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The International Comparative Legal Guide to:

Pharmaceutical Advertising 2017

14th Edition

A practical cross-border insight into pharmaceutical advertising

Published by Global Legal Group, with contributions from:

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Published by
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59 Tanner Street
London SE1 3PL, UK
Tel: +44 20 7367 0720
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Email: info@glgroup.co.uk
URL: www.glgroup.co.uk

GLG Cover Design
F&F Studio Design

GLG Cover Image Source
iStockphoto

Printed by
Stephens & George
Print Group
June 2017

ISBN 978-1-911367-61-1
ISSN 1743-3363

Strategic Partners

General Chapter:

Country Question and Answer Chapters:

EDITORIAL

Welcome to the fourteenth edition of *The International Comparative Legal Guide to: Pharmaceutical Advertising*.

This guide provides the international practitioner and in-house counsel with a comprehensive worldwide legal analysis of the laws and regulations of pharmaceutical advertising.

It is divided into two main sections:

One general chapter. This chapter provides an overview of off-label use in the EU and U.S.

Country question and answer chapters. These provide a broad overview of common issues in pharmaceutical advertising laws and regulations in 29 jurisdictions.

All chapters are written by leading pharmaceutical lawyers and industry specialists and we are extremely grateful for their excellent contributions.

Special thanks are reserved for the contributing editor Ian Dodds-Smith of Arnold & Porter Kaye Scholer LLP, for his invaluable assistance.

Global Legal Group hopes that you find this guide practical and interesting.

The *International Comparative Legal Guide* series is also available online at www.iclg.com.

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PREFACE

It is a pleasure to have again been asked to provide the preface to *The International Comparative Legal Guide to: Pharmaceutical Advertising*, which is now in its fourteenth edition.

This year the guide contains one general chapter written by Arnold & Porter Kaye Scholer LLP and 29 individual chapters, the new ones of which are Russia, Singapore, Taiwan and Ukraine. The general chapter comprehensively covers the area of medicine off-label use in the EU and the U.S. Despite plenty of activity in the area, including a European Commission Report, the chapter suggests that little has been decided in either jurisdiction in this vexed area to provide certainty for manufacturers, and thereby patients, going forward.

As with other current editions in the ICLG series that I use as a reference point, this edition will be my first port of call when faced with thorny questions concerning pharmaceutical advertising.

Tom Spencer
Senior Counsel
Litigation
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Off-label Use: Current Position in the EU and U.S.

Jackie Mulryne

Mahnu Davar

Arnold & Porter Kaye Scholer LLP

Introduction

The terms of a licence to place a medicinal product on the market set out the approved conditions for use of that medicinal product, including the approved indications for use. However, while the licence controls how the licence holder can market its product, it does not regulate how healthcare professionals ("HCPs") prescribe the product. HCPs may decide to prescribe a medicinal product based on their experience and clinical judgment, regardless of its approved indications for use and the other conditions set out in the licence. This is known as off-label use, as the product is intentionally prescribed in circumstances that are outside the approved conditions set out in the product label. Examples include use of a medicinal product for a different indication, in another age group, dose or route to that approved by the regulatory authority.

Off-label use, and the extent to which information can be provided about such use, has become a hot topic in recent years, on both sides of the Atlantic. In the U.S., the focus has been on communications by licence holders of off-label indications for authorised products. In the EU, there have been controversies where governments or national healthcare systems have promoted off-label use for economic reasons where a more expensive approved alternative is available. The limits of communications regarding off-label use have been fought in the Courts in the EU and U.S., and legislative bodies are attempting to grapple with the question of how far a company, or a national healthcare system, can go to promote a product for an indication for which it has not been authorised.

This article sets out the current position in the EU and U.S., as well as some of the areas that will need to be clarified in the future.

