CLIFFORD
CHANCE

Briefing note
October 2011

A Comparative Review of Off-Label Pharmaceutical Use and Promotion in Europe, the US and China

In general terms, the phrase 'off-label' when applied to the use of drugs refers to the application of a pharmaceutical product outside the scope of use approved by the applicable drug administration authorities.[1] Off-label variances in that scope often pertain to its indication, patient group, dosage and duration of treatment.

The primary reason for off-label use is to address a deficit in effective approved drugs. This occurs mainly due to the lag in the discovery and development of effective drugs and their approval for authorised use by the relevant drug authorities. Further, if a drug is discovered to be effective in treating a second indication, obtaining the approval to treat that indication 'on-label' often involves a second regulatory pathway that that can be both lengthy and costly.

How widespread is the practice?

Europe

Studies published in the past 10 years have shown that off-label use in the European Union (EU) of drugs is widespread, in particular in pediatrics, oncology, neurology, infectology and geriatrics. For example, up to 90% of treatment for infants in hospital intensive care units is understood to be off-label.

Further, the costs of drugs prescribed off-label are often reimbursed by public health insurance companies.

United States

As in Europe, off-label prescriptions are reported to be significant, higher than 50% in some cases or some classes of patients. It is common practice for pharmaceutical companies to assess whether a drug that has been approved as safe and effective might also be suitable for new indications or applications. Indeed, such use can lead to new approved indications and uses. Economist Alexander Tabarrok showed that the rate of off-label prescription in the US is so high that most hospital patients receive at least one drug off-label.[2] Perhaps the most telling indicator of off-label prevalence is the tremendous amount of resources dedicated by both federal and state agencies, regulators and prosecutors in policing off-label use, coupled with the head-line making successes in prosecuting off-label cases. Investigation of off-label promotions of drugs remains a leading legal basis for pharmaceutical prosecutions in the US.

China

While effectively prohibited, off-label drug use is much more widespread in China than the law allows. Only a very limited number of surveys are known to have

Key issues

If you would like to know more about the subjects covered in this publication or our services, please contact:

Emma Davies +86 21 2320 721
Campbell Izzard +86 21 2320 7235
Marc Holtorf +49 211 4355 5245
Daryl Fairbairn +49 211 4355 5484

To email one of the above, please use firstname.lastname@cliffordchance.com

www.cliffordchance.com

1 In Europe, the equivalent of the drug label and insert sheet is the summary of the product characteristics (SmPC).

2 Assessing the FDA via the Anomaly of Off-label Drug Prescribing, The Independent Review: A Journal of Political Economy, Volume 5 Number 1 Summer 2000, http://www.independent.org/pdf/tir/tir_05_1_tabarrok.pdf

been conducted to ascertain activity levels. Of those that have, two surveys undertaken in pediatric hospital wards in Beijing and Suzhou respectively show off-label use of up to 22% of all medicines prescribed.[3]

Sources of regulation – in what circumstances is it permitted?

Europe

Despite off-label pharmaceutical use being common practice, there is very little regulation on an EU-wide basis. For example, there is no legal definition of off-label use at EU level.

However, promoting the prescription of a pharmaceutical product for a purpose that has not been authorised is expressly prohibited.[4]

Whether or not physicians are allowed to prescribe pharmaceuticals on an off-label basis depends on the laws of the Member States. For example, in Germany, physicians are permitted to apply pharmaceuticals on an off-label basis. In some cases they are even required to apply pharmaceuticals off-label in order to avoid malpractice claims by patients.

Prior to any off-label treatment, physicians must comprehensively inform patients of the risks associated with use of the drug, including that it lacks a marketing authorization for the intended use and that the risks associated with the treatment are unknown and possible difficulties may arise in connection with the reimbursement of the treatment costs by health insurance companies. Provision of insufficient information on any of these matters can entitle patients to bring damages claims.

US

US laws and regulations do not directly regulate the prescription of medicines by physicians. Instead, physicians are expected to use their medical judgment, acting in the best interests of the patient, in prescribing medications. Provided a physician is well informed about the product, and has a credible clinical justification, they may prescribe any drug product approved by the US Food and Drug Administration (FDA), including for off-label uses.

Drug manufacturers, on the other hand, are prohibited from marketing or promoting off-label uses of their products to induce commercial sales. The legal basis derives from legislation prohibiting the "misbranding" of drugs. After the FDA approves the product as safe and effective for a specified use or indication, any promotion by the manufacturer for other uses which are not specified in an FDA-approved label renders the product misbranded.

Off-label cases are typically prosecuted under the False Claims Act, which prohibits the filing of false claims for payment to the federal government. Liability can arise if a pharmaceutical company causes false claims to be submitted to government healthcare programs by promoting uses that are not medically accepted indications, and therefore not covered by those programs.

The legal framework does not prohibit the exchange or dissemination of truthful and non-misleading information about a product's unapproved uses in specific circumstances. In 2009, the FDA promulgated guidance on "good reprint practices" for distribution of scientific publications on off-label uses.[5] The guidance does not address all potentially permissible ways companies can convey information within the bounds of the law. Moreover, tension remains in the law between the government's goal of regulating off-label promotion and a company's constitutional right to free speech afforded by the first amendment. Some companies have successfully argued that their activities of disseminating truthful, non-misleading information about off-label uses is constitutionally permitted free speech.

China

The legal system in China places a positive obligation on physicians to only prescribe drugs in accordance with their approved use. By law, the approved drug label and insert sheet 'guides' the appropriate use of the drug.[6] Further, physicians must prescribe drugs "in accordance with" the drug label and insert sheet.[7] Whether either of these terms prevents minor deviations from the drug label and insert sheet is not clear. If found to have violated these provisions, physicians will be at risk of a formal warning, suspension of their practice certificate for between six months to one year, or even the withdrawal of their practice certificate. Comparable rules also apply to pharmacists.

