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Ralf Boscheck*

Off-label Drugs vs. the Merits of Centralised Regulatory Control

Escalating health care expenditures are rekindling regulatory interest in the pharmaceutical industry on both sides of the Atlantic. The focus is increasingly on off-label drug use, i.e. the use of a drug for indications different from those for which it has officially been approved – witness the recent rejection by a German court of law of a pertinent legal case brought by Novartis. The very same case in the USA has already created new market realities and potentially far-reaching regulatory challenges. This article looks at developments there in order to assess potential policy scenarios for Europe.

On 4 July 2008, the Social Court in Düsseldorf rejected a charge brought by Novartis against German sickness funds and ophthalmologists for contractually committing to use a low price colon cancer drug (Avastin) off-label in the treatment of an eye disease instead of its own product (Lucentis) that had been specifically developed and clinically tested for that purpose. For Novartis, the contract not only represented an illicit boycott but contravened German health care regulation banning the use of non-tested drugs in any indication for which an effective and certified product exists. The court argued that avoiding additional costs of €1.4 bn associated with the use of the Novartis products justified its decision. Both Avastin and Lucentis had been developed by Genentech and then in-licensed by Roche and Novartis respectively. Whilst, at the time of writing this, observers in Germany are just beginning to speculate about the decision's impact on potential R&D investments and possible policy reforms, the very same case, in the United States, has already created new market realities and potentially far-reaching regulatory challenges.

Offering a focused perspective on these, this article, however, also sheds light on a much broader and interrelated set of policy dilemmas which need to be addressed. On both sides of the Atlantic, market-driven health care reforms are to cap health care and in particular drug expenditures by driving the substitution of generics for branded products, off-label for label prescriptions, and low-cost for high-cost regulations. But will markets guarantee new, safe and efficacious treatments and efficient regulatory standards? Will competition reward the risks associated with invention, innovation and changing treatment guidelines? Will markets punish corporate and political shortsightedness? Can de-centralised coordination tackle

free-riding by health care regulators, payers, users and providers? Conversely, what legitimises private and public interventions in health care markets? Will self-regulation be relied on to supplement failing markets and central regulatory functions and will it be trusted by other stakeholders? Which trade-offs need to be addressed? What are the respective pointers provided by the US experience?

The first part of the article sketches the contours of the US health care market and regulation; the second part synthesises the original case that pales the German discussion; part three evaluates the implications of off-label drug use with respect to maintaining centralised drug safety guidelines and the role of the global regulatory gold standard – the US Food and Drug Administration (FDA). Clearly, even after considering all its drawbacks, replacing the current system with market-driven, delegated safeguards or even more centralised drug certification, as presently suggested by some, is neither obvious nor desirable. Welfare trade-offs must be made explicit.

US Pharmaceutical Market and Regulatory Context

By 2030, 30% of the OECD's GDP is projected to be spent on health care. Attempting to contain costs, authorities and payers are focusing on prescription drugs, now the fastest growing share of health care spending.¹ In 2001, the USA spent \$140.6 bn on pharmaceuticals, three times more than a decade earlier, chiefly due to an increase in drug utilisation, increased retail prices and the more intensive use of more expensive but also more effective biotechnology drugs.² By

¹ OECD: Health Data, Paris 2006.

² Government Accountability Office: Prescription Drugs: Price Trends for Frequently Used Brand & Generic Drugs from 2000 through 2004, Aug. 2005. It is important to note that higher pharmacy costs of new therapies offset other medical costs as evidenced for example by a decade-long reduction in hospital admissions and lengths-of-stay.

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2006, expenditures had nearly doubled to \$274.9 bn.³ Yet, cutting costs by increasing substitution *within* or *for* particular drug classes could impede innovation incentives and safety considerations and invite gaming amongst the various stakeholders involved.

