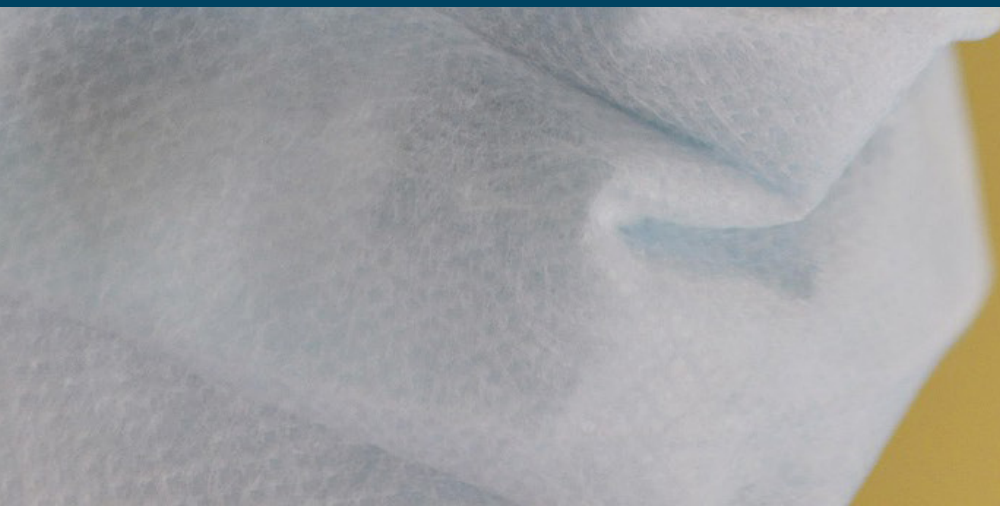




FACT OR FICTION

What Healthcare Professionals Need to Know about
Pharmaceutical Marketing in the European Union



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Acronyms

| | |
|-------|---|
| ABPI | Association of the British Pharmaceutical Industry |
| COPD | Chronic Obstructive Pulmonary Disease |
| DTCA | Direct-To-Consumer Advertising |
| EC | European Commission |
| ECC | European COPD Coalition |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EU | European Union |
| HAI | Health Action International |
| IPCRG | International Primary Care Respiratory Group |
| KOLs | Key Opinion Leaders |
| LIF | Läkemedelsindustriföreningen (Sweden) |
| NHS | National Health System (United Kingdom) |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MPA | Medical Products Agency |
| OTC | Over-The-Counter |
| PMCPA | Prescription Medicines Code of Practice Authority |
| R&D | Research and Development |
| US | United States of America |

Preface

Healthcare professionals are highly exposed to pharmaceutical marketing activities. Evidence shows that exposure to information from pharmaceutical companies does not lead to net improvements in prescribing, but can negatively affect prescribing and professional behaviour (Wazana, 2000; Norris et al., 2005; WHO & HAI, 2009; Spurling et al., 2010).

Education about pharmaceutical promotion can affect trainees' awareness and attitudes, which helps counter the influence of promotional practices (Norris et al., 2005; Carroll et al., 2007; Lea et al., 2010). Healthcare professionals come into contact with promotional materials during their studies. However, most medical students do not obtain adequate education on how to critically respond to pharmaceutical promotion (Mintzes, 2005; Mansfield et al., 2006; Austad et al., 2011). This leaves many healthcare practitioners unprepared for ethically challenging situations that ultimately impact their ability to objectively prescribe, or advise patients about, medicines.

85.2% of medical students surveyed in France (n=2,101) reported feeling inadequately educated about conflicts of interest arising from interactions with the pharmaceutical industry (Etain et al., 2014).

Being able to identify promotional activities and to understand their impact to medical practice enables critical appraisal. In not helping (future) healthcare practitioners to develop such skills, practitioners may be left to interpret misinformation as fact and to prescribe or dispense specific medicines where other treatment options should be considered.

This guide and associated workshops have been developed to address this oversight by providing an overview of pharmaceutical marketing practices and the ethical issues that arise from them.

Learning Objectives

- To identify and assess the methods used in pharmaceutical promotion activities.
- To understand the impact of pharmaceutical promotion techniques on clinical practice and public health.
- To learn about the European Union (EU) regulatory framework on pharmaceutical promotion and the problem of self-regulation.
- To enable critical appraisal of pharmaceutical promotion activities in a way that safeguards evidence-based medicine.

This guide and its workshop series build on the publication, *Understanding and Responding to Pharmaceutical Promotion: A Practical Guide*, produced by Health Action International, in collaboration with the World Health Organization, in 2009.

The examples used in this publication are not exhaustive, but are included to provide insight into the pharmaceutical industry's strategies and resources as case studies.

Most medical students
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Introduction

Medicines are an essential intervention of the healthcare system. However, their potential benefits, harms and affordability must always be weighed against that of alternative treatments, including the option to not medicate. In this way, best care is evidence-based and responsible. The rational use of medicines is crucial to protect patients' safety and the sustainability of healthcare systems.

Pharmaceutical companies fulfill an important role in producing medicines. However, they also have a responsibility to their shareholders to maximise profits and returns on investment. With the potential for sizable profits at stake, the pharmaceutical industry clearly has a vested interest in influencing which medicines are prescribed and dispensed to patients. Companies promote their products via various means to maximise profits.

Prescribers and dispensers of medicines play an important gatekeeper role in the health system. For this very same reason, they are often the key focus of the pharmaceutical industry's promotional activities. Product advertising and promotion is something we encounter on a daily basis. However, unlike other consumer products, the promotion of medicines has significant ethical considerations. Pharmaceutical marketing has three key potential effects:

- A negative impact on health outcomes of individuals and, potentially, their families and communities;
- The undermining of patients' trust in healthcare professionals as independent and evidence-based experts who protect their best interests; and
- A negative impact on the cost and sustainability of health systems.

Pharmaceutical regulations should ensure that commercial interests do not override the values of good clinical care, individuals and society. However, too often, regulatory frameworks are not effective in preventing the provision of deceptive information. Laws on pharmaceutical promotion are not restrictive enough and there is too much reliance on self-regulation for the oversight of promotional activities. Codes of conduct created by the pharmaceutical industry to regulate itself are not dissuasive enough.

Increasingly, healthcare practitioners are relied upon to navigate the overwhelming quantity of pharmaceutical promotion materials and to appraise the therapies and medicines released onto the market. **Understanding the powers at play and how specific promotional activities are designed to influence healthcare professionals' decision-making is key to ethical clinical practice.**

