for a change in Baycol's US labelling to include a contraindication for concurrent Baycol and gemfibrozil treatment.

BAYCOL 0.4 mg

On 24th May, 1999, Bayer obtained FDA approval for a 0.4 mg dosage strength, which became the new starting dose. The 0.4 mg dosage allowed Baycol to compete in the biggest LDL-C efficacy segment of the US market, accounting for about 50 per cent of statin prescriptions. Baycol 0.4 mg was the same price as Baycol 0.3 mg.

In July 1999, Bayer's clinical trial of Baycol 1.6 mg revealed a 'high incidence (about 12 per cent) of severe CK elevation ... partly connected with symptoms', leading to a decision to discontinue the project without publishing the results of the trial.¹³

The 0.4 mg tablet rapidly became Baycol's most prescribed US dose, rising from 31 per cent of Baycol's prescriptions during its first quarter of availability (Q3/1999) to account for 78 per cent in Q2/2000. Baycol's US statin prescription share doubled to 6 per cent (2.7 per cent value) in Q2/2000, allowing it to surpass Lescol and Mevacor.

Spontaneous reports of rhabdomyolysis associated with Baycol were rare. For the

six months between March and August 1999, the prescription-adjusted reporting rate was approximately 0.00002 per cent for the US, or about 20 cases per million prescriptions. An internal analysis discussed during a December 1999 meeting showed that the incidence of rhabdomyolysis in Baycol monotherapy treatment, however low, was still ten times higher than for the other statins.¹⁴

In December 1999, the FDA approved the labelling change requested in May, resulting in a bolded contraindication regarding Baycol and gemfibrozil concurrent treatment.

In June 2000, a group of Bayer executives discussed issues arising from the spontaneous reports of rhabdomyolysis associated with Baycol in the US because of the high proportion of confirmed cases of rhabdomyolysis with Baycol concomitant medication (70 per cent during September 1999–February 2000; 62 per cent during March–July 2000),¹⁵ and concluded that ‘the emphasis should be on making sure that everyone understands the nature of the contraindication of Baycol with gemfibrozil’. One means to achieve this would be a patient package insert, which ‘should be prepared before 12 July 2000 when a meeting is scheduled with the FDA to discuss labelling for the 0.8mg tablet’. The director of Medical Research, however, ‘mentioned that this leaflet should not be distributed prior to 0.8mg Baycol approval, otherwise it will most likely delay the approval’.¹⁶ A second conclusion of the meeting was to have a consultant analyse the spontaneous report data collected by Bayer Global Drug Safety. Internal analysis of ‘confirmed’ FDA-reported US cases of rhabdomyolysis through May 2000 suggested that the reporting rate for Baycol monotherapy was 20 times higher, and 855 higher for concomitant gemfibrozil treatment, than for Lipitor.¹³

The consultant, a former FDA employee, rapidly let Bayer know that ‘it looks like there is a continuing problem which is dose-related’.¹⁷ Noting the potential consequences of this for the approval of the 0.8mg tablet, he warned that ‘If FDA is already tuned in to this, you may have some resistance about the higher dose’.

BAYCOL 0.8 mg

Concerns about the 0.8mg dose had been voiced in January 2000 by a consultant to Bayer who had reviewed the clinical trial data prior to regulatory submission. The incidence of elevated CK levels (CK>10×ULN) was 2.1 per cent for Baycol 0.8mg, compared to 0.9 per cent, the highest level previously seen in any pre-approval statin trial (Lipitor 80mg). The consultant pointed out that ‘It may prove difficult to convince the regulatory authorities that the risk/benefit ratio of the 0.8mg dose is sufficiently low to warrant approval’.¹⁸

In July 2000, Bayer obtained FDA approval for the 0.8mg dosage strength. The US labelling indicated that ‘Caution should be exercised when titrating ... to the 0.8mg dose of Baycol’.

Consistent with Bayer’s past pricing policy for the drug, Baycol 0.8mg was priced significantly below Lipitor’s and Zocor’s equivalent dosage strengths, allowing Bayer to claim ‘With Baycol you get premium power, not premium price’.¹⁹ Detailing effort was stepped up considerably for the launch of the 0.8mg tablet, which ended up capturing 24 per cent of all Baycol prescriptions (Q2/2001).

In August 2000, after the FDA had approved the 0.8mg dose, Bayer submitted an application for a patient package insert that would inform patients that they should not take Baycol if they were taking gemfibrozil, among other information.