Globally, only one in a thousand drugs undergoing animal testing enter clinical trials of which about 20% are ever marketed, and only 20% of these will be commercially successful enough to recoup the investment.⁴ By 2004, the average drug development cost per compound, pre-approval, was estimated to be around \$1.4 bn and the average new drug required \$0.5 bn sales to earn a return just above the industry cost of capital.⁵ Patents, in part, motivate such risky investments. As patents expire, the first generic competitor typically enters the market with a 20% to 30% discount relative to the branded product, capturing about 44% to 80% of total sales within the first full year after launch.⁶ Subsequent entry quickly erodes prices to a cost-plus standard.⁷ To hasten competition and thereby price reductions, the 1984 Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act (FDC Act), regulating the generic drug approval process, provided incentives to challenge patents.⁸

Next to patents, safety and efficacy standards create barriers to competition. Access to the USA prescription market requires approval by the Food and Drug Administration (FDA) based on extensive clinical trials to establish safety, efficacy and side-effects within a narrowly defined indication specified on the product's label. However, once a medication is FDA-approved, it can be legally prescribed to anyone and for nearly anything. In fact, off-label use, i.e. the use of drugs in doses, via routes of administration or in patient populations other than those approved by the FDA, is quite typical. According to the Medicare Rights Centre, more than 20% of prescriptions written for the 500 most commonly used drugs in the USA are for

off-label uses.⁹ This practice is particularly common in cardiology, neurology, psychiatry and oncology, and in the latter case accounts for more than 60% of all treatments. Off-label prescribing of any FDA-approved drug is considered acceptable practice as long as physicians deem it medically appropriate. For that reason, the Centers for Medicare and Medicaid Services (CMS) – the dominant buyer in the USA – historically allowed reimbursement for most off-label uses of all drugs under its purview. Significant price increases, particularly in the area of cancer drugs and biologics, however, have caused Medicare to waver in its commitment to off-label uses and to limit reimbursement of off-label prescriptions to those considered medically acceptable by a limited number of CMS-approved compendia.¹⁰

Navigating this maze of changing policy rationales and regulatory standards, branded drug producers can be expected to pursue four objectives to maximise the return on their R&D investments: (1) attaining dominance within the therapeutic class/reference based on a compound's approved efficacy and side-effect profile;¹¹ (2) sustaining that position through patenting active compounds, preferred formulations, manufacturing methods, protein modifications, co-specialised delivery systems etc.; (3) using life-cycle management to delay substitution through (a) continued differentiation of branding, dosing, formulation or mode of action, (b) sustained market segmentation through exclusive distribution¹² or blocked re-imports,¹³ (c) pricing¹⁴ and product strategies in expectation of entry, (d) legal strategies to protect trademarks¹⁵ and patents, and fi-

⁹ Evidence provided by MRC in its lawsuit at the Manhattan federal district court challenging CMS off-label coverage restrictions, 26 November 2007.

¹⁰ Cf. A. Rusk in: CMS Proposes Changes to Its Policies Governing Off-Label Uses of Anticancer Drugs and Biologicals, FDA/Health Care Regulation, Morgan Lewis at www.morganlewis.com, 18 July 2007.

¹¹ For a discussion see R. Boscheck: Constraining Drug Supply: Product Positioning, Patent Protection & Regulatory Standards, 2008, forthcoming.

¹² See F. M. Scherer: How US Antitrust Can Go Astray: The Brand Name Prescription Drug Litigation, in: International Journal of the Economics of Business, Vol. 4, No. 3, 1997, pp. 239-256.

¹³ In 2004, Pfizer Inc., for example, unveiled a plan to deeply discount its drugs for people without health insurance, a move blunting rising political criticism, while curbing consumer demand for drugs from Canada.

¹⁴ In 2006, Merck, cutting the price of Zocor below that of the generics, claimed that lower prices benefit consumers. Producers of generics argued that these prices made it impossible to fund the development of future generic alternatives. For discussion of an earlier case and the claim of predatory pricing see J. P. Cairns: Predatory Pricing: Notes on Hoffmann-La Roche, in: The Canadian Business Law Journal, Vol. 9, Issue 2, 1984, pp. 242-254.