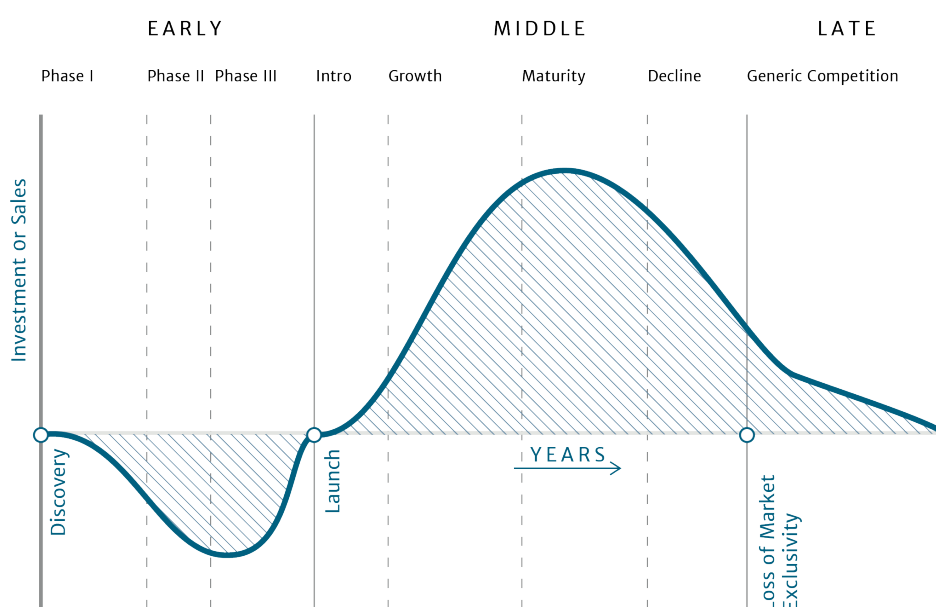


Promotion Across the Pharmaceutical Product Lifecycle

Promotion across the Pharmaceutical Product Lifecycle

The marketing strategy for most consumer goods aims to maximise profitability by increasing sales volumes. Most companies use a standard product lifecycle methodology that focuses on the introduction, growth, maturity and decline of a product to maximise profits. However, as **Figure 1** demonstrates, pharmaceutical company strategists say that a longer lifecycle that reaches across three distinct product stages should be considered: The Drug Life Optimisation Model (DLO).

FIGURE 1. The Drug Life Optimisation Model



Source: Bernard, 2013

As opposed to the more traditional approach, the DLO model incorporates early-stage development planning. According to pharmaceutical competition consultant, Stan Bernard, “successful launches are actually won in the pre-launch years, usually in clinical phases II and III” (2013). DLO advocates claim that this approach allows companies “to plan and execute pre-launch activities much earlier to position the product and generate stakeholder awareness and demand. Moreover, it enables the commercial launch team to pre-empt counter-launches, brand pre-positioning, and unfavourable messaging from competitors.”

One of the main concerns of this model is that it leverages industry-sponsored clinical trials as a marketing tool. Companies are often criticised for favouring the publication of studies with positive results and for practising selective reporting of outcomes within published studies to make the therapy look more promising. Some well-known examples include the misreporting of trials of antidepressants, class I anti-arrhythmic medicines, and selective COX-2 inhibitors (McGauran et al., 2010; Gøtzsche, 2011; Gagnon, 2012; Le Noury et al., 2015). Cases, like that of Tamiflu® (oseltamivir), demonstrate the way in which the lack of transparency of clinical trial data and selective information sharing influence the way in which a product is positioned, and the impact it can have on public health (see **Box 1**)

The DLO approach also calls for pharmaceutical companies to abandon the idea that product support should decline at the point of patent expiration, but to initiate generic competitive planning before a brand's market launch. Some of the strategies proposed to maximise business impact throughout the medicine's entire life involve the use of regulatory and legal tools, manufacturing, distribution and formulation changes, mergers and acquisitions, public relations and stakeholder reputation advocacy.

FIGURE 2. Advertisement by Farmaindustria, Spain's pharmaceutical industry association, regarding branded medications

Cuando se elige un Medicamento de Marca se obtiene mucho más. Aunque cueste lo mismo.

Cuando eliges un medicamento de marca, no sólo estás eligiendo un medicamento que se adecúa perfectamente a lo que necesitas, sino que estás obteniendo mucho más. Porque eligiendo la marca apoyas la investigación de nuevos fármacos, el desarrollo científico y la adherencia terapéutica. Y además, cuesta lo mismo. Elige marca.

farmaindustria

This advertisement by Farmaindustria pushes the use of originator (branded) medicines over generic medicines. It depicts a branded (originator) medicine. The caption at the bottom reads: When you choose a branded medicine, you are not only choosing a drug that meets your needs perfectly—you are getting much more. By choosing the brand, you support the investigation of new medicines, scientific development and therapeutic adherence. Besides, it costs the same. Choose a brand. The words rising from the bottle say: investigation, corporate responsibility, easy recognition, trust, high-quality standards, adherence, therapeutic progress and scientific development.

Source: Farmaindustria, 2014

BOX 1

The Tamiflu Case

The case of Tamiflu® (oseltamivir) is a well-known example of reporting bias and illustrates the negative impact that a lack of clinical trial data transparency has on public health.

The use of Tamiflu® was widely recommended during the outbreak of the 2009 flu pandemic. The United States (US) Department of Health and Human Services, the Advisory Committee on Immunization Practices (which issues recommendations to the US Centers for Disease Control and Prevention), the Australian Therapeutic Goods Administration and the European Medicines Agency (EMA) all praised Tamiflu®, saying it was effective in reducing complications from influenza (Doshi et al., 2012).

Claims on the effectiveness of Tamiflu® were largely based on a 2003 company-sponsored meta-analysis. This review combined 10 randomised clinical trials conducted during the late 1990s by the manufacturer, Roche. The analysis suggested that oseltamivir treatment for influenza reduced secondary complications and hospital admissions (Gøtzsche, 2011; Doshi et al., 2012). This led governments worldwide to stockpile large quantities of this expensive medicine.

Public understanding about the true effects of Tamiflu® started to shift following a systematic review initiated in 2010 by independent researchers from Cochrane. The inclusion in the review of previously unpublished clinical study reports (comprehensive documents prepared by the pharmaceutical industry for marketing authorisation applications) was crucial to uncovering its true effects.

The Cochrane review concluded that there is no credible evidence that Tamiflu® is effective in reducing complications from influenza (particularly pneumonia), nor reducing the risk of hospitalisation or death. Its findings also suggested a minimal effect when Tamiflu® is used as a prophylactic agent to prevent the occurrence of influenza. According to the authors, the small benefits noted in symptomatic improvement and lack of efficacy in preventing serious outcomes need to be balanced against the adverse effects found in the medicine (Jefferson et al., 2014).

This independent assessment revealed a multisystem failure in the reporting of clinical data. Whilst a number of serious adverse events were mentioned in the unpublished trial records, they had been omitted—even denied—in some of the most cited publications. In some cases, published studies were also found to be ghostwritten (Cochrane, 2014; Loder et al., 2014).

The Tamiflu® case serves as a further example of the extent to which the lack of transparency of clinical trial data puts people at greater risk of harm and leads public health systems to waste resources on expensive and ineffective treatment options.

True Innovation or Just Marketing?

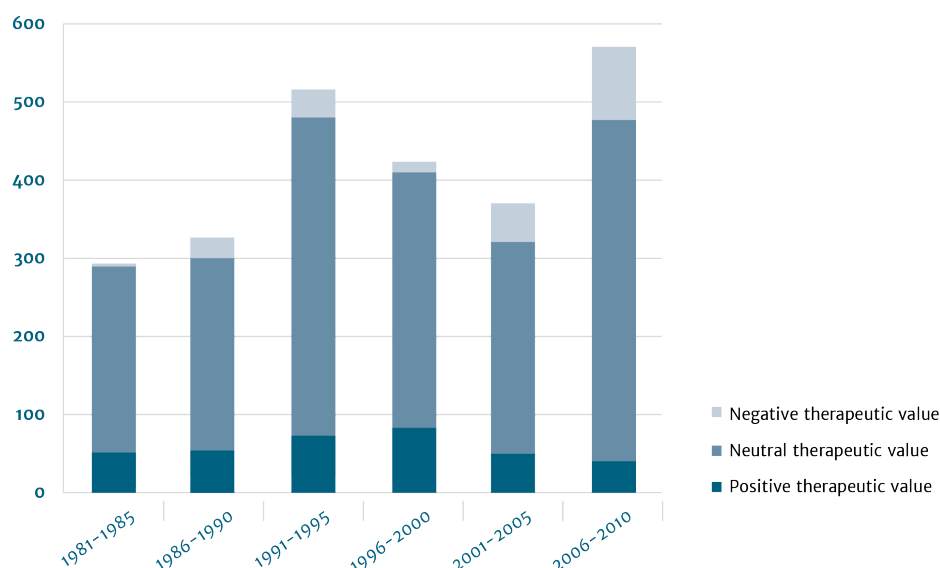
The race to commercialise the next blockbuster medicine has long dominated the pharmaceutical business model. Under this model, true product innovation has been limited. Most product releases have instead focused on the creation of me-too medicines, which are priced 20–40% higher than existing products, for large population groups and are widely marketed to prescribers as the latest technology (Gagnon, 2015).