Current Position in the EU

The general rule is that a medicinal product may not be placed on the market unless a marketing authorisation has been granted by a competent regulatory authority which is satisfied that the criteria relating to quality, safety and efficacy are satisfactorily met.[i] The approved conditions of use are described in the Summary of Product Characteristics ("SmPC") which sets out the agreed position on how the product may be used safely and effectively. The marketing authorisation gives the holder the right to market the product within its terms, and the approved indications determine the uses for which it may be promoted. However, neither the marketing authorisation nor the legislation determine the circumstances in which a medicinal product may be *prescribed*; a doctor may choose to prescribe a product outside the terms of the marketing authorisation on the basis of his/her clinical judgment.

Article 5(1) of the Directive sets out an exemption to the requirements to have a marketing authorisation for the purposes of named patient supply. Under this exemption, a doctor may decide at his/her discretion and under his/her responsibility, to recommend or prescribe use of a medicinal product for the patients under his/her care "to fulfil special needs", even if the medicine has not been granted a marketing authorisation. Member States are required to give effect to this provision through transposition into their domestic laws. In addition, article 83(1) of Regulation (EU) No 726/2004 creates an option allowing Member States to make available on a compassionate use basis, medicinal products which may be the subject of an application for an EU marketing authorisation under articles 3(1) and 3(2) of the same Regulation. Such compassionate use programmes are limited to patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily with an authorised medicinal product. The particular arrangements for such programmes are governed by individual Member State legislation, and the specific requirements may vary between Member States. While these provisions do not specifically apply to off-label use, and the Court of Justice of the European Union ("CJEU") has confirmed that "*off-label prescribing is not prohibited, or even regulated, by EU law*",[ii] these provisions are used, by analogy, to circumstances where a product is supplied outside the terms of its marketing authorisation. Recently, some Member States have also put in place programmes sanctioning off-label use, in circumstances where an alternative licensed product is available, because of cost considerations.

In terms of advertising and communication of off-label indications, article 87(2) of the Directive provides: "*All parts of the advertising of a medicinal product must comply with the particulars listed in the [SmPC].*" The proactive provision of information by a pharmaceutical company about an unauthorised use of a medicine is very likely to be seen as unlawful promotion. However, while the definition of advertising is very broad, it does not include responses to unsolicited requests for information, received by pharmaceutical companies in relation to their products, or the legitimate exchange of medical and scientific information during the development of a medicine, if such information is accurate, balanced and up-to-date. However, each one of these activities must be considered on a case-by-case basis, as the context in which such information is provided will be important in determining whether the activity is acceptable.

Current interest in off-label use has focused on the prescription and use of off-label products, especially where promoted by national authorities. In particular, the Italian and French authorities introduced cost-saving policies in 2014 to permit prescribing of bevacizumab (Avastin) for ophthalmic indications, particularly wet age-related macular degeneration ("AMD"), despite the availability of other

medicinal products, including ranibizumab (Lucentis) and aflibercept (Eylea), authorised for intra-vitreal injection for the treatment of such conditions. Avastin and Lucentis/Eylea have a similar mechanism of action, but Avastin is indicated only for intravenous administration in oncology (for the treatment of colon, breast and kidney cancers).

Following the introduction of these controversial policies in Italy and France, the European Commission received a number of questions from Member States and other stakeholders in relation to the issues, and the associated legal and medical implications. In January 2015, EFPIA, EUCOPE and EuropaBio filed a complaint against the Italian law of May 2014 which provides for reimbursement of medicinal products used off-label even though a licensed alternative is available.[iii] A further complaint was issued in September 2015 in relation to an amendment to the French system, which allows the French medicines regulator to issue a temporary recommendation for use of a product in an unauthorised indication, for economic purposes, notwithstanding the existence of an authorised alternative treatment.[iv]

These complaints highlight the inconsistency between the strict regulatory process for authorisation of medicinal products, and the promotion by national authorities of unauthorised indications for products which have not been subject to those stringent requirements, for economic reasons. The position set out by EFPIA, EUCOPE and EuropaBio is also in line with a 2012 decision of the CJEU,[v] which considered the supply of unlicensed medicinal products under article 5(1) of Directive 2001/83/EC. In that case, the CJEU specially stated that financial considerations cannot, in themselves, lead to recognition of the existence of special needs capable of justifying the unlicensed use of a medicinal product in preference to a product with a marketing authorisation for the indication in question.