THE BAYCOL–GEMFIBROZIL COMBINATION

During the second half of 2000, Bayer Drug Safety noticed an increase in the number of rhabdomyolysis reports associated with the combination of Baycol and gemfibrozil, both from the US and other countries. Reports from non-US countries increased ‘materially (15 cases) compared to the preceding period (9 cases between 1 September 1998 and 29 February 2000). Since launch in April 1997, a total of 38 cases have been reported from these countries, almost all with gemfibrozil’.²⁰

Unlike the US prescribing information, which had included a contraindication for Baycol’s use with gemfibrozil since December 1999 and, as of November 2000, a patient package insert highlighting this contraindication, the EU prescribing information still carried merely the original general warning and precaution statements. In December 2000, Bayer Drug Safety and Regulatory proposed that the UK Medicines Control Agency (MCA), as the reference member state agency (the lead agency for EU labelling changes), be asked to strengthen the statements to a contraindication. But Eric Pauwels, head of the Baycol Global Strategic Marketing Team, was not in favour of this move, finding the data unconvincing: ‘A material increase from 9 to 15 cases? A total of 35 cases over the last 3.5 years? 10 cases per year — an average of less than 1 case per month?’²¹ Until now, the 0.8mg had been approved only in the US, and Pauwels feared that the requested changes might delay the introduction of the 0.8mg elsewhere, a ‘critical dose in the lifecycle management of Lipobay needed for Bayer follow through with marketing the efficacy perception against (the forthcoming new statins from AstraZeneca and Novartis). Any delays to the timeline will

significantly cost the company dollars’. In response, Ernst Weidmann, director of Global Safety, argued, ‘Time is running out. The use of gemfibrozil in Europe (Germany and France) is in the range of 0.03 to 0.05 per cent. This means our reporting rates in Europe are about 50 times higher than estimated previously on the basis of a 2.5 per cent usage. This puts us in the range of the US. That is why we need a contraindication, and because we are going to 0.8mg, even more’.²²

In February 2001, following the assessment of the latest spontaneous reporting data and responding to a request by the UK MCA,²³ Bayer asked that Baycol’s EU prescribing information be updated to include a contraindication with gemfibrozil.

RISING BAYCOL-ASSOCIATED FATALITIES

Between September 2000 and February 2001, 18 cases of Baycol-associated fatal rhabdomyolysis were reported worldwide, compared to eight and two, respectively, for the preceding two six-month periods.

During a teleconference on 26th March, 2001, E. Weidmann (director of Global Drug Safety), F. Monteagudo (VP of Drug Safety Assurance), Prof. K. Sprenger (Global Drug Safety) and R. Celesk (associate director of Drug Safety) reviewed the spontaneous reports of deaths in the US, which amounted to 12 since the beginning of 2001. The group noted that only one of the fatal cases involved concomitant use of gemfibrozil, the others being overwhelmingly associated with the use of the 0.8mg dose. Current prescribing information appeared inadequate to discourage a starting dosage of 0.8mg.²⁴ Bayer therefore requested a change in US prescribing information, and stopped shipping 0.8mg samples to US physicians.²⁵

On 21st May, the FDA updated Baycol's prescribing information by emphasising that the starting dose should be 0.4mg. A 'Dear Healthcare Professional' letter was prepared to inform healthcare professionals of these changes and remind them of the gemfibrozil contraindication. Bayer sales reps were told on 24th May to communicate the contents of the letter, which was sent out on 17th June.²⁵

In the meantime, Baycol 0.8mg had been launched in the UK in April. During the same month, the Spanish authorities raised concerns about a number of reports in Spain of fatal cases of rhabdomyolysis associated with Baycol.

May 2001 saw the launch of Baycol 0.4mg in France and Italy. The availability and role of the different Baycol dosage strengths varied greatly across countries. The US was at one extreme with the highest starting dose (0.4mg) and largest share of the high-dosage strength tablets (0.4mg, 0.8mg), followed by the UK, the only other country with Baycol 0.8mg. Japan, where 0.15mg was the highest approved Baycol dosage, was at the other extreme.

