Marketing, e-commerce and advertising in the pharmaceutical industry: France, the UK and the US

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This article considers the differences and similarities between the EU laws (in particular the UK and French systems) and the US laws as they relate to marketing, e-commerce and advertising in the pharmaceutical industry. Specifically, the article examines:

- Who regulates pharmaceutical advertising?
- Basic advertising rules, including:
  - off-label promotion;
  - advertising of prescription-only medicines to consumers;
  - advertising to healthcare professionals or consumers;
  - advertising to consumers in the EU;
  - additional requirements for advertising to healthcare professionals;
  - pre-authorisations;
  - gifts and hospitality.
- Patient contact.
- Comparative advertising.
- Sanctions for non-compliance.

WHO REGULATES PHARMACEUTICAL ADVERTISING?

Governments

In Europe, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Directive) provides the basic rules regarding the advertising of medicinal products. The Code for Human Medicines Directive is then enacted into the individual laws of the 27 EU member states which each regulate the advertising of medicinal products through their own legal and, in some countries, industrial bodies. The enactment of the Code for Human Medicines Directive in different member states can vary, sometimes quite substantially, and particularly in relation to the methods of enforcement and sanctions imposed. There is also variation in the extent to which the competent authorities of member states take responsibility for the regulation of advertising, rather than the court systems or national industry bodies.

In France and the UK, the competent authorities (*Agence Française de la Sécurité Sanitaire des Produits de Santé* (AFSSAPS) in France and the Medicines and Healthcare Products Regulatory Authority (MHRA) in the UK) have the legal authority to regulate the advertising of medicinal products. These competent authorities issue non-legally binding guidelines and codes of practice with respect to pharmaceutical advertising. These provide much more detail on the regulation of particular situations. They also hear cases regarding breaches of the law, the guidelines and codes.

In the US on the other hand, prescription drug advertising and labelling is regulated by the Food and Drug Administration (FDA) under the authority of the Federal Food, Drug, and Cosmetic Act. The Federal Trade Commission (FTC) is responsible for regulating the advertising of non-prescription (or "over-the-counter" (OTC)) pharmaceutical products, although the FDA continues to be responsible for regulating OTC labelling, which in some cases may include advertising. (*See 21 U.S.C. §§ 352(a), (n), (q), and (r); 15 U.S.C. § 52. See also 36 Fed. Reg. 18539 (16 September 1971)*). The regulatory distinction between drug labelling and advertising is, at best, a blurry line.

Industry codes

In some countries in Europe, notably the UK, pharmaceutical advertising regulation is substantially undertaken through self-regulation carried out with the support of industry bodies. The European Federation of Pharmaceutical Industries and Associations, which brings together the national associations, has issued a Code of Practice on the Promotion of Medicines (EFPIA Code). The rules in the EFPIA Code have found their way into many national laws, as well as guidelines and codes of practice of member states (although not always precisely as written). The national industry bodies issue their own codes and have their own or related tribunals for hearing cases on the breach of these codes. Through the agreement of their member companies, in some countries national industry bodies also have the right to issue sanctions of fines and ultimately, expulsion from membership.

In the UK, the Association of the British Pharmaceutical Industry (ABPI) has a code of practice including rules on the content of prescription-only medicines. The equivalent for OTC and general sales list medicines is the Proprietary Association of Great Britain (PAGB). This has two codes: one for advertising addressed to consumers and another for advertising addressed to health professionals. There is a memorandum of understanding between these industry bodies and the MHRA so that there can be no overlap of jurisdiction. Generally the industry bodies will take on most cases, with the MHRA hearing only cases where the companies involved are not members of the industry bodies.

The position in France is very different. The Ethics and Mediation Committee of the Pharmaceutical Industry takes a monitoring role and settles disputes between its member companies, but lacks supervisory or enforcement duties and the right to impose sanctions.

In the US, the role of the industry bodies is more similar to that in France. The Pharmaceutical Research and Manufacturers of America (PhRMA) provides some guidance for its members but, rather than taking an active enforcement role, PhRMA has a lobbying role on behalf of its members to temper FDA enforcement.