The policies in Italy and France have also resulted in litigation in the national courts. In Italy, in 2014, the antitrust authority fined Novartis and Roche over €180 million after concluding the companies had established a cartel aimed at preventing the off-label promotion of Avastin in order to foster the promotion of (on-label) Lucentis. In particular, it was found that the companies had agreed to portray the cheaper Avastin product as having certain safety issues compared to Lucentis because it was not authorised for use in AMD. The antitrust authority found that the companies had earned profits to the detriment of market efficiency, and this had impaired competition. Following a number of appeals, in June 2016, the Italian Council of State (the Administrative Supreme Court), issued – at the parties' request – a request for a preliminary ruling to the CJEU asking a number of questions about whether an agreement between Novartis and Roche to promote the sale of Lucentis breaches European antitrust rules; the decision of the CJEU is awaited.[vi]

Most recently, in February 2017, the Conseil d'Etat, the French Administrative Supreme Court, rejected a challenge by Novartis against the recommendation issued by the French authorities sanctioning the use of off-label Avastin in wet AMD, despite the availability of Lucentis.[vii] The Conseil d'Etat concluded that the provisions of the French Public Health Code were in line with EU law, as the case law of the CJEU[viii] shows that pursuant to article 5(1) of the Directive, an authorised medicinal product may, in certain circumstances, be used off-label, notably if its active ingredient is different from that of the product authorised for such indication, provided that the prescribing doctor deems it indispensable to use this medicine to meet the therapeutic needs of his patient.

European Commission Study

In 2013, the European Parliament adopted a resolution requesting the EMA to draw up a list of off-label medicines which were used despite the existence of an approved alternative, and to develop guidelines on off-label use. The Commission responded that such action was premature, and it would commission a study to understand better the scope and ramifications of the issue. The report of this study (the "Study")[ix] was ultimately published in February 2017 by the European Commission.

The Study provides a factual analysis of off-label use across the EU. This includes its legal framework, its prevalence (cited in the Study as around 20% of prescriptions), a description of its drivers and a review of the existing and potential policy tools that could be used to better regulate the practice. A review of literature and case law was performed, as well as consultation with a number of key stakeholders, including representatives from regulatory authorities, health technology assessment bodies, patients, HCPs, industry and experts.

The Study is said to cover the public health aspects related to off-label use, and the balance between the benefits and risks for patients. While the purpose of the Study was principally to describe the situation from a factual perspective, some sectors, particularly the industry, have been disappointed with the lack of recommendations provided, and in particular, the lack of consideration given to important issues such as off-label prescribing in the context of licensed alternatives and the promotion of off-label prescriptions for purely financial reasons. The widespread criticism of the policies of the authorities in Italy and France in relation to off-label prescribing, together with the fact that such policies have been supported by their respective courts, reflects uncertainty in this area and demonstrates an urgent need for clarification at EU level.

The drivers

The Study lists a number of reasons why off-label use is so prevalent in the EU:

- *Regulatory incentives*: Directive 2001/83/EC provides for one additional year of marketing protection if a new indication is registered in the first eight years after an authorisation is granted, provided this new indication brings significant clinical benefit over existing therapies. However, this additional year of marketing protection provides only limited benefit, particularly as doctors may prescribe a product off-label even without a company investing in such new indications. Furthermore, generic competition, low prices for off-patent medicines, and increases in regulatory requirements mean there may be little incentive for a company to make such an investment.
- *Supply issues*: Disruption in the manufacturing of a product or its withdrawal (for commercial or safety reasons) from the market can provoke a need for off-label use of a different product. Similarly, some products (or some indications) may be authorised in some Member States but not in others, or a product may be authorised but not made available, triggering the need for off-label prescribing of available products.
- *Lack of authorised alternatives*: The prescriber may have no choice but to prescribe off-label in circumstances where particular patient groups were not included in the clinical trials and are therefore not reflected in the SmPC for particular products.
- *Cost*: The most controversial drivers for off-label use are related to pricing and reimbursement. In this context, the Study recognises that pricing may be the reason for off-label use in those cases where the on-label product is more expensive than the off-label product and both are reimbursed. Further, there are circumstances where the off-label use of a product is reimbursed while use of the on-label product is not, leading to off-label prescribing despite the availability of the on-label product.[x]

The Policy Options

On the basis of these findings, the Study identifies a number of policy tools that could be used to better regulate off-label use:

- *Regulating off-label prescription for specific products* – Competent authorities might evaluate the risk-benefit profile of the medicine in its off-label use; only medicines with a favourable risk-benefit profile would be granted a permit to be prescribed off-label, as currently occurs in Hungary and France. In France, patients should be monitored through a protocol, and the marketing authorisation holder is required to collect safety and efficacy information, and to provide all available data to the regulatory authorities. Such systems serve to increase patient safety, and strengthen the prescriber's position with regards to liability. Their downside is that a refusal may be disadvantageous for individual patients, as off-label use may be prohibited, based on an evaluation of the average risk/benefit ratio across the population, rather than in an individual patient. The option also encounters reluctance from some companies and physicians due to the burden that these reporting obligations entail.
- *EU guidance to assist with development of national guidelines of off-label prescribing* – EU guidance could be provided to establish a common ground for national treatment guidelines in Member States. In fact, on 8 April 2017, the CPME (the Standing Committee of European Doctors) adopted a policy on off-label use.[xi] This sets out some best practice for prescribing a product off-label, including the fact that it should only take place where there is no alternative authorised treatment that would better serve patients' needs.
- *Treatment guidelines for specific products* – Off-label prescription could be regulated using protocols or professional standards prepared by the relevant professional bodies on specific off-label use, as is the case in the Netherlands. Such guidelines would provide information on the risk-benefit balance of the product, so prescribers and patients could make an informed decision.
- *Changes in data requirements* – Data, other than from industry-based randomised controlled trials, could be accepted as evidence for applications for authorisations; for example, by accepting monitoring data on efficacy and safety, real-world data from patient registries, or pharmacovigilance data. However, in order to ensure patient safety, it should be clear which quality standards apply for these data to be acceptable.
- *Incentives for pharmaceutical companies to register new indications* – The authorisation of new indications enhances patient safety and supports prescription by HCPs. Industry stakeholders argued that additional incentives should be added to the EU legal framework to reward the investment needed to develop new indications, although other stakeholders considered the current incentives (including those under the Paediatric Regulation and the Orphan Drug Regulation) to be sufficient.
- *Reimbursement measures* – Reimbursement systems could be amended to allow for off-label use, including: (i) reimbursing off-label use where a product is included in treatment guidelines; (ii) reimbursing off-label use for which there is no competitor on the market; and/or (iii) reimbursing off-label use where the off-label product is less expensive than its on-label competitor. The last option caused controversy among stakeholders. The authors of the Study noted the decision of the CJEU in *European Commission v Poland*,[xii] which confirmed that the exemption to the requirement for a medicinal product to be supplied in accordance with a marketing authorisation, under article 5 of Directive 2001/83/EC, cannot be applied for financial reasons only. They commented that:

  "*[I]t can be debated whether allowing reimbursement of off-label use in case it is less expensive than its on-label competitor is (always) against the medical need of an individual patient. Moreover, medicinal products may become available to patients who otherwise would not have access to these medicines.*"

  The Study states that industry was opposed to this option, but does not present any analysis of its lack of consistency with the EU medicines regulatory framework.
- *Awareness campaigns* – HCPs and patients could be informed about off-label use via awareness campaigns. However, campaigns for HCPs were not considered useful, as needs differ per country and per specialism. Nor were they considered useful for patients, as off-label use is not relevant for a large majority of patients.