On 15th June, Bayer communicated to the UK's MCA the results of a Bayer-commissioned study on the relationship between statins and muscle weakness (myopathy), based on claims data from a California-based health insurance/health maintenance organisation. An analogous study had been proposed by Bayer Drug Safety/Epidemiology back in March 2000, but not carried out because someone at Bayer US was 'not enthusiastic' about such an analysis.²⁶ The study showed that the incidence of muscle weakness (myopathy) with Baycol monotherapy was no different from other statins. The combination of gemfibrozil and Baycol, however, increased the risk of myopathy 25.5-fold compared to monotherapy, while the other statins showed no increase in risk when combined with gemfibrozil.²⁷

These results, together with preliminary results from a study by the Spanish authorities showing that two-thirds of the Spanish Baycol rhabdomyolysis cases involved Baycol-gemfibrozil co-medication, led to an Urgent Safety Restriction in the EU for Baycol on 26th June. The changes to the EU prescribing information included the following: a contraindication to the concomitant use of Baycol and gemfibrozil, restriction of the maximum dose to 0.4mg and reinforcement of the importance of dose titration.²⁸ Health professionals in the different member states were informed of this action by Bayer and its partners through 'Dear Doctor' letters.

In parallel to this EU-level change, on 21st June Bayer voluntarily suspended the marketing and distribution of the 0.8mg dosage strength in the UK, barely two months after its launch. This suspension was immediately exploited by Bayer's competitors in the US. When Bayer finally informed its US reps on 13th July about the recent developments in Europe, it pointed out that 'competitive counter-detailing has occurred in recent weeks and we fully expect the competition to try to spin this information as proof that Baycol is gaining a "black box" or is being pulled from the UK market'.²⁹ Sales reps should be prepared to respond to physicians' questions about this issue but were instructed to 'not initiate this discussion'. The first response to a physician's question regarding Baycol in Europe should be to focus on the gemfibrozil contraindication: 'This is old news to us in the US because, as you know, the US placed the same contraindication into labelling back in 1999, but the Europeans are just now implementing this'. Only in cases where the doctor 'pushed back' about the UK activities should the sales rep inform the physician about the voluntary suspension of Baycol 0.8mg in the UK. The US field force was urged to 'continue delivering

our key power and safety messages ... continue delivering the message that YOU want the doctors to hear'.

On 24th July, during a meeting between the FDA and Bayer, the FDA presented an analysis of spontaneous reports showing that 'The crude reporting rates for fatal rhabdomyolysis with Baycol 0.8mg alone or in combination with gemfibrozil were in marked excess over reporting rates for this event in association with certain other marketed statins'.³⁰

On 1st August, Bayer decided to suspend the marketing of Baycol 0.8mg in the US and met again with the FDA to discuss additional risk-management plans and safety analyses for Baycol up to 0.4mg. Bayer proposed the following black box warning: 'Concurrent treatment of Baycol with gemfibrozil is contraindicated due to a risk for rhabdomyolysis. The maximum total daily dose of Baycol must not exceed 0.4mg due to a risk for rhabdomyolysis'. But the FDA requested a differently formulated black box warning on 3rd August: 'Concurrent treatment with Baycol and gemfibrozil is contraindicated due to a significantly increased risk for potentially fatal rhabdomyolysis over the risk with either drug alone ... The maximum total daily dose of Baycol must not exceed 0.4mg due to a significantly increased risk for potentially fatal rhabdomyolysis at higher total daily doses'.

BAYCOL AND BAYER PHARMACEUTICALS IN MID-2001

Among the large countries, Baycol's Q2/2001 statin prescription share was highest in Bayer's home country market Germany (22 per cent), followed by Japan (12 per cent), France (12 per cent), Italy (10 per cent), the US (9 per cent) and the UK (7 per cent). Worldwide, Baycol's 4 per cent value share of the statin

market made it the number four brand in 2000.

The US market accounted for almost two-thirds of the 2000 worldwide statin market and more than one-third of Baycol's 2000 sales. Currently at 9 per cent, Bayer's 'minimum aspiration' was a 15 per cent US market share: 'We talk about a potential \$1 billion product in the United States'.³¹ Baycol's US prescriptions were growing by 41 per cent compared with 10 per cent for all statins.