BASIC ADVERTISING RULES

Off-label promotion

In both the US and the EU, the advertising of products outside the indications for which they are authorised (off-label promotion) is prohibited (*Article 87(1), Code for Human Medicines Directive* and *21 U.S.C. §§ 331 and 352*). The US and the EU do however allow for the free exchange of scientific information where this is in response to specific and individual physician requests. Determining the boundaries between exchanges of scientific information and promotion is not always straightforward. In the jurisdictions considered here, the question is whether there is a link between the sale of the product and the dissemination of the information.

In the UK, the point has been illustrated by cases before the PMCPA. In one such case, postcards on trade stands asked doctors to check a box if they wanted information on off-label uses (*Abbot v Roche, Case Auth. 1100/11/00*). In another case, "medical liaison executives" characterised as scientific advisors organised meetings in response to individual questions from doctors on off-label uses of a particular product. Both of these cases were found to be in breach of the ban on off-label promotion (*Pfizer, Case Auth. 1186/5/01*).

Advertising of prescription-only medicines to consumers

This is where the laws of the US and the EU diverge. In the US, prescription medicinal products can be promoted to consumers within the terms of their authorisations but cannot be false or misleading. In the EU however, it is not permitted to advertise prescription-only medicines to consumers or medicines which are psychotropic or narcotic by international convention (*Article 88(1), Code for Human Medicines Directive*). There are also certain chronic conditions which cannot be mentioned in advertising to the general public.

The Code for Human Medicines Directive permits member states to each decide whether to ban, on their territory, advertising to the general public of medicinal products which can be reimbursed by the state (*Article 88(3)*). In the UK, there is no such additional restriction. In France, however, direct to consumer advertising is only allowed for a product which is not reimbursable and for which a prescription is optional and which is designed for use without the intervention of a medical practitioner (*Article R.5122-3, French Public Health Code*).

Advertising to healthcare professionals or consumers

In the EU, all parts of any advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics (*Article 87(2), Code for Human Medicines Directive*). Further, the advertising of a medicinal product must encourage its rational use by presenting it objectively and without exaggerating its properties or being misleading (*Article 87(3)*).

The MHRA Blue Guide (which contains its general guidelines on advertising) states that advertising should be factually correct (so that it might be independently verifiable, including any scientific results). It also requires the advert to be specific about any limitations on the claims made for the product. The advertising should not be misleading, particularly as to the potential benefits or possible risks of a medicine (*paragraph 4.3, Blue Guide*). The AFSSAPS guide on pharmaceutical advertising includes similar recommendations.

In the US, there is a concept of "misbranding" in relation to pharmaceutical advertising. This includes, among other things, if the advert:

- Is false or misleading in any particular (*21 U.S.C. §§ 331(a)-(c)*).
- Does not provide a "true statement" with respect to side effects, contraindications, or effectiveness (*21 U.S.C. § 352(n)*).
- Is false, lacking in fair balance, or otherwise misleading (*see box, Advertising that is false, lacking in fair balance, or otherwise misleading*).

Advertising to consumers in the EU

In the EU, advertising to consumers is treated differently from advertising to healthcare professionals. Because of this there are additional rules which must be complied with. Any consumer advertising must make it clear it is publicity about a medicinal product and must include the product name, the common name, information necessary for correct use and a clear invitation to read the instructions (*Article 89(1), Code for Human Medicines Directive*). There is also a long list of items or suggestions which must not be included in consumer advertising.

In the UK, the MHRA's Blue Guide supplements these rules by including additional guidelines for advertising addressed to consumers. Interestingly, it leaves the regulation of the content of broadcast advertising to the voluntary codes, namely, the PAGB code which regulates consumer advertising. In France, the AFSSAPS similarly issues guidelines which are accessible from their website and some of which are specific to consumer advertising.

Additional requirements for advertising to healthcare professionals

In the US, the requirements for adverts addressed to healthcare professionals are the same as for consumers (*see above, Advertising to health professionals or consumers*).