¹⁵ In 2005, Eisai of Japan took twelve generic producers to court to protect its pharmaceutical trade dress embodied in the pill colour and the PTP packaging.

³ IMS Health Inc.: IMS Reports 2006 US Prescription Sales, Press Release, 8 March, 2007, available at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80415465,00.html.

⁴ P. G. Sherman, E. F. Oakley III: Pandemics and Panaceas: The World Trade Organization's Efforts to Balance Pharmaceutical Patents and Access to AIDS Drugs, in: American Business Law Journal, No. 353, 2004, pp. 404-05.

⁵ Marakon Associates: What Crisis? A fresh diagnosis of Pharma R&D Productivity Crunch, presentation, 2004.

⁶ Congressional Budget Office: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, Washington DC, July 1998.

⁷ Bernstein Research: US Specialty Pharmaceuticals, Paragraph IV Reaching Saturation, 2007, p. 28.

⁸ The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. Ko. 98-417, 98 Stat 1585 (1984), (codified as amended 21 USC §355 (1994)).

nally (4) companies will seek to expand a compound's market by increasing its off-label use or seeking approval for new indications based on extensive clinical trials. The following focuses solely on policy-strategy interactions related to off-label prescriptions.¹⁶

Reversing Blindness - Genentech's Dilemma

On 19 October 2007, Herb Kohl, the chairman of the US Senate's Special Committee on Aging, asked Genentech to clarify its decision to limit the availability of its product Avastin in favour of its more expensive drug Lucentis, both applied in the treatment of wet age-related macular degeneration (wAMD). In 2007, age-related macular degeneration (AMD) was the leading cause of severe vision loss in people over the age of 65 in the Western world. In the USA, more than 1.6 million people had one or both eyes affected by the advanced stage of AMD, another 7 million were estimated to be "at risk" and more than 230,000 people were deemed to be legally blind due to it. The direct cost of illness associated with AMD was estimated to be above \$10 bn annually. wAMD accounted for 10% to 15% of the cases.¹⁷

Originally approved by the Food and Drug Administration in February 2004 to treat colorectal cancer, Avastin was subsequently used off-label by ophthalmologists to treat and actually reverse wAMD at a monthly cost of \$40. Lucentis, a fragment of Avastin with which it shared the same mechanism of action, received FDA approval in July 2006 specifically to treat the eye disease. Treatment costs amounted to \$2,000 a month. In both cases, treatment required injection into the eye. Lucentis was co-developed by Genentech and Novartis, and as a result, Genentech had North American rights for the drug and Novartis had rights in the rest of the world. In the third quarter of 2007, sales of the drug in the USA reached \$198 million, and \$122 million elsewhere.

In mid-2007, Genentech declared that Avastin, while generally available to US hospitals and physicians, would no longer be sold to compounding pharmacies, i.e. intermediaries that split the product, originally in a single-use, preservative-free vial, into multiple doses for off-label use. Commenting on its decision, the company expressed its unease about the off-label ocular use of Avastin and also cited earlier FDA con-

cerns that dose splitting may compromise the sterility of the drug. The FDA commented that, although it had expressed such apprehension in one particular case, it had not asked Genentech to limit the availability of the drug. Genentech responded that it would reinstate its supply of Avastin to compounding pharmacies if the regulator explicitly authorised the company to do so. Some industry observers were quick to identify the policy dilemma that made the FDA an unwilling supporter of Genentech's position; others noted that prior to the launch of Lucentis, the company had never expressed concern about the sterility of repackaging and in fact was supporting off-label use of both products across a variety of areas and dosages. Only a few pointed to lingering reimbursement issues.