The European Commission now needs to consider the results of the Study, and how it will respond to the questions raised, and whether new legislation or guidance should be published.

Current Position in the U.S.

In the U.S., when the Food and Drug Administration ("FDA") approves a new prescription drug or a new indication of a previously-approved prescription drug, FDA also approves the professional labelling for that drug, known as the "package insert" ("PI"). The Federal Food, Drug, and Cosmetic Act ("FDCA"), related FDA regulations, and FDA enforcement policy historically prohibited the manufacturer of a prescription drug from marketing or promoting that drug for any use other than the one approved by FDA and described in the approved PI.[xiii] The language of the relevant statutes and regulations do not explicitly prohibit off-label promotion. Nevertheless, FDA and the U.S. Department of Justice have used the statutory and regulatory definitions of "labelling" and "intended use" to prohibit proactive communications involving off-label uses.[xiv] A violation of the FDCA is a criminal act and the statute permits prosecution even where an individual or company has not acted with intent in the conventional sense.[xv]

By contrast, the FDCA prohibits FDA from regulating the independent practice of medicine under these and other FDCA provisions. HCPs commonly, and appropriately, prescribe unapproved uses of approved prescription drugs for their patients. Furthermore, these off-label uses are often endorsed by treatment guidelines, drug compendia, and other authoritative sources representing the standard of care. FDA has recognised that certain non-promotional communications to HCPs by companies about those off-label uses may be permissible when other controls are present.[xvi] But those advocating for allowing broader communications regarding off-label uses have noted that the narrow exceptions permitting such communication are insufficient to allow a full exchange of medical information that would benefit patient care. There are also concerns about the legal ramifications of communicating outside the narrow boundaries established by FDA, given the possibility of severe sanctions under the FDCA. On the other hand, there are concerns that FDA permission to freely disseminate information on off-label uses would undermine the incentives for companies to seek new and supplemental approvals for drugs already on the market.

For many years, industry has asked FDA to evaluate its policies and regulations and to update its position on manufacturer communications to better align with the modern healthcare system. The tension between FDA and industry have recently come to a head as a result of recent court decisions.

In recent years, the Courts have acknowledged that restrictions on the communication of truthful and non-misleading speech about medically accepted unapproved uses to HCPs violate manufacturers' First Amendment right to free speech, that they do not serve the legitimate regulatory objective to protect patient health, and they do not meet the highest standard of scrutiny afforded such speech.[xvii] Most recently, the U.S. District Court for the Southern District of New York held in *Amarin* that "*[w]here the speech at issue consists of truthful and non-*

misleading speech promoting the off-label use of an FDA-approved drug, such speech […] cannot be the act upon which an action for misbranding is based".[xviii] The Amarin court specifically held that truthful and non-misleading speech cannot be used as "evidence of intent" for the purposes of an FDCA misbranding violation.[xix] These trends in First Amendment jurisprudence have spurred the legislative, regulatory, and policy changes discussed below.

Healthcare economic information

On December 13, 2016, President Obama signed into law the 21st Century Cures Act ("Cures Act").[xx] Most relevant to this article, Section 3037 of the Cures Act amended Section 114 of the Food and Drug Administration Modernization Act ("FDAMA"), which was enacted in 1997 to create a safe harbor for manufacturers to proactively communicate or disseminate certain healthcare economic information ("HCEI") that met a "competent and reliable" evidence standard. However, communications were considered false or misleading unless the information "*directly relate[d]*" to an approved indication for the drug. Furthermore, the communication could be made only to a "*formulary committee, or other similar entity*" (*i.e.*, not to product prescribers), and so limited the scope of manufacturer communications about their products.