Figure 3 summarises the ratings performed by the independent French drug bulletin, Prescrire, about the therapeutic value of pharmaceutical treatments released onto the market since 1981. This assessment shows some distinct trends and suggests that the vast majority of medicines provide no true advance over existing treatments.

A 'blockbuster medicine' is a term used to describe a medicine that generates worldwide annual sales of at least \$1 billion.

'Me-too medicines' are medicines that are structurally similar to existing medications on the market with similar mode of action, but no evidence of therapeutic advantage over existing alternatives.

FIGURE 3. Prescrire's ratings for new drugs and indications (1981-2010)



The categories used here are a simplified version of those used by Prescrire. "Positive therapeutic value" corresponds to a Prescrire rating of "Bravo", "A real advance" or "Offers an advantage"; "Neutral therapeutic value" includes Prescrire ratings of "Possibly helpful" and "Nothing new"; and "Negative therapeutic value" equates to the Prescrire rating "Not acceptable" (Prescrire ratings in Gagnon, 2012).

A revealing inquiry by the European Commission's Directorate-General for Competition shows that between 2000 and 2007, originator pharmaceutical companies spent an average of 17% of their turnover from prescription medicines on research and development (R&D) worldwide. Expenditure on marketing activities accounted for 23% of their turnover (European Commission, 2009). This highlights a focus on increased commercial returns over true clinical advancement.

Since the mid-2000s, a more attractive regulatory environment for the development of orphan medicines has contributed to a move by pharmaceutical companies away from blockbusters towards 'niche busters' which target narrow and specialised markets. These speciality drugs often provide a marginal added therapeutic value (Gagnon, 2015).

The fact that such therapies initially target a small population group is used by companies as an excuse to justify exorbitant prices. The profitability of this model is evidenced by the fact that some of these niche busters have even achieved blockbuster status. One of the main concerns of the 'niche buster model' is that it increases the potential for off-label use as this becomes a tool to expand the market for medicines that have been approved for a very narrow indication (Gagnon, 2015; Gibson et al., 2015). Often, pharmaceutical companies facilitate promotional strategies that encourage prescribing beyond approved indications.

ACTIVITY 1

Create Your Own Marketing Campaign

Break into small groups (three to six people) and create a pharmaceutical product that addresses a specific health need. Prepare a presentation to the company board that follows the lifecycle of your product and present it back to the group.

- What key activities would you engage in during the development/clinical trial phase to maximise future sales of your product?
- What activities and techniques would you employ to increase sales of your product once it is released on the market?
- How will you protect your product's market share against competitors and, particularly, late in its lifecycle when patents expire?
- What kind of return on investment should your shareholders expect?



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Pharmaceutical Marketing

Pharmaceutical Marketing

The world is one big marketplace. We are bombarded with marketing messages daily, and whether we are aware of it or not, we are influenced by many.

FIGURE 4. Iconic brands



Traditional marketing techniques address the product, its price point, placement (distribution) and promotion. Positioning is a newer concept that addresses how a consumer perceives a brand or product, and is about how the mind processes and accepts or rejects new information based on prior knowledge and experience.

BOX 2

Marketing is a Battle of Perception, Not Products

Marketing strategist, Jack Trout, is best known for his concept of 'positioning', which revolutionised strategic marketing. In his 2008 book, *In Search of the Obvious: The Antidote for Today's Marketing Mess*, Trout argues that marketing is a battle of perception, not products.

He says that facts are an illusion—that there are no better products, but simply what the customer perceives to be true. Marketing is therefore about understanding and addressing how perceptions are formed and influencing what is perceived to be true.

According to Trout: "Truth is nothing more or less than one expert's perception. And who is the expert? Someone who is perceived to be an expert in the mind of someone else." He provides the following example:

"Some soft-drink executives believe that marketing is a battle of taste. Indeed, Coke has conducted some 200,000 taste tests that 'prove' the New Coke Formula tastes better than Pepsi-Cola. These tests also concluded that Pepsi-Cola tastes better than the original Coke formula, now referred to as Coca-Cola Classic. But who is winning the Cola battle? Sales of the 'best tasting' cola, New Coke Formula, is in third position and the apparently worst tasting cola is in first. You believe what you want to believe. You taste what you want to taste. Soft drink marketing is a battle of perception, not of taste."

Trout has also (by no coincidence) consulted for pharmaceutical giants, including Merck and Procter & Gamble.

If we use the above example and replace taste with the effectiveness of medicines, we can see that the highest-selling medicines may be those with the strongest marketing campaign—not the most effective.

Pharmaceuticals are not just a consumer good. They are substances with safety implications that are taken by patients often on the recommendation of a healthcare professional. They are also products that are subsidised (to a greater or lesser extent) by governments across the EU. In 2012, pharmaceutical expenditure accounted for 20% of all EU health expenditure, making it the third-largest cost after inpatient and outpatient care (OECD, 2014).

Prescribers and dispensers play a very important role in the rational use of medicines. For pharmaceutical companies, they often play a key role in their profitability.

In attempting to influence prescribing behaviours, pharmaceutical companies leverage some inherent characteristics of healthcare professionals:

1. Healthcare professionals are motivated by ‘better patient care’.

Healthcare professionals’ primary focus is the patient. They have both an ethical and fiduciary responsibility to place patients’ interests and care first. Therefore, anything that is to be marketed to a health professional must appeal to their interest in improving patient care outcomes.

2. Healthcare professionals are time-poor.

With full clinics, waiting lists and a full inbox, healthcare professionals are more time-poor than ever. They are seeking evidence-based shortcuts. This might include decision-making shortcuts, such as relying on information that is provided to them in clear, concise, peer-endorsed statements and pretty packages.

3. Healthcare professionals respect the scientific process and outcomes.

Clinicians are scientists. They need to understand the scientific process and data outcomes in order to prescribe a product. By providing scientific data in promotional activities, the pharmaceutical company builds trust and credibility in its product. But often, this information does not provide the full picture of a medicine’s effects.