There have however been circumstances in which off-label use in China has been permitted. One such circumstance occurred during the SARS outbreak in 2004 when certain forms of antibiotic were permitted, even encouraged, by authorities to be prescribed in excess of their permitted dosages specified on the approved product label and insert sheet. In March 2010, 20 senior chief pharmacists from 17 hospitals in Guangdong province issued a statement on off-label prescriptions. Many of the recommendations in the statement are similar to the principles already adopted in some EU countries, but tend to be

[3] ZHANG, Wei,门诊超药品说明书用药的调查分析(Survey and Analysis of Outpatient Drug Use that Goes Beyond the Scope of Package Inserts), 中国医院用药评价与分析2010年02期, Evaluation and Analysis of Drug-Use in Hospitals of China, 2nd Issue (2010) and WANG, Hai-ying, 北京大学第三医院儿科门诊超说明书用药调查与分析 (Analysis of Outpatient Off-label Use in the Third Hospital of Peking University) 中国医院用药评价与分析2011年02期, Evaluation and Analysis of Drug-Use in Hospitals of China, 2nd (2011).

[4] Article 87, Directive 2001/83/EC.

[5] http://www.fda.gov/oc/op/goodreprint.html

[6] Article 9, Provisions on the Administration Drug Labels and Insert Sheets (《药品说明书和标签管理规定》).

[7] Article 14, Measures on Administration of Prescriptions (《处方管理办法》).

© Clifford Chance, October 2011

more specific than the requirements in the US. [8]

Responsibility for enforcement and potential consequences for non-compliance

Europe

Manufacturers who are found to have illegally promoted off-label use of their drugs face serious consequences in the EU with such consequences dependent on the national laws of the EU Member States. In Germany, the healthcare supervisory authorities might render administrative fines of up to EUR 50,000 per case. However, the authorities have rarely been active and even more rarely rendered an administrative fine.

In saying that, there has been extensive litigation in the EU between pharmaceutical manufacturers illegally promoting off-label use on the one hand and their competitors, or consumer and fair trade protection organizations on the other hand. At present, the associated risks for drug manufacturers are comparatively low and do not normally exceed more than a small fraction of the costs of a given marketing campaign.

Product liability is considered a more relevant area of concern for pharmaceutical manufacturers illegally promoting off-label use. EU product liability law operates a strict liability regime i.e. pharmaceutical manufacturer are liable even without fault. The crucial question in connection with product liability and off-label use is whether the off-label use could reasonably be expected. The instructions for use, the summary of product characteristics (SmPCs), labelling, advertisements and other information provided by a pharmaceutical manufacturer are important resources in that context. Moreover, even tolerating an off-label use can lead to a drug manufacturer incurring liability under relevant product liability laws.

US

Off-label cases are vigorously prosecuted in the US. Pharmaceutical companies have in numerous cases over the past decade paid fines and fees to settle criminal and civil cases of tens or hundreds of millions of dollars, and in some recent notable cases, more than a billion dollars. Cases are brought by numerous parties, most commonly the US Department of Justice, the Office of Inspector General of the US Department of Health and Human Services, the Attorney Generals of the individual states, and the fraud control units of multiple federal and state agencies. The FDA has been particularly active, launching a healthcare fraud prevention initiative called HEAT in May 2009, as well as the Bad Ad outreach program with the goal of encouraging health care professionals (HCPs) to recognize and report suspected untruthful or misleading drug promotion in May 2010.

These activities have together generated many billions of dollars in fines and settlements in recent years. The government has been successful in encouraging the participation of private individuals (e.g., current or former employees, competitors, HCPs) as whistle-blowers in so-called "qui tam" actions, where whistle-blowers are entitled to a percentage of the recovery of the penalty as a reward for exposing the off label usage. In these cases, the whistle-blower is entitled to receive significant payments, frequently millions of dollars.

Prosecutors have in some cases sought to impose individual accountability by pursuing criminal cases against the executives involved. In addition to facing prison sentences, individual executives and managers may be targeted under provisions which lead to their exclusion from participating in federal health care programs or debarment from regulatory activities before the FDA, effectively preventing them from working in the industry.

China

As described above, the "off-label" prescription of drugs is not permitted in China. Under the current Chinese regulatory regime however, the promotion of drugs off-label is not directly addressed and a formal legal sanction or remedy where a civil claim arises does not fit easily under current pharmaceutical regulatory, product liability, criminal or tort law. Advertising drugs off-label is more clearly prohibited, and any advertisement of a drug must conform to its State Food and Drug Administration approved product label and insert sheet.[9]

Conclusion

Markedly different approaches to the regulation of off-label drug use and promotion exist in the world's largest pharmaceutical markets. Despite the commonplace nature of off-label use, the legal regime on an EU-wide basis remains underdeveloped compared with that of many of the EU's Member States where the concept of informed consent is prevalent. While the United States permits both off-label use and now, in certain circumstances, its promotion, this issue remains contentious and commonly litigated as pharmaceutical companies and the court systems adapt to an evolving regulatory regime. Notwithstanding the potential benefits of regulating and supervising off-label drug use, China has yet to introduce a permissive regulatory regime. There are signs, however, that the Chinese authorities are reviewing the existing regime with a view to introducing a more comprehensive and nuanced approached in the future.

[8] Zheng and Xu, The Journal of Managed Care Pharmacy, October 2010 http://www.amcp.org/data/jmcp/640.pdf

[9] Article 61, Drug Administration Law (《药品管理法》), Article 6 of the Standards for Drugs Advertisement Censorship and Publishing (《药品广告审查发布标准》).

© Clifford Chance, October 2011