The amendments introduced by the Cures Act sought to clarify and expand the scope of permitted manufacturer communications regarding HCEI. Specifically, the Cures Act broadened the definition of HCEI to include:

> "*Any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug.*"

Additionally, Section 3037 expands the scope of the audience to whom a manufacturer may communicate HCEI, so that a manufacturer may now communicate HCEI to "payors" and to formulary committee or other similar entities with knowledge and expertise of healthcare economics. Furthermore, section 3037 clarifies that HCEI must only "relate" to an FDA-approved indication of a drug, rather than be "directly" related to an approved indication. This change permits manufacturers to communicate HCEI regarding off-label uses of their products, thereby greatly expanding the scope of permitted communications.

Stakeholder Input and Draft FDA Guidance Documents

Over the years, FDA has indicated that it would revise its policies on manufacturer communications. For example, in 2011, FDA opened a docket requesting comments on scientific exchange regarding both FDA-approved and investigational products.[xxi] Similarly, in 2014, in a federal register notice regarding a Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drug and Biological Products, FDA stated that it "*plans to issue, by the end of the calendar year, additional guidance that addresses manufacturer responses to unsolicited requests, distributing scientific and medical information on unapproved new uses, manufacturer discussions regarding scientific information more generally, and distribution of health care economic information to formulary committees and similar entities*".[xxii] Although many years went by without modifications to FDA regulations or guidance regarding manufacturer communications, the final days of the Obama Administration did see proposed changes to FDA guidance.

In November 2016, FDA held a public hearing to solicit comment from stakeholders – including industry trade groups – on its approach to regulating manufacturer communications on off-label uses.[xxiii] In addition, FDA opened a formal docket to receive written comments on such issues. Although the written comments were originally due on January 9, 2017, 10 days after the comments were due, FDA published a Memorandum on Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products ("First Amendment Memorandum") and reopened the docket comment period.[xxiv] The First Amendment Memorandum describes FDA's response to the trends in First Amendment jurisprudence and sets forth the public health interests FDA wants to protect through its regulation of manufacturer communications. In response to this docket, many industry stakeholders submitted comments stating that although FDA's stated interests are valid and important, FDA could continue to protect those interests while expanding the scope of permissible manufacturer communications. Many respondents recommended that FDA amend its current regulations to better align with recent First Amendment jurisprudence to broaden the ability of manufacturers to communicate truthful and non-misleading information about off-label uses of their products.

In January 2017, FDA simultaneously published two draft guidance documents that further expand the scope of permissible manufacturer communications. FDA's Draft Guidance on Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers addresses manufacturer communications to all HCPs regarding information that is not contained in the FDA-required labelling, but that is "*consistent with the FDA-required labeling*".[xxv] Although the Draft Guidance leaves some questions open as to the evidentiary support that must be included with such communications, the Draft Guidance does provide helpful information to manufacturers about the permissible scope of the communications.

In the Draft Guidance, FDA proposes that it will exercise enforcement discretion regarding truthful and non-misleading manufacturer communications "consistent with" the FDA-required labelling if a communication meets each of three factors. First, the manufacturer communication must be consistent with the: a) indication; b) patient population; c) limitations and directions for handling/use; and d) dosing/administration contained in the FDA-required labelling. Second, the manufacturer communication should not make representations or suggestions that "*increase the potential for harm to health relative to information in the FDA-required labeling*". Third, the manufacturer communication must not represent or suggest conditions for use under which the product could not be safely and effectively used.[xxvi]

FDA's Draft Guidance on Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers addresses manufacturer communications with sophisticated healthcare audiences and implementing section 3037 of the Cures Act, discussed above.[xxvii] Generally, the Draft Guidance explains FDA's current thinking regarding the communication by manufacturers about HCEI. In the Draft Guidance, FDA defines the scope of the audience to whom a manufacturer may communicate HCEI to include "*payors, formulary committees (e.g., pharmacy and therapeutic committees, drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis for health care organizations*".[xxviii] Importantly, the Draft Guidance clarifies that HCEI "*pertains to the economic consequences related to the clinical outcomes of treating a disease (or specific aspect of a*

disease) or of preventing or diagnosing a disease" and offers various examples when HCEI "relates to" an approved indication.[xxix]

