GlaxoSmithKline

2012 criminal and civil settlement

Overview

In July 2012, GSK pleaded guilty in the United States to criminal charges, and agreed to pay US$3 billion, in what was the largest settlement until then between the Justice Department and a drug company. The US$3 billion included a criminal fine of US$956,814,400 and forfeiture of US$43,185,600. The remaining US$2 billion covered a civil settlement with the government under the False Claims Act. The investigation was launched largely on the basis of information from four whistleblowers who filed qui tam (whistleblower) lawsuits against the company under the False Claims Act.[9]

The charges stemmed from GSK's promotion of the anti-depressants Paxil (paroxetine) and Wellbutrin (bupropion) for unapproved uses from 1998 to 2003, specifically as suitable for patients under the age of 18, and from its failure to report safety data about Avandia (rosiglitazone), both in violation of the Federal Food, Drug, and Cosmetic Act. Other drugs promoted for unapproved uses were two inhalers, Advair (fluticasone/salmeterol) and Flovent (fluticasone propionate), as well as Zofran (ondansetron), Imitrex (sumatriptan), Lotronex (alosetron) and Valtrex (valaciclovir).[9]

The settlement also covered reporting false best prices and underpaying rebates owed under the Medicaid Drug Rebate Program, and kickbacks to physicians to prescribe GSK's drugs. There were all-expenses-paid spa treatments and hunting trips for doctors and their spouses, speakers' fees at conferences, and payment for articles ghostwritten by the company and placed by physicians in medical journals.[9] The company set up a ghostwriting programme called CASPPER, initially to produce articles about Paxil but which was extended to cover Avandia.[111]

As part of the settlement GSK signed a five-year corporate integrity agreement with the Department of Health and Human Services, which obliged the company to make major changes in the way it did business, including changing its compensation programmes for its sales force and executives, and to implement and maintain transparency in its research practices and publication policies.[9] It announced in 2013, that it would no longer pay doctors to promote its drugs or attend medical conferences, and that its sales staff would no longer have prescription targets.[112]

Rosiglitazone (Avandia)

Further information: Rosiglitazone § Adverse effects, and Rosiglitazone § Lawsuits

Rosiglitazone

The 2012 settlement included a criminal fine of US$242,612,800 for failing to report safety data to the FDA about Avandia (rosiglitazone), a diabetes drug approved in 1999, and a civil settlement of US$657 million for making false claims about it. The Justice Department said GSK had promoted rosiglitazone to physicians with misleading information, including that it

conferred cardiovascular benefits despite an FDA-mandated label warning of cardiovascular risks.[9]

In 1999, John Buse, a diabetes specialist, told medical conferences that rosiglitazone might carry an increased risk of cardiovascular problems. GSK threatened to sue him, called his university head of department, and persuaded him to sign a retraction.[113] GSK raised questions internally about the drug's safety in 2000, and in 2002, the company ghostwrote an article in *Circulation* describing a GSK funded clinical trial that suggested rosiglitazone might have a beneficial effect on cardiovascular risk.[114] From 2001, reports began to link the thiazolidinediones (the class of drugs to which rosiglitazone belongs) to heart failure.[115] In April that year, GSK began a six-year, open-label, randomized trial, known as RECORD, to examine rosiglitazone and cardiovascular events.[116] Two GSK meta-analyses in 2005, and 2006, showed an increased risk of cardiovascular problems with rosiglitazone; the information was passed to the FDA and posted on the company website, but not otherwise published. By December 2006, rosiglitazone had become the top-selling diabetes drug, with annual sales of US$3.3 billion.[115]

In June 2007, *The New England Journal of Medicine* published a meta-analysis that associated the drug with an increased risk of heart attack.[117] GSK had reportedly tried to persuade one of the authors, Steven Nissen, not to publish it, after receiving an advance copy from one of the journal's peer reviewers, a GSK consultant.[118][119] In July 2007, FDA scientists suggested that rosiglitazone had caused 83,000 excess heart attacks between 1999 and 2007.[120]:4[121] The FDA placed restrictions on the drug, including adding a boxed warning, but did not withdraw it.[122] (In 2013, the FDA rejected that the drug had caused excess heart attacks.)[123] A Senate Finance Committee inquiry concluded in 2010, that GSK had sought to intimidate scientists who had concerns about rosiglitazone.[120] In February that year the company tried to halt publication of an editorial about the controversy by Nissen in the *European Heart Journal*.[124]

The results of GSK's RECORD trial were published in June 2009. It confirmed an association between rosiglitazone and an increased risk of heart failure and fractures, but not of heart attack, and concluded that it "does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs."[116] Steven Nissan and Kathy Wolkski argued that the study's low event rates reduced its statistical power.[125] In September 2009, rosiglitazone was suspended in Europe.[126] The results of the RECORD study were confirmed in 2013, by the Duke Clinical Research Institute, in an independent review required by the FDA.[127] In November that year the FDA lifted the restrictions it had placed on the drug.[128] The boxed warning about heart attack was removed; the warning about heart failure remained in place.[123]