Given the significant difference in wholesale acquisition costs,¹⁸ the US Centers for Medicare & Medicaid Services (CMS) calculated that limiting the availability of Avastin could add \$2 billion to \$3 billion a year. In Europe's top three markets, Germany, UK and France, a Lucentis list price of €1,000 to €1,200 per dose was expected to consume 1% of total prescription drugs expenditure and limit its use to only 10% of the patient population. An Avastin per vial price of around €300, however, was expected to account for only 0.2% to 0.3% of prescription drug expenditure and allow nearly complete patient coverage. Policy reactions differed across countries.

In France, the introduction of Lucentis resulted in reimbursement being shifted away from Avastin, which has since been restricted to hospitals only; in Spain only Lucentis was reimbursed. The German case, *de jure*, matched the Spanish situation; *de facto*, however, rumor had it that a number of ophthalmologists accepted substantial financial incentives from payers to commit to continued Avastin use. Novartis brought the case, as decided on 4 July 2008, and at the same time agreed to a total expenditure cap on Lucentis of around €315 million p.a. which, at a 2007 manufacturer price of €1,235 per vial, covered 10% of patients; at €175 per vial, benefits could be extended to three-quarters of the total patient population. Italy reimbursed ophthalmic treatment up to a total cost of €2,500 p.a., which only allowed for wAMD treatment using Avastin. In the UK, the National Institute for Clinical Excellence (NICE) had to reverse its decision to only reimburse Lucentis for 20% of patients with wAMD, and then only in the most severe cases. In August 2007 the institute proposed a ground-breaking dose-capping scheme for Lucentis whereby the NHS covered a maximum of 14 injections, considered suf-

¹⁶ For a discussion of generic substitution and the antitrust implications of private contracting in the wake of the Hatch-Waxman Act, cf. R. Boscheck, *op.cit.*

¹⁷ It involves the growth of new blood vessels behind the retina, the leaking of which results in scarring and rapid visual loss. Avastin (bevacizumab) and Lucentis (ranibizumab) both work by binding to and inhibiting the Vascular Endothelial Growth Factor, or VEGF, a protein that is believed to play a critical role in the formation of new blood vessels.

¹⁸ In December 2007, the US wholesale acquisition cost of Avastin was \$550 for 100 mg, while that of Lucentis was \$1,950 for 0.5 mg.

ficient in the majority of cases. At the same time, the NHS, following a similar initiative by the US National Eye Institute, commissioned one of its most expensive trials ever to establish the substitutability of Avastin and Lucentis. Genentech stated that it had no intention of funding or even subsidising clinical trials for Avastin as a treatment for macular degeneration, given that Lucentis had obtained FDA approval. Some observers wondered about the legitimacy of establishing equivalence of drugs against the interests of manufacturers.

On 22 December 2007, following widely publicised protests by payers and patients, Genentech announced that it had agreed with major patient organisations to temporarily reinstate the supply of Avastin to compounding pharmacists to give patients and direct care personnel sufficient time to adjust.

Clearly, this case could be discussed on very different levels with very different explanatory objectives. For one, from the point of view of Genentech, the question is how to maximise the return on R&D outlays to boost shareholder returns as well as ongoing and future R&D. This would involve a technical discussion on how to structure clinical trials, sequence product and geographic market entries, and present pharmacoeconomic arguments to justify reimbursement/pricing targets. Secondly, there is an obvious debate about the welfare implications of differential pricing, single-price strategies and reference pricing. Thirdly, one may ponder the legitimacy of pricing, reimbursement, health care rationing decisions and contest the role of publicly financed equivalence testing of drugs across different therapy areas. What are their respective implications in terms of allocative and productive efficiency as well as the level of “relevant” technological advance? The following focuses on a fourth aspect – the systemic context of off-label drug use – its impact on the role of the global regulatory gold standard – the US FDA – and some recent suggestions to abolish centralised controls over drug safety and efficacy.