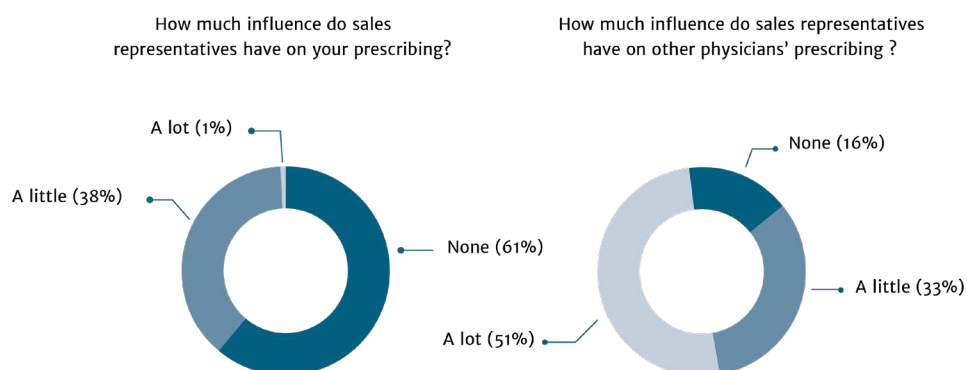
4. Many healthcare professionals are overwhelmed by product choice and availability.

The continuous deluge of new products onto the market has long strained the ability of healthcare professionals to remain on top of the new therapeutic choices available (Podolsky & Greene, 2008). At the same time, the internet provides a 24-hour global source of information for patients and their families to search for the latest and greatest product. This often translates into concrete demands to healthcare professionals about treatment. In addition, the promotion of ‘me-too’ medicines compounds this phenomenon. With increasingly more choices for healthcare professionals to prescribe and dispense for the same diagnosis, the stronger marketing campaign often wins.

5. Many healthcare professionals believe that they are not personally influenced by pharmaceutical promotion, but that their colleagues are.

Believing that only others are misled by marketing techniques is actually a common human trait that psychologists refer to as the illusion of ‘unique invulnerability’ (Sagarin et al., 2002).

FIGURE 5. Perceptions of influence on prescribing amongst internal medicine residents (n=102)



Source: Steinman et al., 2001

This attitude is also apparent in medical students. A 2012 survey of 1,038 medical students across eight German university hospitals found that 24.6% of respondents believed gifts would influence their future prescribing behaviour, while 45.1% thought gifts would influence their classmates' future prescribing behaviour (Lieb & Koch, 2013). **Figure 5** reveals similar findings from another study.

The First Step is to Admit You Are Human

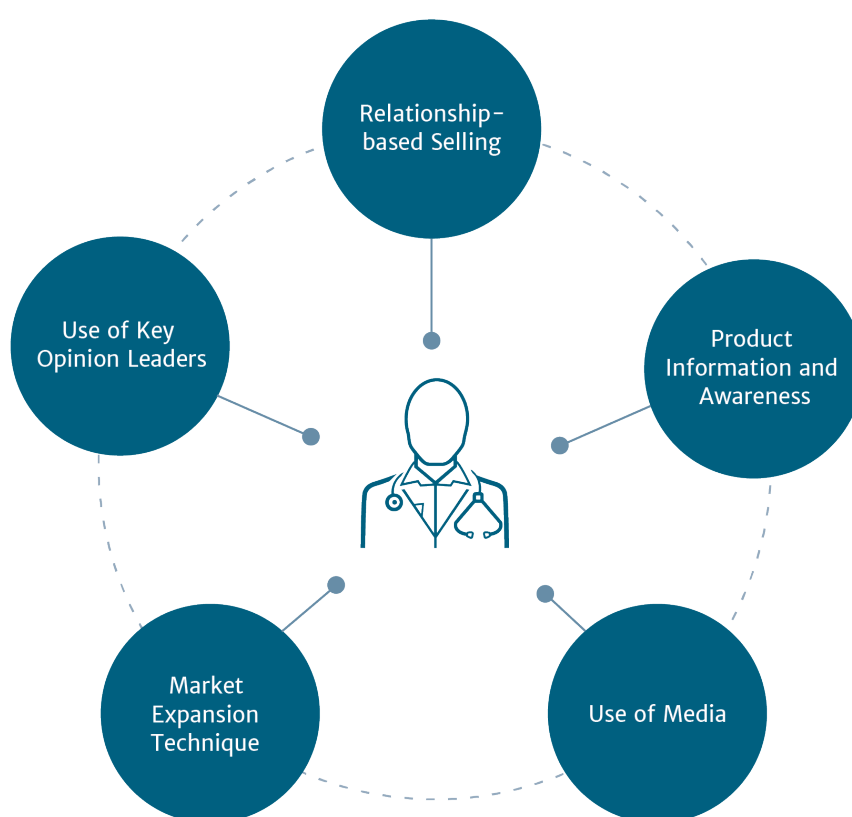
Healthcare professionals who are unaware of the use of social psychology to manipulate their behaviour will not try to avoid the resulting conflicts of interest. Such unrealistic optimism—that is, the belief that one is less at risk of a specified hazard than one's peers—is independent of age, gender and educational or occupational group (Sah & Fugh-Berman, 2013).

The first step towards critically appraising promotional activities is to understand and accept that you are individually vulnerable to subconscious bias.

Promotional Strategies Used by Pharmaceutical Companies

Pharmaceutical companies use what is called a ‘multi-channel’ approach to ensure health-care professionals receive the same messaging about products from different information sources (see **Figure 6**). Only by understanding the techniques used is it possible to critically appraise these messages and respond appropriately.

FIGURE 6. Promotional strategies used by pharmaceutical companies to influence product perceptions



A description of these strategies and their key implications for medical practices are outlined below:

1. RELATIONSHIP-BASED SELLING

Instead of using traditional sales tactics, relationship-based selling is a sales technique that focuses on building lasting relationships with clients—in this case, between healthcare professionals and pharmaceutical companies. The approach uses social psychology theory to foster a positive relationship and the development of trust and loyalty.

A. Sales Representatives

One of the most effective techniques for developing relationships that influence prescribing behaviour is one-to-one contact with sales representatives, or what is commonly referred to in the pharmaceutical industry as 'detailing'. In fact, sales representatives are highly trained in persuasion and influencing skills—nothing is coincidental or unplanned.

"It's my job to figure out what a physician's price is. For some it's dinner at the finest restaurants, for others it's enough convincing data to let them prescribe confidently, and for others, it's my attention and friendship...but at the most basic level, everything is for sale and everything is an exchange".

— Shahram Ahari, former pharmaceutical representative (Fugh-Berman & Ahari, 2007)

Interactions occur in both formal and informal settings. For example, sales representatives participate and speak at conferences and educational sessions. They also visit hospitals, pharmacies and general practitioners' surgeries. Exposure begins during the academic period. A 2010 survey amongst students at the University of Goettingen Medical School in Germany revealed that the proportion of students with direct contact with sales representatives increased from 21% in the first clinical year to 77% in the last year (Jahnke et al., 2014). Similarly, another survey found that 74% of the Norwegian students studied had experienced interactions with the pharmaceutical industry in the form of meetings or conversations involving a sales representative (Lea et al., 2010).

A 2009–2010 study of 179 doctors in Brittany, France, showed a statistically significant correlation between the number of meetings doctors had with pharmaceutical sales representatives and the number and cost of their prescriptions. The study found that **doctors who met most frequently with sales representatives were the most likely to prescribe drugs in ways that responded more to companies' commercial interests, instead of patients' best interests.**

Source: Foissset, 2012

The issue is that many healthcare professionals report relying on sales representatives for current medicines information. Some even list sales representatives and promotional literature as a key source of information (Norris et al., 2005). This is of significant concern because the **information provided by pharmaceutical sales representatives has been found to be incomplete and biased towards the benefits of the products being marketed** (Othman et al., 2010; Mintzes et al., 2013). The study by Mintzes and colleagues, which assessed information provided to physicians (n=255) during sales visits in Canada, the US and France, revealed that fewer than 2% of the reported 1,692 medicine-specific promotions included "minimally adequate safety information".¹ Even in France, where regulations on pharmaceutical promotions are stricter, information on serious adverse events were rare, and sales representatives made more unqualified safety claims. In spite of the lack of information on harm, in many cases physicians considered the information to be of good quality and expressed their intent to prescribe the medicine.