Additionally, the Draft Guidance clarifies when FDA would not consider HCEI to be false or misleading. FDCA section 502(a) states, in part, that HCEI "*shall not be considered to be false or misleading [...] [if it] is based on competent and reliable scientific evidence [CARSE]*".[xxx] The Draft Guidance provides guidance to manufacturers regarding how to meet this standard, stating that "*FDA considers HCEI to be based on CARSE if the HCEI has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results*".[xxxi]

Amended FDA Regulations

In the final days of the Obama Administration, on January 9, 2017, FDA published its final rule amending, in part, FDA's regulation on "intended use" ("Final Rule").[xxxii] The concept of "intended use" is central to FDA's regulation of drugs. If any article is "*intended for use in the diagnosis cure, mitigation, treatment, or prevention of disease*",[xxxiii] then the article is a drug and is subject to FDA approval and FDA regulation. Additionally, FDCA § 502(f)(1) states that an approved drug is misbranded unless its labelling bears "*adequate directions for use*". Although Congress exempted prescription drugs from this requirement, FDA regulations state that a prescription drug is exempt only if the drug's labelling contains "adequate information" for a use for which the drug "is intended".[xxxiv] Under current regulation, drug manufacturers may not include "information" in labelling regarding an unapproved use. Therefore, if an unapproved use is the manufacturer's "intended use". FDA considers the drug misbranded in violation of FDCA § 502(f)(1) and subject to FDA enforcement action.

In the Final Rule, FDA did not adopt the interpretation of "intended use" supported by drug manufacturers, who strongly disagree with FDA's current interpretation. In particular, industry believes that FDA's interpretation is contrary to the holding by various courts, such as the *Amarin* court, that truthful and non-misleading speech cannot provide evidence of a new intended use.

However, on February 7, 2017, FDA delayed the effective date of the Final Rule until March 21, 2017. Only one day later, MIWG, PhRMA, and BIO submitted a Petition to Stay and for Reconsideration of the Final Rule ("Petition").[xxxv] In response to the Petition, FDA published a notification, further delaying the effective date of, and seeking comments on, the Final Rule and the Petition ("Request for Comments"). As of this writing, public comments on the Request for Comments are due July 18, 2017.

Conclusion

Despite, or possibly because of, the recent activity in this area, there is still significant uncertainty regarding communication of off-label uses of products in both the EU and U.S., by companies and national authorities.

In the EU, it remains to be seen how the European Commission will respond to the suggestions set out in the recent Study, and what changes, if any, will be implemented. None of the proposals involve implementing the same rigorous standard for assessment as that required by Directive 2001/83/EC to place a product on the market. In the meantime, the circumstances in which off-label use is permitted, and promoted, by national authorities in the different Member States shows substantial divergence across the EU, particularly where financial considerations are included in the decision whether to prescribe products off-label.

Similarly, in the U.S., although FDA's positions may not change in the short term, recent court decisions on the First Amendment rights of manufacturers and the current Administration's policies lend weight to regulatory changes that would allow manufacturers to more broadly communicate about their products. In position papers and comments to FDA, industry trade associations, such as PhRMA, BIO, and other groups have proposed regulatory frameworks that they believe to be rational approaches to off-label promotion. Arguably, the most compelling of these proposals would permit truthful and non-misleading communication regarding off-label uses (consistent with the decision of the court in *Amarin*) to sophisticated audiences, as long as appropriate contextual information and disclosures were included with the communications. To implement such a framework, FDA must amend existing or add new regulatory safeguards.

Given the uncertainty, companies should keep a close eye on these developments before disseminating off-label information, and should work closely with regulatory and legal counsel to understand whether a particular communication, either by the company or by a national authority, may be challenged in the current regulatory environment.