Central Regulatory Control and the Challenge of Off-label Drug Use

Established by Congress in 1906 in response to fraudulent and unsavoury practices in the food and drug industry, the FDA's authority expanded in 1938 and 1962 to require proof of safety and efficacy, respectively, before drugs could be marketed.¹⁹ As a re-

¹⁹ Failure to test medications before prescribing them led to the Food, Drug and Cosmetic Act of 1938. Sulfanilamide, a drug used to treat strep infections, had shown great success as a cure in the 1930s and was used safely in tablet and powder form. Doctors wanted a liquid form, primarily for children. Dissolving the sulfa drug with diethylene glycol proved lethal to more than 100 people, mostly children.

sult, prescription drugs in the USA today must have at least passed phase I clinical trials, establishing safety by examining toxicity in healthy volunteers; phase II and III trials prove efficacy for label specifications. Off-label drugs are consequently regulated according to pre-1962 rules. Widespread off-label use is often seen to reflect the fact that actual treatment conditions do not match the accepted scientific set-up or that peer-reviewed, scientific progress outpaces the FDA certification process. This raises concern about the efficiency of centralised drug approval and the true risk of drug misuse – both touch the very *raison d'être* of the federal regulator.

FDA authorisation is increasingly expensive and time consuming. Over the last three decades, the time to approval, including the permission to conduct clinical trials and subsequent new drug applications rose from 6.5 years in the 1970s to presently around 9.5 years. Increases in approval time and costs increase “drug lag”, i.e. the delayed introduction of new beneficial drugs, “drug lack”, i.e. the reduction of the total number of new drugs developed, and “drug loss”, i.e. the death and suffering of hundreds of thousands of people that might have been avoided had drugs been sped to use.²⁰ In addition, central regulators, like the FDA, do err. Bayer's anticholesterol drug Baycol, Warner-Lambert's diabetes drug Rezulin, Johnson & Johnson's antiheartburn drug Propulsid and, most recently, Merck's arthritis drug Vioxx had all been FDA-approved and yet resulted in massive legal claims. Finally, the regulator's inability to block the prescription of some non-approved drugs, such as practolol/propranolol, arguably saved the life of numerous heart attack patients. And yet, if off-label use reflects the limits of centralised regulation, who or what verifies off-label claims and how may such claims be used?

The FDA requires physicians to base off-label use on sound scientific and medical evidence. However, it has also drastically limited drug promotion, making it impossible for manufacturers, except in limited circumstances, to disseminate to physicians peer-reviewed journal articles, textbooks, or compendia pro-

²⁰ For example, the FDA first approved a beta blocker, propranolol, in 1968, three years after that drug had become available in Europe; it waited until 1978 to approve the compound for the treatment of hypertension and angina pectoris, its most important indications. For a review of FDA critique cf. among others S. Peltzman: An Evaluation of Consumer Protection Legislation: the 1962 Drug Amendments, in: *Journal of Political Economy*, Vol. 81, No. 5, 1973, pp. 1049-91, reprinted in G. J. Stigler (ed.): *Chicago Studies in Political Economy*, Chicago 1988, University of Chicago Press, pp. 303-48; H. G. Grabowski, J. M. Vernon: *The Regulation of Pharmaceuticals: Balancing the Benefits and the Risks*, Washington DC 1983, American Enterprise Institute; A. T. Tabarrok: Assessing the FDA via the Anomaly of Off-Label Drug Prescribing, in: *Independent Review*, Vol. 5, No. 1, 2000, pp. 25-43.

posing off-label uses of drugs. The reason for this, the agency argues, is fraud.