While healthcare professionals may believe that they are immune to promotional activities, the key reason pharmaceutical companies invest in sales representatives is that they are proven to increase sales. In fact, companies use 'response curves' to track the differential impact of varied promotional approaches on sales of a specific medicine, refining their techniques to target the right doctors with the right message at the right frequency through the right channel (Sah & Fugh-Berman, 2013).

1 By "minimally adequate safety information", the authors mean situations in which the sales representative mentioned at least one approved indication AND one serious adverse event AND one common non-serious adverse event AND one contra-indication and NO unapproved uses or unqualified safety claims (e.g., "this drug is safe").



Evidence about the lack of reliable information provided by sales representatives suggests that healthcare professionals would be better off avoiding such interactions. When confronted with sales representatives, claims about medicines' therapeutic profile should always be contrasted with regulatory information. Checking independent sources of information also aids in understanding treatments' effects.

B. Gift-giving

Gift-giving by pharmaceutical companies to healthcare professionals begins as early as in their academic training. Students may receive meals, sponsored lectures and social activities, textbooks, bags, stethoscopes and other items related to medical practice (Lieb & Koch, 2013; Jahnke et al., 2014). Inducements to healthcare professionals are aimed at indirectly influencing medical education, research habits and treatment decisions.

The more indirect the gift, the easier it may be for healthcare professionals to deny that accepting these gifts influences their practice. However, **all gifts create feelings of obligation and self-serving bias, which negatively influences prescribing practices** (Sah & Fugh-Berman, 2013; Smith et al., 2013). A study by Brennan et al. (2006) confirms that the impulse to reciprocate for even small gifts is a powerful influence over people's behaviour. Often unconsciously, it affects their objectivity causing them to reweigh information and choices in light of the gift.

Similarly, a 2009 study of medical students showed that subtle exposure to small pharmaceutical promotional items influences implicit attitudes toward marketed products (Grande et al., 2009). The authors of this study also observed a reversal of this effect in the setting of restrictive policies and more negative school-level attitudes towards pharmaceutical marketing.

Studies have shown that industry inducements are associated with prescribing patterns inconsistent with evidence-based guidelines, reduced generic prescribing, increased drug costs and biased requests for additions to hospital formularies.

Source: Smith et al., 2013

Gift-giving is not allowed in many professional settings to avoid undue influence. Just because the practice is permitted in some places does not make it ethical—and healthcare professionals should be wary of the practice.

2. PRODUCT INFORMATION AND PRODUCT AWARENESS BUILDING

A key marketing strategy of pharmaceutical companies is to ensure healthcare professionals know about their product, have information on the benefits of their product, and have easy access to trialling the product.

A. Clinical Guidelines

Clinical practice guidelines should help healthcare professionals make evidence-based decisions on treatment. However, **conflicts of interest amongst sponsors and authors of clinical guidelines have turned many of them into a pharmaceutical industry marketing tool** (Lenzer et al., 2013). A study conducted by Bindslev et al. (2013) examined conflicts of interest amongst the authors (n=254) of 45 clinical guidelines of drug treatments from 14 Danish medical speciality societies. The research revealed that 53% of the authors had conflicts and 43 of the 45 guidelines had one or more authors with a conflict of interest.²

² Conflicts of interest were coded to be present if authors had an affiliation with a company up to three years prior to the published guideline. The study authors noted that although some ties might be related to companies producing drugs not relevant to the guideline, this will likely be less important as guideline authors are usually affiliated with companies producing drugs in the areas where they are experts.

Only one of the 45 guidelines disclosed author conflicts of interest. The most common conflict was being a consultant, an advisory board member, or a company employee. Methods used for guideline development were only provided in 10 guidelines (22%) and just 27 (60%) used references in the text.

The case of the German S3 guideline on the treatment of psoriasis vulgaris with Raptiva® (efalizumab) shows that the involvement of experts with conflicts of interest in guideline development leads to medicines being judged more positively in comparison with judgements made by independent authors (Schott et al., 2013). The S3 guideline judged the available evidence as good and recommended the use of efalizumab for induction and combination therapy in psoriasis vulgaris. It also said that the medicine improved patients' health-related quality of life. Raptiva® ended up being withdrawn from the market in 2009 (EMA, 2009).

It is vitally important to ensure full transparency of guideline development for doctors' awareness about potential biases. In Box 3, Lenzer et al. (2013) provide a list of red flags that should raise substantial skepticism amongst guideline readers.

BOX 3

Red Flags for Clinical Guidelines

- Sponsor is a professional society that receives substantial industry funding.
- Sponsor is a proprietary company, or is undeclared or hidden.
- Committee chair(s) have any financial conflict*.
- Multiple panel members have any financial conflict*.
- Any suggestion of committee stacking that would pre-ordain a recommendation regarding a controversial topic.
- No or limited involvement of an expert in methodology in the evaluation of evidence.
- No external review.
- No inclusion of non-physician experts/patient representatives/community stakeholders.

* Includes a panellist with either, or both, a financial relationship with a proprietary healthcare company and/or whose clinical practice/specialty depends on tests or interventions covered by the guideline.

But even more important than transparency, safeguards to avoid conflicting situations in guideline development must be put in place to uphold evidence-based medicine and patients' health. When confronted with clinical guidelines with conflicts of interest, independent sources of information can help inform optimal treatment decisions.

B. Samples

Providing samples or 'market seeding' is a highly successful strategy for companies to increase the sales of new (and often more expensive) medicines. Pharmaceutical companies use sampling to increase brand awareness amongst healthcare professionals and patients.

Doctors might suggest they accept samples to reduce patients' cost barriers to access, but **pharmaceutical companies rely on converting a percentage of sample users to repeat users.**

In fact, evidence reveals that patients receiving free samples end up facing higher out-of-pocket prescription costs than those who do not (Alexander et al., 2008). For patient care and the healthcare system, medicine sample availability can also involve poorer compliance with clinical guidelines. A study from Boltri et al. (2002) assessed prescribing practices amongst doctors in a family practice outpatient clinic. It found that, following prohibition of sample use, the prescription of first-line anti-hypertensive therapy rose from 38% to 61%. Another study revealed that resident physicians who received free samples were more likely to prescribe heavily advertised and more expensive medicines than their peers who did not receive free samples (Adair & Holmgren, 2005).

3. USE OF MEDIA

Pharmaceutical companies use health media to reach professionals and influence their perception of specific treatments or medicines. Key to this is ensuring that the product information appears as a credible source of medical information. Increasingly, media is also being used to reach consumers, either directly or through covert advertising. Companies are also investing more and more in digital marketing, which provides a new range of venues for the promotion of their products. Commonly-used media methods used by the pharmaceutical industry include:

A. Journals and Medical Literature

Peer-reviewed journals are an excellent source of information on scientific findings. But all is not as it seems. The information included in these journals might include information directly or indirectly provided by pharmaceutical companies as part of their marketing strategies in the form of:

— Advertising and sponsored content

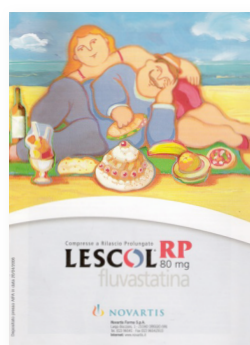
Journal and website editors often fill space with commercial advertising and sponsored content because they rely on the revenue stream as part of their business model.