In the EU however, there are specific rules on the content of advertising addressed to professionals. The following rules are translated directly into the legislation of the UK and France and require that advertising to healthcare professionals includes (*Article 91(1) and 91(2), Code for Human Medicines Directive*):

- Essential information compatible with the summary of product characteristics.
- The supply classification of the medicinal product.
- The date of the document, or date of last revision.

US RULES ON ADVERTISING THAT IS FALSE, LACKING IN FAIR BALANCE OR OTHERWISE MISLEADING

The US rules require that where an advert includes a product's name and its use, it must present a "fair balance" between the risks and the benefits of the drug (*21 C.F.R. § 202.1(e)(6)*). Fair balance means that the risks of the product must be clearly identified in contrast to its benefits (*21 C.F.R. § 202.1(e)(5)(ii)*). Fair balance applies equally to the content and format of promotional materials. The way in which fair balance is achieved is by including, as required by the FDA, a "brief summary" or "major statement" with an advert. A brief summary is required on most print adverts and must include all risks listed in the approved product labelling, including side effects, contraindications, warnings, and precautions (*21 U.S.C. § 352(n); 21 C.F.R. § 202.1(e)(1) and (e)(3)(iii)*). A major statement is required for all broadcast adverts.

The FDA has recently adopted a more practical approach to the content of a brief summary, permitting manufacturers to choose how they present the information from at least three recommended options:

- Present all risk information from the FDA-approved professional labelling.
- Reproduce the FDA-approved patient labelling, either in its entirety or as modified to omit less important risk information.
- Provide the risk information that would be appropriate for the proposed the FDA-approved Highlights Section in prescription drug labelling.

A major statement must include the product's major risks and make "adequate provision" for the dissemination to viewers of the product labelling, which includes all of the risks associated with the product. Instead of listing each risk as provided in a drug product's label, a broadcast advert must at least include information about the major risks of the drug in either the audio, or the audio and visual part of the presentation (s*ee "Consumer Directed Broadcast Advertisement, the FDA Guidance for Industry" 64 Fed. Reg. 43197 (8 August 1999)*). The FDA expects broadcast adverts to include all of the following components:

- An operating toll-free telephone number through which a consumer can hear the labelling read or have the labelling mailed to him in a timely manner (mailed within two business days, received within four to six days).
- A statement directing consumers to pharmacists and/or physicians, who can provide additional product information.
- A web page (URL) address that provides full access to the product labelling.
- Reference to an alternative way of obtaining package labelling information for consumers who do not have access to technology such as the internet.

- Information that is accurate, up to date, verifiable and sufficiently complete to form an opinion of the therapeutic value of the product.
- Quotations that are accurately reproduced with precise sources indicated.

The first two bullet points are optional under the Code for Human Medicines Directive, but the UK and France have chosen to include them in their national laws.

Pre-authorisations

Pre-authorisation is required in France for all adverts targeting the general public. If no objections are received within one month, then the authorisation is deemed to have been granted. Advertising targeting health professionals must be filed with AFSSAPS within 8 days of it being issued, but does not require specific authorisation.

In the UK, there is no blanket requirement for pre-authorisation under the applicable laws, but the MHRA has the power to require marketing authorisation holders to submit their advertising for approval. The MHRA generally exercises this power with respect to:

- Newly licensed products subject to intensive monitoring.
- Recently reclassified products.
- Products for which there have been previous breaches of the law.
- New active substances granted marketing authorisations since 7 November 2005.

In addition, the PAGB consumer code requires all advertising aimed at the consumer to be submitted in advance to the PAGB for compliance monitoring.

In the US, although all prescription drug adverts are required to be supplied to the FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) at the time of publication (*21 C.F.R. § 314.81(b)(3)(i)*), with one recent exception (*see below*), the FDA is expressly prohibited from requiring prior approval of the content of any "advertisement," except in "extraordinary circumstances" (*21 U.S.C. § 352(n)*). For example, adverts for accelerated approval drugs that are intended for dissemination within 120 days of approval must be submitted to the FDA during pre-approval (*21 C.F.R. § 314.550*).