Paroxetine (Paxil/Seroxat)

Main article: Study 329

Paroxetine, known as Paxil and Seroxat

GSK was fined for promoting Paxil/Seroxat (paroxetine) for treating depression in the under-18s, although the drug had not been approved for pediatric use.[9] Paxil had US$4.97 billion worldwide sales in 2003.[129] The company conducted nine clinical trials between 1994, and 2002, none of which showed that Paxil helped children with depression.[130] From 1998, to

2003, it promoted the drug for the under-18s, paying physicians to go on all-expenses paid trips, five-star hotels and spas.[9] From 2004, Paxil's label, along with those of similar drugs, included an FDA-mandated boxed warning that it might increase the risk of suicidal ideation and behaviour in patients under 18.[9]

An internal SmithKline Beecham document said in 1998, about withheld data from two GSK studies: "It would be commercially unacceptable to include a statement that [pediatric] efficacy had not been demonstrated, as this would undermine the profile of paroxetine."[129][131] The company ghostwrote an article, published in 2001, in the *Journal of the American Academy of Child and Adolescent Psychiatry*, that misreported the results of one of its clinical trials, Study 329.[9][132] The article concluded that Paxil was "generally well tolerated and effective for major depression in adolescents."[133] The suppression of the research findings is the subject of the 2008 book *Side Effects* by Alison Bass.[134][135]

For 10 years GSK marketed Paxil as non-habit forming. In 2001, 35 patients filed a class-action suit alleging they had suffered withdrawal symptoms, and in 2002, a Los Angeles court issued an injunction preventing GSK from advertising that the drug was not habit forming.[136] The court withdrew the injunction after the FDA objected that the court had no jurisdiction over drug marketing that the FDA had approved.[137] In 2003, a World Health Organization committee reported that Paxil was among the top 30 drugs, and top three antidepressants, for which dependence had been reported.[138][n 2]

Bupropion (Wellbutrin)

The company was also fined for promoting Wellbutrin (bupropion) – approved at the time for major depressive disorder and also sold as a smoking-cessation aid, Zyban – for weight loss and the treatment of attention deficit hyperactivity disorder, sexual dysfunction and substance addiction. GSK paid doctors to promote these off-label uses, and set up supposedly independent advisory boards and Continuing Medical Education programmes.[9]

2010 Pandemrix connected with narcolepsy

The Pandemrix influenza vaccine was developed by GlaxoSmithKlinefIn in 2006. It was used by Finland and Sweden in the H1N1 mass vaccination of the population against the 2009 swine flu pandemic. In August 2010, The Swedish Medical Products Agency (MPA) and The Finnish National Institute for Health and Welfare (THL) launched investigations regarding the development of narcolepsy as a possible side effect to Pandemrix flu vaccination in children,[139] and found a 6.6-fold increased risk among children and youths, resulting in 3.6 additional cases of narcolepsy per 100,000 vaccinated subjects.[140]

In February 2011, The Finnish National Institute for Health and Welfare (THL) concluded that there is a clear connection between the Pandemrix vaccination campaign of 2009 and 2010 and the narcolepsy epidemic in Finland. A total of 152 cases of narcolepsy were found in Finland during 2009–2010, and ninety percent of them had received the Pandemrix vaccination.[141][142][143] Sweden however observed very few influenza cases totally in 2009 and especially 2010 as compared to most other years.[144] In 2015 it was reported that the British Department of Health was paying for Sodium oxybate medication for 80 patients who are taking legal action over problems linked to the use of the swine flu vaccine, at a cost to the government of £12,000 per patient per year.[145]

1973 Antitrust case over griseofulvin

In the 1960s Glaxo Group Ltd. (Glaxo) and Imperial Chemical Industries (ICI) each owned patents covering various aspects of the antifungal drug griseofulvin.[146]:54, nn. 1–2[147] They created a patent pool by cross-licensing their patents, subject to express licensing restrictions that the chemical from which the "finished" form of the drug (tablets and capsules) was made must not be resold in bulk form, and they licensed other drug companies to sell the drug in finished form and subject to similar restrictions.[146]:54–55[147] The effect and intent of the bulk-sale restriction was to keep the drug chemical out of the hands of small companies that might act as price-cutters, and the effect was to maintain stable, uniform prices.[148][149][150]

The United States brought an antitrust suit against the two companies—*United States v. Glaxo Group Ltd.*—charging them with violation of the Sherman Act and also seeking to have the patents declared invalid.[146]:55[147] The trial court found that the defendants had engaged in several unlawful conspiracies, but dismissed the part of the suit seeking invalidation of patents and refused to grant as relief mandatory sales of the bulk drug chemical and compulsory licensing of the patents.[146]:56[147] The government appealed to the Supreme Court, which reversed, in *United States v. Glaxo Group Ltd.*, 410 U.S. 52 (1973).[147]

2000s Ribena

Old Ribena bottle, year unknown, made by Beecham Products, Brentford, Middlesex; the label states: "widely used in hospitals and clinics."