Print advertisements in medical journals are of high value to pharmaceutical companies because they increase sales effectively. Companies generally invest in advertising the newest,

A study of German continuing medical education journals identified an increased occurrence of positive editorial commentary regarding specific medication in instances where the journal ran advertisements for the same product. This relationship was more prominent for free journals that rely significantly on advertising revenue.

Source: Becker et al., 2011

FIGURE 7. Advertisement sending the message that “only the pill can make the difference”



This advertisement for Lescol® (fluvastatin sodium) was published in the April 2008 issue of Rivista SIMG (Journal of the Italian Society of General Practitioners). Lescol® is a statin class of medicines used to treat high cholesterol when diet and other lifestyle changes do not work. The summary of the product characteristics states, “For best results in lowering cholesterol, it is important that you closely follow the diet suggested by your doctor.” The doctor who provided this example said: “What I can understand, as a doctor, after looking at this image? It doesn’t matter what I advise my patients to eat; it isn’t worth them trying to change their lifestyle behaviours. Only the pill can make the difference!”

Source: Healthy Skepticism, 2009

FIGURE 8 Advertisement showing unsubstantiated and misleading claims

8,000,000 AMERICANS WITH TYPE 2 DIABETES HAVE NOT REACHED THE ADA A1C TARGET^{1,2}

13,000,000 ARE OVERWEIGHT³

It's time for plan B

BYETTA[®] delivered powerful A1C reductions with weight loss,* giving your patients with type 2 diabetes a chance at success.

When BYETTA 10 mg BID was added to a patient's type 2 diabetes treatment plan in a 30-week clinical trial (N = 147),* there was a

1.5% A1C reduction

8-lb weight loss

unpublished 'data on file'

surrogate outcome

unapproved indication

small open-label unpublished trial

BYETTA is not indicated for the management of obesity, and weight change was a secondary outcome in clinical trials.

BYETTA is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control.

Important Safety Information

BYETTA is not a substitute for insulin in insulin-requiring patients, and should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Patients should be observed for signs and symptoms of acute pancreatitis (persistent severe abdominal pain which may be accompanied by vomiting). If pancreatitis is suspected, BYETTA and other potentially suspect drugs should be discontinued.

Patients should be observed for signs and symptoms of hypoglycemia.

BYETTA is not recommended for use in patients with end-stage renal disease, severe renal impairment, or severe gastrointestinal disease.

Patients should be observed for signs of altered renal function, including those who are taking concomitant agents known to affect renal function/hydrolytic status.

Patients receiving BYETTA concomitantly with a sulfonylurea have an increased risk of hypoglycemia. To reduce the risk of hypoglycemia, clinicians may consider reducing the sulfonylurea dose.

The most common adverse events associated with BYETTA were nausea, vomiting, diarrhea, feeling tired, dizziness, headache, and dizziness.

For additional safety information and other important prescribing considerations, please see following page for Brief Summary of Prescribing Information.

Visit www.ByettaUSA.com for more information.

Byetta[®] exenatide injection

This advertisement for Amylin and Eli Lilly's Byetta® (exenatide injection) for type 2 diabetes appeared in the 20 August, 2008, issue of the Journal of the American Medical Association and elsewhere. It promotes a medicine for type 2 diabetes on the basis of a surrogate outcome assessed in unpublished trials, and as an off-label treatment for obesity. Three of the four references provide information about diabetes, but not about the specific medicine, Byetta®. The fourth reference is "data on file" and has not been subjected to peer review.

Source: Healthy Skepticism, 2009

most expensive drugs (Fugh-Berman et al., 2006). The **low quality of journal advertising has been identified as a global issue**, with advertisements containing unsubstantiated and misleading claims and the omission of essential information, such as on contraindications, side-effects and warnings (Othman et al., 2009).

Ideally, medical journals should not include advertisements promoting health products. But if they do, advertisements, at a minimum, should contain the information listed by the WHO's Ethical Criteria for Medicinal Drug Promotion (1988):

- Name(s) of the active ingredient(s) using either international nonproprietary names (INN) or the approved generic name of the drug;
- Brand name;
- Content of active ingredient(s) per dosage form or regimen;
- Name of other ingredients known to cause problems;
- Approved therapeutic uses;
- Dosage form or regimen;
- Side-effects and major adverse drug reactions;
- Precautions, contra-indications and warnings;

- Major interactions;
- Name and address of manufacturer or distributor; and
- Reference to scientific literature, as appropriate.

This list can serve as a basis for healthcare professionals to critically appraise advertisements. It is also important to check whether the references correspond to research sponsored by the company commercialising the product and if the referenced articles have been published in peer-reviewed journals (WHO & HAI, 2009).

Sponsored content should also be critically appraised. This information is likely to come from companies manufacturing health products. Sponsored content can take the form of disease-specific articles and conference updates, for example, and be part of a sponsored supplement. According to Steinbrook and Kassirer (2014), even supplements hamper a journal's reputation. The sources of funding for such materials can bias their content because of preferential treatment for certain topics and points of view. Serious ethical considerations particularly arise when it is not clearly indicated to the reader that journal content is sponsored. The absence, or hidden nature, of branding may make readers more susceptible to accepting the information as independent when, in fact, it promotes the sponsor's interests. A prominent example involved the collusion of Elsevier, publisher of *The Lancet*, and Merck to produce a fake journal, *The Australian Journal of Bone and Joint Medicine* (AJBJM) to promote Vioxx® (rofecoxib) and other products from the company. The AJBJM was only one of a series of fake journals published by Elsevier (Jureidini & Clothier, 2009).

— Ghostwriting and Guest Authorship

The use of key opinion leaders (KOLs) to either endorse or co-author publications is another strategy used widely by pharmaceutical companies. Academic authorship enhances the credibility of industry publications and masks their commercial function to promote a product (Matheson, 2011).

In fact, **health technology companies often engage renowned researchers and clinicians to “author” papers despite having little or no involvement** in the its writing or the research reported in it (Gøtzsche et al., 2009; Murray et al., 2010). Specific ‘medical communications’ agencies facilitate this practice by ghostwriting a manuscript that is then, by agreement, published under the name of a KOL. At the same time, the role of commercial writers is not acknowledged or is simply downplayed by listing them as contributors in the small print instead of authors (Matheson, 2011).

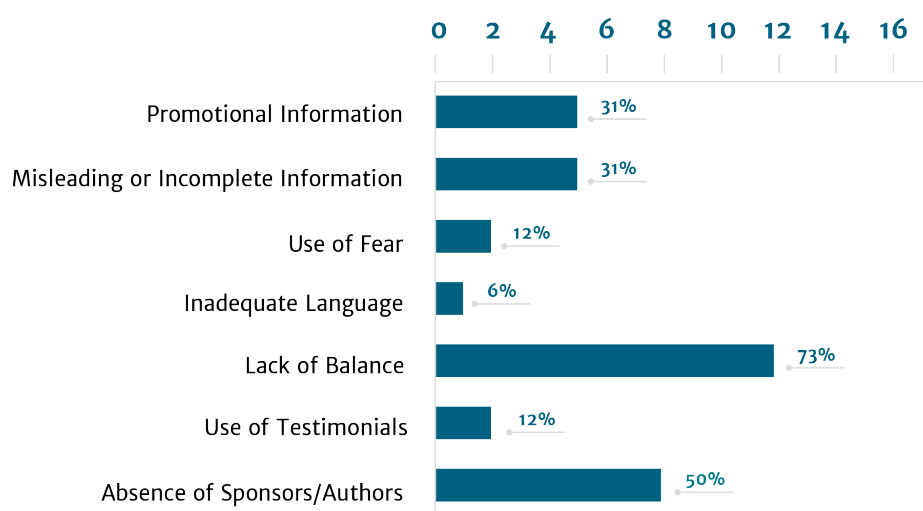
The industry claims these activities are ethical, but this is disingenuous and rests on two strategies: a) Leveraging weak definitions or convenient understandings of concepts, such as accountability, responsibility, authority, intellectual contribution, contributorship, guest authorship, and ghostwriting; and b) the exploitation of flaws in publication guidelines (Matheson, 2011).