On 1 October 2007, a new law came into force that allows the FDA to require the submission of television adverts for a drug 45 days before dissemination for pre-review (*Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85); §901(d) (amending the FDCA by adding §301(kk) and §503B (21 U.S.C. § 331)*). Under this law, the FDA can propose any changes to the adverts considered necessary to protect consumer well-being or that are otherwise consistent with the drug's prescribing information. The FDA can now also require disclosure of a serious risk listed on the drug's labelling if it determines that the advert would be false or misleading without such disclosure.

Gifts and hospitality

Issues around gifts and hospitality tend to capture media publicity whenever information escapes into the public domain about inappropriate entertainment of the medical profession. EU law provides the following basic rules which are reflected in UK and French national laws (*Code for Human Medicines Directive*):

- Gifts are not permitted, unless they are "inexpensive" and relevant to the practice of medicine or pharmacy (*Article 94(1)*).
- Hospitality must be limited to the main purpose, except if it is for "purely professional and scientific purposes", and must not be extended to third parties (*Article 95*).
- Free samples can only be given in limited numbers, in response to a written request and must be accompanied by the summary of product characteristics (*Article 96*).

In addition to EU law, the EFPIA has published a document on gifts and hospitality giving more precision to the content of their Code. In most member states, these rules are supported by specific regulations or the professional rules for doctors and pharmacists.

In the UK, the Blue Guide contains more detailed rules. These include the rule that only inexpensive gifts can be offered, defined as those valued at less than GB£6 (about US$12) including VAT, and which must be relevant to the profession or the professional's employment. These "promotional aids" must include no more than the brand, and indication that the name is a trade mark and the name of the company responsible for marketing the product.

In France, Article L. 4113-6 of the French Public Health Code regulates the financial advantages and hospitality that can be provided to healthcare professionals. Only gifts below EUR30 (about US$44) are authorised (*see Guidelines of interpretation of Article L 4113-6, Medical Doctor Society*).

Hospitality offered as part of the promotion of medicines must be strictly limited to the main purpose of the meeting or event. Where hospitality is offered as part of an educational meeting, any sponsorship must be prominently disclosed and the meeting must have clear educational content as the main purpose (there must be no stand-alone entertainment). Some countries apply stricter standards and ban all "secondary entertainment". In France all such advantages or compensation must be provided for in a written contract which is provided to the professional board for review before implementation.

In the US, these rules are known as "anti-kickback" and there is a substantial body of case law and legislation. The anti-kickback statute prohibits anyone from knowingly or wilfully offering, paying, soliciting, or receiving remuneration, to induce or reward business reimbursable under federal or state healthcare programmes.

Pharmaceutical manufacturers have a variety of remunerative relationships with those in a position to refer, order, or prescribe or influence the referral, ordering, or prescribing of the manufacturers' products, even though those persons or entities may not themselves purchase the products. These relationships include not only physicians, but also persons in a position to influence referrals, such as pharmacists and other healthcare professionals.

Regulatory authorities will question a manufacturer providing goods or services that eliminate an expense the physician would have otherwise incurred (that is, that have independent value to the physician), or providing items or services at less than their fair market value. The PhRMA Code on Interactions with Health care Professionals (PhRMA Code) provides useful and practical advice for reviewing and structuring these relationships (available at *www.phrma.org*). However, US regulatory authorities characterise the PhRMA Code as a "good starting point" or "floor" and warn that arrangements not meeting the PhRMA Code "are likely to receive additional scrutiny from government authorities". Problematic relationships between manufacturers and physicians, include "switching" arrangements, consulting and advisory payments, payments for detailing, business courtesies and other gratuities, and educational and research activities. Such gifts should be modest in value and be related to the physician's practice of medicine (for example, golf balls or golf clubs would be improper).

PATIENT CONTACT

Companies often try to push out the boundaries of what they can communicate to patients. At the same time patients are becoming better informed and more actively involved in their treatment decisions.