Consider the case of Neurontin. Produced by Warner-Lambert, subsequently acquired by Pfizer, Neurontin was FDA-approved as an anti-convulsant for partial seizures in adults and children. However, the company marketed the product as a general analgesic and for off-label use to treat among other things Lou Gehrig's Disease, bipolar disorder, restless leg syndrome as well as other pain and attention deficit disorders. Although several executives are said to have known that the drug was ineffective in some of these applications, Warner-Lambert commissioned articles promoting off-label uses and sought to enlist doctors to lend their names as authors for \$1,000 "honorariums." According to US Attorney Michael Sullivan, "[Warner-Lambert's] illegal and fraudulent promotion scheme corrupted the information process relied upon by doctors in their medical decision making, thereby putting patients at risk."²¹ In 2003, Neurontin sales were around \$2.7 bn, an estimated 90% of which was due to off-label prescriptions. In May 2004, Warner-Lambert pleaded guilty on two accounts of misbranding and paid \$430 m as part of the settlement. Today, the drug is causally linked to more than 2,300 suicides or suicide attempts and Pfizer is facing civil litigation related to these claims.

Between 2001 and 2006, the US government imposed more than \$2 bn of fines on drug companies charged with fraudulent sales and marketing tactics. And yet, US legislatures and courts are growing less supportive of the agency's restrictive view on off-label prescriptions and permissible promotional allegations. For them, the regulator's view that promotional restrictions will drive increased clinical testing is tantamount to even more drug lag, lack and losses. Rejecting the FDA's apparent "paternalism" as often counter-productive, economically inefficient and not always backed by superior performance, some have proposed looking beyond central regulatory approval. But what are the alternatives?

Off-label use involves a trade-off between prescribing a potentially unsafe medicine and the cost of not prescribing a potentially life-saving drug. The FDA, given its regulatory mandate as well as public scrutiny, can be expected to emphasise the former, also because the latter is less visible and speculative at best. Alternatively, rather than requiring private sponsors to conduct their own clinical trials and allowing them to

control access to the resulting data, one could rely on publicly funded clinical trials to generate valuable public information. Relative to the current FDA-type system, however, this approach is neither market-based nor does it answer the question who decides on what for whom. Moreover, its implied bureaucratic process may increase rather than reduce the actual or perceived level of drug lag and lack.

Similarly, decentralised governance options, relying on industry self-regulation or tort law, may not be adequate either. In the former, it is not clear who would be given access to verify proprietary information, whether pharmaceutical producers would optimally certify products, or if doctors would at all be willing to prescribe "privately tested" drugs. Finally, in a private system, would special cases, such as small-market orphan drugs, retain their current, necessary "special protection"? In the same way, reliance on tort liability may not be efficient either. Enforcement costs would expectedly be higher than under central regulatory control, the plaintiff would have the burden of proof, and decisions may ultimately rest with popular tribunals rather with those professionally qualified. Clearly, there are significant disadvantages that challenge the attractiveness of making off-label use "a natural experiment in *laissez faire*."²² Welfare trade-offs need to be addressed.

Summary

Escalating health care expenditures are rekindling regulatory interests in the pharmaceutical industry on both sides of the Atlantic. The focus is increasingly on off-label use and generic substitution. Concentrating entirely on the former and largely in the US context, the above account nevertheless points to a much broader set of policy dilemmas to be addressed. Market-driven health care reforms, aiming to contain costs by increasing substitution within, or for, particular drug classes, treatment regimes and regulatory standards, challenge and may in fact impede innovation incentives, safety considerations, and policy and reimbursement principles. And yet, both centralised and de-centralised coordination mechanisms leave much to be desired. Rather, the question is which mix of governance mechanisms most efficiently limits the gaming amongst private and public stakeholders and retains the system's integrity. As Europe is entering largely uncharted territory, discussions should be informed by US developments, relevant legislation and case law, not to identify directly applicable solutions but to assess potential policy scenarios.

²¹ Quoted from D. Klein, A. Tabarrok: Who certifies off-label? in: Regulation, Vol. 27, No. 2, 2004, pp. 60-63.

²² Cf. D. Klein and A. Tabarrok, op. cit., for this suggestion.