Whilst this lack of transparency is a blatant violation of scientific integrity, it appears to be widespread. A 2008 survey assessing the prevalence of honorary and ghost authors in six leading general medical journals found evidence of guest and ghost authorship in 21% of articles. In particular, the prevalence of ghost authorship was 12% in research articles, 6% in reviews and over 5% in editorials (Wislar et al., 2011).

B. Direct-to-Consumer Advertising

Direct-to-consumer advertising (DTCA) is banned in the EU for prescription medicines, but is allowed for companies to provide the public with information on health and diseases as long as there is no direct or indirect reference to a pharmaceutical product. However, such campaigns raise concerns from the perspective of their underlying purpose and the quality of information provided. A study from Leonardo Alves et al. (2014), which explored the presence of industry-sponsored disease-awareness campaigns in printed Dutch media, revealed low compliance with national and international regulatory guidelines (Figure 9). According to the authors, a key concern is that the context in which the information is provided is likely to support treatment with the sponsor's product. Available research shows that public information and disease awareness campaigns prompt people to seek medical care (van Nuland & Damen, 2010) and that **prescription rates increase for the medicine marketed by the campaign's sponsor, even if the drug is not explicitly mentioned** ('t Jong et al., 2004).

FIGURE 9. Non-compliance of disease awareness campaigns (n=16) per key criteria



Source: Leonardo Alves et al., 2014

CASE STUDY

Use of Public Health Campaigns

This 2007 campaign by Pfizer in Portugal aimed to encourage smoking cessation. It reads, "More than six weeks without smoking and no arguments yet. Stop smoking without dramas. Visit your doctor."

What is not included is why Pfizer has an interest in people 'kicking the habit'. Pfizer manufactures a prescription-only medicine used for smoking cessation. Pfizer ran a promotional campaign for this product under the guise of a public health campaign. It flirts with the edges of the EU-wide ban on direct-to-consumer advertising.

Pfizer, along with GlaxoSmith-Kline, Boehringer Ingelheim and Novartis, have all funded the European COPD Coalition (ECC) "an alliance of stakeholders involved in preventing and treating [chronic obstructive pulmonary disorder or COPD], and caring for COPD patients."

Other members are listed as the International Primary Care Respiratory Group (IPCRG) and the Dutch Lung Alliance (LAN), both of which list some of the above-mentioned companies as corporate members on its website, as of July 2015.



Source: HAI & CEO, 2012

C. Digital Marketing

The introduction of new digital technologies continues to change the way in which we access information. With the rise of smart devices, both healthcare professionals and consumers are increasingly reliant on the internet for medical information.

Pharmaceutical companies currently spend 25% of their marketing budgets on digital technologies.

Source: Manz et al., 2014

The benefits of using digital resources cannot be ignored. In fact, the possibilities of digital technology provide an exciting opportunity for how we practice health care.

At the same time, it is important to bear in mind that digital also has the ability to surpass other marketing methods by turning a transactional consumer into a fan (Sashi, 2012). The engagement of healthcare professionals and consumers through digital mediums is becoming entwined with everyday activities and looks only to increase in coming years with the influx of the Millennial Generation into the workforce.

Companies are currently investing in this trend, replacing traditional promotional activities with product websites, search engine optimisation and social media campaigns. Digital marketing is changing the way pharmaceutical companies communicate with healthcare professionals through online events, product updates to their inbox, webinars, and leveraging customer service portals. Sites, such as Doximity (US) and Sermo (global presence, including European countries), used by healthcare professionals to read medical news, obtain continuing medical education (CME) credits and liaise with peers, incorporate promotional tools, like advertisements, sponsored discussion forums and recruitment of doctors, for focus group participation (Manz et al., 2014). Such platforms can also incorporate games that serve a marketing purpose. One example is Sermo's 'Alzheimer's Challenge' game, which, according to Manz and colleagues (2014) "allowed physicians to read through clinical trial data (in a format similar to print journal advertisements) for a brand name medication and answer questions about its indications to earn points redeemable for cash."

Consumers are also increasingly targeted through social media channels. Allergan plc has launched the **#ActuallySheCan** advertising campaign, which targets tech-savvy 'Millennials' through social media channels, like Facebook, Twitter and Instagram (Tadena, 2015). The campaign focuses on female empowerment using celebrity spokespeople, but, in fact, leads healthcare professionals and consumers to branded and unbranded information on birth control, a product manufactured by Allergan plc.

FIGURE 10. Advertisements, including celebrity endorsements, from the #actuallyshecan campaign.



Source: www.actuallyshecan.com, 2015; www.instagram.com/mirandakerr, 2015



Companies are increasingly investing in the development of self-diagnosis applications (known as 'apps') for consumers. Information apps for doctors are also being widely used. One example is Epocrates, an app that provides information about medicine indications, interactions and insurance coverage. Users' search history is tracked and targeted 'DocAlerts' (often sponsored by companies) appear on the screen (Manze et al., 2014). Promotional messages try to sway healthcare professionals' choice of which medicines to prescribe. Concerns have been raised about the fact that apps promote more expensive and sometimes less effective drugs (Wilson, 2011).

Digital marketing poses some important challenges to healthcare professionals. It reinforces companies' direct contact with patients. The pharmaceutical industry is calling this the move towards 'patient-centric' care or 'patient solutions'. At face value, this is in line with empowered consumers. But it also signals a potential shift away from healthcare professionals and towards the patient as a customer. For the patient, this likely encourages self-diagnosis. For the healthcare professional, this may result in increased demands from patients for a specific treatment.

In addition, the dissemination of misinformation on medicines is prolific. Healthcare professionals must try to be vigilant in understanding the evidence in order to identify and counter false claims.

4. MARKET EXPANSION

Creating a need for a product is a core marketing strategy to create or expand markets and identify untapped revenue sources. Market expansion techniques redefine the use of a product or the target market to which it applies. It therefore expands sales and revenue. Pharmaceutical marketing tries to expand medicines use through various means:

A. Disease Mongering

Disease mongering consists of widening diagnostic boundaries to expand markets for new medicines and promote 'awareness' of the disease to boost demand. The most significant impact of disease-mongering is when diagnostic criteria become blurred and patients receive unnecessary treatment or the wrong treatment. In one instance, up to 76% of the total adult population of a county in Norway could have been considered to be at 'increased risk' of cardiovascular disease because of the continual lowering of thresholds for the treatment of blood pressure and lipids (Heath, 2006). Disease mongering can include turning ordinary conditions into medical problems, considering mild symptoms as serious, treating personal problems as medical, seeing risks as diseases, and framing prevalence estimates (Moynihan et al., 2002).