Already Bayer's third-largest pharmaceutical product in 2000, Baycol's forecasted €1b sales for 2001 sales would make it the number two product, with Bayer expecting it to reach peak sales of €2.5bn.³² Bayer was said to be investing \$125m in clinical trials involving over 20,000 patients to strengthen Baycol's efficacy claims and gain approvals for further indications.³³

THE BAYCOL WITHDRAWAL

On 7th August, 2001, Bayer took the decision to withdraw Baycol from all markets except Japan. The next morning (8th August), Bayer Investor Relations made an *ad hoc* announcement, posted on the internet, saying that 'Bayer has withdrawn all dosages of ... Baycol/Lipobay ... with immediate effect throughout the world, except in Japan ... The reason for this voluntary action lies in increasing reports of side effects involving muscular weakness (rhabdomyolysis), especially in patients who have been treated concurrently with the active substance gemfibrozil, despite a contraindication and warnings contained in the product information. Japan is unaffected by this move because gemfibrozil is not available there'.

On the same day, the FDA issued an 'FDA Talk Paper' that informed the American public about the withdrawal. Except for the FDA, the other regulatory

agencies had access to Bayer's press release at more or less the same time as the financial markets and the general public. The same was true for healthcare professionals, who were informed by Bayer in the days following the withdrawal. Completely taken by surprise, healthcare professionals and the European regulatory agencies were left scrambling to provide answers to questions raised by patients, the media and politicians. Bayer had never mentioned the idea of a complete withdrawal to the European agencies, nor did the data of which they were aware justify such a radical course of action.

On 23rd August, Bayer announced Baycol's withdrawal from the Japanese market. The decision was motivated by the forthcoming approval of gemfibrozil in Japan.

REACTIONS TO THE BAYCOL WITHDRAWAL

Baycol's withdrawal unleashed a global media furore. For the rest of the summer of 2001, the recall made headlines in the press and served as the leading item on radio and television news around the world. Although concentrated on Bayer, the media attention left none of the healthcare players unscathed.

Bayer's decision to inform its investors before the regulatory agencies and healthcare professionals was heavily criticised. 'It is unacceptable that information is provided rapidly about financial aspects, and not when medicine safety is at stake', complained the president of the federation of the German pharmacy associations.³⁴ 'Bayer decided on the timing of the withdrawal based on stock market considerations, without providing prior information to the tens of thousands of physicians and pharmacists concerned', commented the president of the largest French GP association.³⁵

Alarmed by the media reports, heart patients were jamming phone lines to doctors' surgeries. Many of the callers were taking Baycol, others were on other statin brands. Public Citizen, an influential Washington-based advocacy group, petitioned the FDA to add a black box warning to the labels of all statins.

The press highlighted the questionable promotional practices of Bayer and other pharmaceutical companies. For example, *Bild-Zeitung*, Germany's largest circulation newspaper, carried an article entitled 'Are our doctors open to bribes?' referring to Bayer's alleged reward of a trip on the Orient Express for doctors who prescribed Baycol for at least 25 patients, among other examples of inducements offered to physicians by pharmaceutical companies.³⁶

Faith in the healthcare system and the pharmaceutical industry was shaken. For example, in an opinion poll in Italy, 93 per cent of respondents believed the Baycol case to be just the tip of the iceberg. For 73 per cent of respondents, drug companies deserved criticism and disapproval because they disregarded patient safety in order to make a profit. Only 17 per cent looked favourably on the industry.³⁷

Unprepared as they were for the recall, the European regulatory agencies did not look good. 'The communication provided by Afssaps was not up to standard', commented the president of the largest French GP association.³⁵ The German agency was characterised as having been in a hopeless situation for a long time, which had further deteriorated as a result of the loss of experienced staff, accentuated by a deficient organisation.³⁸

Agencies and governments in turn blamed Bayer, which was accused of 'irresponsible information provision' by the German Ministry of Health. 'Bayer did not inform correctly, precisely, and timely', criticised the deputy secretary of health,³⁹

an accusation that the company firmly rejected.

One US group that was delighted by Bayer's problems were the product liability lawyers, who leapt into action as soon as the company announced that it was withdrawing Baycol. 'If you took Baycol, you might have a claim', announced a late-night television commercial. A billboard in Texas asked, 'Got Rhabdo?' A website declared: 'You could be due money!' At least 50 law firms set up websites, with online questionnaires to allow people to check if they had a case. Organisers set up seminars, dubbed 'Baycol School', where lawyers swapped strategies, documents and the names of experts.⁴⁰

IMPACT OF BAYCOL'S WITHDRAWAL ON BAYER

Bayer's share price dropped from €45 to €33 within a week of the withdrawal announcement. This sharp decline was based on two assumptions: (1) the direct impact of the Baycol withdrawal on Bayer's profits (loss of margin, write-offs, etc), and (2) the cost of litigation, estimated at €10bn.⁴¹