There were concerns in the 2000s about the sugar and vitamin content of Ribena, a blackcurrant-based syrup and soft drink owned by GSK until 2013. Produced in England by H.W. Carter & Co from the 1930s, the company's unbranded syrup was distributed to children as a source of vitamin C during World War II, which gave the drink a reputation as good for health. Beecham bought H. W. Carter in 1955.[151]

In 2001, the British Advertising Standards Authority (ASA) required GSK to withdraw its claim that Ribena Toothkind, a lower-sugar variety, did not encourage tooth decay. A company poster showed bottles of Toothkind in place of the bristles on a toothbrush. The ASA's ruling was upheld by the High Court.[152] In 2007, GSK was fined US$217,000 in New Zealand over its claim that ready-to-drink Ribena contained high levels of vitamin C, after it was found to contain no detectable vitamin C.[153] In 2013, GSK sold Ribena and another drink, Lucozade, to the Japanese multinational Suntory for £1.35 billion.[55]

SB Pharmco Puerto Rico

In 2010, the US Department of Justice announced that GSK would pay a US$150 million criminal fine and forfeiture, and a civil settlement of US$600 million under the False Claims Act. The fines stemmed from production of improperly made and adulterated drugs from 2001 to 2005, at GSK's subsidiary, SB Pharmco Puerto Rico Inc., in Cidra, Puerto Rico, which at the time produced US$5.5 billion of products each year. The drugs involved were Kytril, an antiemetic; Bactroban, used to treat skin infections; Paxil, the anti-depressant; and Avandamet, a diabetes drug.[154] GSK closed the factory in 2009.[155]

The case began in 2002, when GSK sent experts to fix problems cited by the FDA. The lead inspector recommended recalls of defective products, but they were not authorised; she was

fired in 2003, and filed a whistleblower lawsuit. In 2005, federal marshals seized US$2 billion worth of products, the largest such seizure in history. In the 2010 settlement SB Pharmco pleaded guilty to criminal charges, and agreed to pay US$150 million in a criminal fine and forfeiture, at that time the largest such payment ever by a manufacturer of adulterated drugs, and US$600 million in civil penalties to settle the civil lawsuit.[155]

China

Main article: GSK China Scandal

In 2013, Chinese authorities announced that, since 2007, GSK had funnelled HK$3.8 billion in kickbacks to GSK managers, doctors, hospitals and others who prescribed their drugs, using over 700 travel agencies and consulting firms.[156] Chinese authorities arrested four GSK executives as part of a four-month investigation into claims that doctors were bribed with cash and sexual favours.[157] In 2014, a Chinese court found the company guilty of bribery and imposed a fine of US$490 million. Mark Reilly, the British head of GSK's Chinese operations, received a three-year suspended prison sentence after a one-day trial held in secret.[158] Reilly was reportedly deported from China and dismissed by the company.[159]

Market manipulation in the UK

In February 2016, the company was fined over £37 million in the UK by the Competition and Markets Authority for paying Generics UK, Alpharma and Norton Healthcare more than £50m between 2001, and 2004, to keep generic varieties of paroxetine out of the UK market. The generics companies were fined a further £8 million. At the end of 2003, when generics became available in the UK, the price of paroxetine dropped by 70 percent.[160]

Miscellaneous

Italian police sought bribery charges in May 2004, against 4,400 doctors and 273 GSK employees. GSK and its predecessor were accused of having spent £152m on physicians, pharmacists and others, giving them cameras, computers, holidays and cash. Doctors were alleged to have received cash based on the number of patients they treated with a cancer drug, topotecan (Hycamtin).[161] The following month prosecutors in Munich accused 70–100 doctors of having accepted bribes from SmithKline Beecham between 1997, and 1999. The inquiry was opened over allegations that the company had given over 4,000 hospital doctors money and free trips.[162] All charges were dismissed by the Verona court in January 2009.[163]

In 2006, in the United States GSK settled the largest tax dispute in IRS history, agreeing to pay US$3.1 billion. At issue were Zantac and other products sold in 1989–2005. The case revolved around intracompany transfer pricing—determining the share of profit attributable to the US subsidiaries of GSK and subject to tax by the IRS.[164]

The UK's Serious Fraud Office (SFO) opened a criminal inquiry in 2014 into GSK's sales practices, using powers granted by the Bribery Act 2010.[165] The SFO said it was collaborating with Chinese authorities to investigate bringing charges in the UK related to GSK's activities in China, Europe and the Middle East.[166] Also as of 2014, the US Department of Justice was investigating GSK with reference to the Foreign Corrupt Practices Act.[167]

In October 2020, GSK told some staff that while at work they should disable the contact tracing function of the NHS test-and-trace app which monitors the spread of Covid-19. GSK explained the reason for this was due to social distancing measures in place at their sites rendering the technology unnecessary.[168]

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