Disease awareness campaigns

There have been increasing numbers of companies sponsoring adverts relating to particular diseases rather than to products. In response to this, the MHRA has published guidelines on disease awareness campaigns. The essence of the guidance is that the campaign must only increase awareness of a disease and not stimulate a demand for a particular medicine. If there is only one medicinal product for the particular disease, the MHRA is likely to find that the campaign is actually to promote that product. The material should:

- Be factual (and of course accurate, up to date and capable of being substantiated).
- Focus on the condition and its recognition rather than treatments.
- Not be sensationalist.

In France, the position is similar (if not so categorically stated), in that disease awareness campaigns which do not refer to a particular product or treatment are not considered to be advertising.

In the US, the FDA applies similar criteria to distinguish a disease awareness advert from a product promotional advert.

Patient groups

These groups are generally interested in chronic diseases and want to be informed of and participate in discussions about trials of new products. They also need funding and support to provide services to sufferers. Obvious sponsors are pharmaceutical companies. However, caution needs to be exercised in working with patient groups. There are no specific regulations in either France or the US on this type of sponsorship, although obviously companies should avoid any implication that they might be providing gifts to the medical profession. In the UK there are also no regulations on the point, although the ABPI Code gives some guidance on how these relationships might be conducted.

The guidance can be summarised as follows:

- Sponsorship of materials (even if not promotional) must be declared.
- All involvement must be declared and transparent (the company's website or annual report must list all patient organisations to which they provide support).
- There must be no advertising of prescription only medicines or unauthorised medicines.
- Meetings are subject to the same rules as those applying to medical professionals.
- There must be a written agreement setting out what has been agreed in relation to every significant activity or ongoing relationship.

INTERNET ADVERTISING

English and French law each essentially restate the Code for Human Medicines Directive and do not include more detailed provisions to deal with issues arising from advertising on the internet. However, the competent authorities of each of these countries have drafted a more detailed set of guidelines including requirements for internet advertising, using some of the guidance available from the EFPIA code. The guidance suggests that the target audience of any website, that is, healthcare professionals, patients or the general public be clearly identified.

In the US, the FDA applies the same criteria to internet advertising as it does to print and broadcast advertising. How the FDA applies the criteria to internet advertising is not set out in policy or regulation, but rather is revealed on a case-by-case basis through individual enforcement letters.

Compliance

In France, the AFSSAPS has developed a code on communications over the internet for pharmaceutical companies (AFSSAPS internet code). Websites aimed at an audience in France must:

- Identify the company advertising its products, including its postal address.
- State who the website is aimed at and the kind of information that will be provided.
- Clearly identify any information for foreign countries (language being an insufficient indication in that respect).
- Clearly identify which pages have informational content and which are merely promotional.
- Be regularly updated and show the date of the latest update.

The AFSSAPS internet code requires that where there is advertising aimed at professionals, access to the site should have "real" restrictions on access by consumers. There is a strong recommendation that a personal access code should be attributed to each professional after their qualification has been verified.

In the UK, the Blue Guide is slightly less prescriptive. It states that "sections of a website aimed at healthcare professionals and containing promotional material should ideally be access restricted". If there is no access restriction to sections of a site where there is prescription only medicine advertising, the Blue Guide requires that additional precautions be taken to encourage consumers not to view these sections. These include:

- The site should be divided into clearly demarked sections for each target audience.
- The sections should be labelled as being for the particular audience.
- Adequate non-promotional information must be provided in public areas so that consumers do not need to access sections for healthcare professionals unless they choose to seek further detailed information.
- Members of the public should not be encouraged to access information which is not intended for them. Specifically, actively directing members of the public to advertising material for prescription only medicines is likely to be unlawful.

This suggests that the home page, which individuals can be directed to through an internet search engine, should not include prescription only medicine advertising and nor should any page on which individuals register for access to the site. For sites aimed at professionals, if an individual categorises themselves as a consumer on registration, they should either:

- Be encouraged to leave the site (if the site has only pages for healthcare professionals).
- If there are two separate sections of the site (one for consumers and one for healthcare professionals), not be directed by the search engine to materials found only in the section for healthcare professionals.