BAYCOL LITIGATION

The total number of persons treated with Baycol worldwide was estimated at 6 million,⁴² including around 2 million in the US, 1 million in Japan, with the remainder mostly in Europe.⁴³

Bayer was named as a defendant in many cases worldwide, most of them in the US. For each case Bayer had to decide whether to settle out of court or go to trial. The first trial took place in February/March 2003, after Bayer had refused to yield to the plaintiff lawyer's demands and high-pressure tactics, which included playing the stock markets. 'I was feeding a lot of information to European and US papers', admitted the lawyer. 'It was part of my strategy to affect the stock

price, which I was very successful at'.⁴⁰ Indeed, news from the trial drove Bayer's stock price down to little more than €10. The claim was for \$50m in compensatory damages and \$500m in punitive damages. When the jury decided Bayer had no liability, Bayer's stock soared.

As of 18th August, 2006, the number of Baycol/Lipobay cases pending against Bayer worldwide was approximately 3,000 (approximately 2,900 of them in the US, including several class actions). At the same date, Bayer had settled approximately 3,115 Baycol/Lipobay cases worldwide without acknowledging any liability and resulting in settlement payments of approximately \$1,154m. In the US, five cases have been tried to date, all of which were found in Bayer's favour.⁴⁴

OVERALL FINANCIAL AND STRATEGIC IMPACT

Baycol's withdrawal contributed to a significant decline in the sales and profits of Bayer's pharmaceutical business. Sales declined from €6.1bn in 2000 to €4.1bn in 2005. Profitability declined from 19 per cent in 2000 to -9 per cent in 2003, before increasing to 12 per cent in 2005. Bayer's pharmaceutical business slipped from number 16 in 1999 to 19th position in 2003. Failing to find a partner for the business, Bayer decided in 2004 to 'position pharmaceuticals as a medium-sized enterprise'⁴⁵ and to focus its US pharmaceutical business on speciality and biotech products for specialist physicians.⁴⁶

In mid-2006, Bayer acquired Schering AG. This acquisition nearly doubled the size of Bayer's pharmaceutical business to €8bn (\$9.4bn), making Bayer-Schering the 13th largest prescription pharmaceutical company, behind Amgen (\$12bn) and slightly ahead of Boehringer-Ingelheim (\$9.4bn).

Primary care now accounted for only 31 per cent of sales of Bayer-Schering.

This has accelerated Bayer's transformation into a specialty pharma company, with Bayer-Schering emphasising its position as the number seven specialty company.⁴⁷ Analysts generally applauded the acquisition. One called Bayer's pharmaceutical franchise a 'sleeping beauty'.⁴⁸ Another saw similarities to Roche's situation in 2003, in that by accepting ex-US rights to specialty products, Bayer-Schering could become one of US Biotech's European 'partners of choice' and generate Roche-like margins.⁴⁹

IMPACT OF BAYCOL'S WITHDRAWAL ON THE PHARMACEUTICAL INDUSTRY

The Baycol withdrawal significantly changed the dynamics of the statin market by turning statin safety from a nonissue and class-effect (all statins were seen to be safe) into a sensitive issue and differentiator. The heightened concern with statin safety favoured the incumbent statins and raised the entry barriers for AstraZeneca's Crestor, slowing down its market entry and speed of market penetration, thus contributing to the continued sales growth of Pfizer's Lipitor (\$12.2bn sales in 2005).

The much publicised Baycol/Lipobay withdrawal, followed by the similarly high-profile withdrawal of Merck & Co's Vioxx on 30th September 2004, and the attendant litigation have cast a shadow of doubt on the safety and effectiveness of pharmaceutical products, and have negatively affected the image of the regulatory agencies and the industry.⁵⁰ In response, the drug-safety system has been analysed, in particular in the US, and recommendations for improvements been made.⁵¹⁻⁵³ For example, the recent Institute of Medicine study on drug safety points out that the FDA lacks a systematic

approach to identifying possible pre-marketing drug-safety problems and translating them into high-quality post-marketing studies. It recommends a 'life-cycle approach' in which the risks and benefits of medications are examined during their entire market lifecycle, involving an 'ongoing systematic effort to identify safety signals, translate them into high-quality studies, and communicate the findings to patients and physicians'.⁵⁴

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