Endnotes

i. Directive 2001/83/EC, Article 6.

ii. Case T-452/14 *Laboratoires CTRS v Commission* [2015], para. 79.

iii. Statement on bio-pharmaceutical industry complaint to the European Commission against a new Italian law Promoting off label use of medicines for economic reasons, 20 February 2015.

iv. Biopharmaceutical industry files complaint against French law promoting government-initiated off-label use without the involvement or consent of patients and their physicians, 1 September 2015.

v. Case C-185/10 *Commission v Poland* [2012], para. 38.

vi. Case C-179/16 *F. Hoffmann-La Roche and Others*.

vii. Conseil d'Etat, 1st–6th Chambers, 24 February 2017, No. 392459.

viii. The Conseil d'Etat referred to C-185/10 *Commission v Poland* and to C-535/11 *Novartis Pharma GmbH v Apozyt GmbH*.

ix. European Commission, Study on off-label use of medicinal products in the European Union, 27 February 2017.

x. For example, in 2014, France excluded Lucentis® from drug coverage and replaced it with Avastin®.

xi. CPME policy on off-label use of medicinal products, 8 April 2017, CPME/AD/Board/08042017/006_Final/EN.

xii. C-185/10 *Commission v Poland* [2012].

xiii. *See* 21 U.S.C. § 331(a), (b), (c), (k); 21 U.S.C. § 352.

xiv. *See* 21 U.S.C. § 321(m); 21 C.F.R. § 201.128; *see e.g., Bradley v U.S.*, 264 F. 79 (5th Cir. 1920); *U.S. v 46 Cartons, More or Less, Containing Fairfax Cigarettes*, 113 F. Supp. 336 (D.N.J. 1953); *American Health Products Co., Inc. v Hayes*, 574 F. Supp. 1498 (S.D.N.Y. 1983).

xv. *See* 21 U.S.C. § 333.

xvi. *See e.g.,* FDA, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices 6 (Feb. 2014).

xvii. *See Sorrell v IMS Health, Inc.* 564 U.S. 552, 567 (2011); *United States v Caronia*, 703 F.3d 149, 166 (2d Cir. 2012).

xviii. *Amarin Pharma, Inc. v FDA*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).

xix. *Id*. at 227–228.

xx. 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1105 (2016).

xxi. Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 Fed. Reg. 81508 (Dec. 28, 2011).

xxii. Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices; Availability, 79 Fed. Reg. 33569 (June 11, 2014).

xxiii. Notification of public hearing; request for comments, 81 Fed. Reg. 60299 (Sept. 1, 2016).

xxiv. Docket FDA-2016-N-1149, FDA, Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Jan. 2017).

xxv. FDA, Draft Guidance for Industry, Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers (Jan. 2017).

xxvi. *Id*. at Questions and Answers 3–5.

xxvii. FDA, Draft Guidance for Industry, Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers (Jan. 2017).

xxviii. *Id*. at Questions and Answers 4.

xxix. *Id*. at Questions and Answers 1.

xxx. 21 U.S.C. § 352(a) (FDCA § 502(a)).

xxxi. FDA, Draft Guidance for Industry, Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers (Jan. 2017), Questions and Answers 9.

xxxii. *See* 82 Fed. Reg. 2193 (Jan. 9, 2017).

xxxiii. 21 U.S.C. § 321(g); *see also* Pure Food and Drugs Act, ch. 3915, 34 Stat. 768, 769 (June 30, 1906).

xxxiv. 21 C.F.R. § 201.100(c)(1).

xxxv. Docket FDA-2015-N-2002, MIWG, PhRMA, and BIO, Petition to Stay and for Reconsideration (Feb. 8, 2017).

Acknowledgment

The authors would like to thank Ashley Bender, an associate at Arnold & Porter Kaye Scholer, for her assistance with this article.

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