In the UK, the ABPI Code adds an additional layer of compliance. The ABPI Code applies to promotional material on the internet where this is "directed to a UK audience". Where the material is placed on the internet outside the UK, the ABPI code will apply if the material "was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it makes specific reference to the availability or use of the medicine in the UK". The ABPI Code provides details of the information that should be included in an advert for prescription only medicines placed on the internet.

COMPARATIVE ADVERTISING

In France, comparative advertising of pharmaceuticals is only permitted in advertising addressed to healthcare professionals. It is regulated by the general principles on comparative advertising of the French Consumer Code as well as the AFSSAPS guideline on comparative advertising to professionals of medicinal products.

The guideline requires that the comparison be as complete as possible, by for example, including not just the facts in favour of the medicinal product being advertised. It is also important that the integrity of the competitor's trade marks is not compromised by there being any possibility of confusion or any unfair advantage

being taken or any denigration of the competitor's trade marks. There has been an interesting debate in the French courts around the use by generic companies of the names of the original product in their advertising. The most recent decision on this point was in September 2007, when Sandoz was fined EUR400,000 (about US$546,000) for having stated in advertising that their product "replaces [*original product*] prescribed by your medical doctor" (*Decision of Paris Court of Appeal dated 6 September 2007 (Sandoz v AstraZeneca)*).

Under UK law there is no explicit prohibition on comparative advertising, and a competitor's brand can be used as long as their reputation is not used as leverage for the product being advertised. The MHRA Blue Guide does however require that there is no suggestion that one product is better than or equivalent to another in adverts directed at consumers. Comparative advertising must comply with all the general advertising rules and must be fair and balanced. Comparative advertising is particularly at risk from complaints because the company that is the subject of the comparison is likely to scrutinise the advertisement particularly carefully.

In the US, comparative advertising will render a drug misbranded if there is a representation or suggestion that a prescription drug is safer or more effective than another drug in any way, when the difference has not been shown by substantial evidence. An advert for a prescription drug cannot, either directly or by implication (for example, by use of comparative test data or reference to published reports) represent that the drug is safer or more effective than another drug. Further, an advert cannot contain a quantitative statement of safety or effectiveness unless the representation has been approved as part of the labelling or the representation of safety or effectiveness is supported by substantial evidence derived from adequate and well-controlled studies (*21 C.F.R. § 202.1(e)(6)*).

SANCTIONS FOR NON-COMPLIANCE

The sanctions for non-compliance with laws of the EU member states are different in each country. In some countries (such as the UK) breaches of the advertising laws applicable to drugs can be a criminal office. In most countries, fines can be imposed for breaches of the advertising legislation. In France, the AFSSAPS sends warning letters, which can require the advert be suspended or amended or that it be amended by way of a correction notice following the advert's prohibition. If an advert is prohibited, the institution dealing with pricing and reimbursement in France (*Comiteé Economique des Produits de Santé*) can even decrease the reimbursable price of the product. In some countries in Europe, however, it is often the industry organisations that exercise their jurisdiction over breaches of the advertising legislation through the regulation of their codes. This is the case in the UK.

In France and some other countries, competitors can apply to the court for a judgment prohibiting the unlawful activities on the basis that these are giving the company acting unlawfully an unfair advantage (rules of unfair competition). The legal costs and the fallout from the adverse publicity are likely to cost the advertisers more than the fines imposed by the courts. The fact that the advertisers have the most at stake in these various sanctions is another reason justifying imposing on them the responsibility for ensuring that their adverts comply with the laws which are most likely to apply.

In the US, a company breaching the rules on advertising medicinal products can lead to any one or more of the following enforcement actions:

- Requiring the manufacturer to issue a Dear Doctor letter.
- Recalling the product.
- Prohibiting its distribution or production.
- Withdrawing marketing approval.

The 2007 amendments to the FDCA added civil monetary fines for disseminating a violative consumer-directed advert. The fines cannot be more than US$250,000 (about EUR183,000) for the first violation in a three-year period and not more than US$500,000 (about EUR366,000) for a subsequent violation in each three-year period (*FDAAA, § 901(d) amending the FDCA by adding § 301(kk) and § 503B (21 U.S.C. § 331)*).