BOX 4

The Viagra and Addyi Stories

Erectile dysfunction (ED) is clinically defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. However, there is **no universal consensus or agreed criteria** as to how consistent the problem must be, and for what duration it should last to fulfil this definition (Tsertsvadze et al., 2009).

Pfizer famously seized the opportunity created by this ambiguity in the clinical definition presented and repositioned ED as a 'lifestyle' medical problem affecting a much broader group (Lexchin, 2006). In doing so, Pfizer increased the perceived prevalence of ED, which immediately expanded the potential Viagra® (sildenafil) market to 'normal' men who wished to enhance their ability to achieve and maintain an erection.

On its website, Pfizer states that, "About 50% of men over 40 have some degree of ED (July 2015)."

Had the use of Viagra® been limited solely for cases of ED due to organic causes (such as spinal cord damage, vascular issues, or diabetes), the medicine would probably have been a modest success for Pfizer. Instead, it became a blockbuster reported to be earning the company £1 billion per year (Sample, 2009).

In August 2015, the US Food and Drug Administration (FDA) approved Addyi® (flibanserin) for the treatment of premenopausal women with hypoactive sexual desire disorder. Warnings include severely low blood pressure and loss of consciousness, particularly when drinking alcohol (FDA, 2015). The company, Sprout Pharmaceuticals, had instigated a grassroots marketing campaign for the medicine to be approved. It accused the FDA of sexism for approving medicines for male, but not female, sexual dysfunction with the help of advocacy groups sponsored by the company (Roehr, 2015). Public Citizen, an independent consumer organisation, criticised the FDA's decision and predicts that the drug will cause "serious dangers to women, with little benefit" (Clarke & Pierson, 2015).

B. Promoting Off-label Uses

Off-label use is the prescription of a medication in a manner different from that approved by the authorities. This may include use for a different clinical indication or dosage, or for a different sub-population, such as children (Radley, 2006).

Commercially, increasing off-label use means larger revenues from larger user populations, especially for products with narrow indications. To increase sales, pharmaceutical companies often covertly promote off-label use even where such promotion is illegal. Off-label use is promoted, for example, through industry-paid KOLs, CME sponsored by companies, abstracts and posters published as part of a conference, and in medical journals (Fugh-Berman & Melnick, 2008).

Off-label prescribing occurs for almost all medicine classes and is particularly common for certain therapies. A well-known example is new biological medicines for cancer treatment.

Some studies show that off-label administration of these medicines is as much as 75% (Carneiro & Costa, 2013). Off-label prescribing of otherwise approved indications may be clinically acceptable in some justified situations. However, such use is experimental and has not been subject to regulatory review of efficacy and safety for that indication. This mandatory review protects the patient, but with off-label use, this safety net often does not exist (Fugh-Berman & Melnick, 2008). For this reason, off-label use should always be addressed with caution, following the review of high-quality, unbiased information and close monitoring.

BOX 5

The Mediator Story

Mediator® (benfluorex) was licensed to treat diabetes, but was widely misprescribed as an appetite suppressant for people with common weight problems. The medicine was on the market for 30 years and was available in France, Portugal, Luxembourg, Greece, Italy and Spain. Despite a succession of safety warnings, it was only withdrawn in France—its biggest market—in 2009. Mediator® was estimated to cause up to 2,000 deaths (Schofield, 2011; European Parliament, 2012).

A factual chronology about the events surrounding Mediator®, compiled by the independent drug bulletin, Prescrire (2011), showed that Prescrire had flagged the poor level of evidence and the dubious harm-benefit balance for benfluorex as early as 1997. In June 2010, a book by the pneumologist, Irène Frachon, began to show the extent of the harm caused by Mediator®. Despite this, a lawsuit by the marketing authorisation holder, Servier, forced the book's subtitle, "How Many Deaths?" to be censored. The issue with Mediator® hit the headlines in October 2010 when the French newspaper, Le Figaro, published the results of an official study, which estimated a high number of deaths due to the medicine as a result of pulmonary adverse effects and heart valve damage (Prescrire, 2011).

The Mediator® disaster was a wakeup call for French policy-makers. In late 2011, several new regulations were passed, including greater transparency, better management of conflicts of interest, and new restrictions on off-label prescribing—the latter seen as a response to the off-label promotion of the medicine (Prescrire, 2012; Gaffney, 2013). The EU legislation on pharmacovigilance was amended in 2012 following review of the case (European Commission, 2012).

C. Volume through Adherence

Not all incremental pharmaceutical sales volumes come through additional consumers. The pharmaceutical industry is motivated clinically, but also financially, to solve the problem of non-adherence (when patients do not start or refill their prescription). This can equate to billions in lost sales for companies (Lamkin & Elliott, 2014; Davies, 2015).

Pharmaceutical companies design adherence programmes mainly for expensive, patented drugs. The problem of such programmes lies in their underlying financial motive. Whilst they might be delivered by someone that patients' trust, such as a nurse, pharmacist, or even other patients, and come across as medical care, they are part of companies' marketing strategies.

The ultimate goal is to keep patients on the therapy longer (Lamkin & Elliott, 2014). In this way, adherence is not one-off advertising; it involves changing attitudes and beliefs through long-term programmes with consistent, ongoing touch points with the patient.

The benefits of modern technology also come into play here with use of text messaging and smart device applications.

Adherence initiatives reported to be in use include:

- text message reminders;
- point-of-sale packs and/or loyalty cards;
- app-based logs and reminders;
- use of online medication or condition management services;
- online patient education and/or adherence coaching;
- comprehensive phone-based relationship programmes to motivate and educate patients; and
- connected medication devices.

In a recent survey of pharmaceutical companies, 97% of respondents thought that lack of adherence has a significant impact on patient outcomes and 84% indicated that lack of adherence has a significant impact on revenues. Two out of three respondents had attempted, were planning, or were currently implementing or piloting adherence initiatives (Davies, 2015).

From a clinical perspective, patients' compliance with treatment decisions informed by accurate and unbiased information is of utmost importance. Independent initiatives that genuinely promote compliance with treatment and rational use can help to improve health outcomes. However, appropriate medicine use should never be the pretext under which pharmaceutical products are being covertly promoted. Pharmaceutical company-led adherence programmes should be critically appraised.

5. USE OF KEY OPINION LEADERS (KOLS)

In marketing, the use of KOLs (also called key influencers) is a common practice used to affect purchasing behaviour by associating a product or brand with a person who is respected and trusted by the target audience (Sah & Fugh-Berman, 2013). In mainstream marketing, examples include use of celebrity product endorsements, opinion editorials, social media campaigns, guest speakers and product placement on, or near, iconic people.

The idea is that if a KOL mentions, is seen with, or endorses a product, the product becomes more credible and viewed positively by the target audience.

In pharmaceutical marketing, **KOLs range from highly respected academics, healthcare professionals or researchers**. They are often either under a commercial agreement, or simply receive some sort of agreed benefit or return for their services, like travel, accommodation, public profile and publicity.

"Key opinion leaders were salespeople for us and we would routinely measure the return on our investment by tracking prescriptions before and after their presentations. If that speaker didn't make the impact the company was looking for, then you wouldn't invite them back."

— Kimberly Elliott, former US-based pharmaceutical sales representative (Moynihan, 2008)

"Never forget that, on average, your expensive, hard-fought efforts to get new patients on your drug are delivering half of what they should be delivering. It's worth some effort and reflection to figure out how to put together a cohesive adherence approach to change this."

Source: Dolgin in the industry publication, *eye for pharma*, 2015

KOLs turn out to be an effective source of revenue for companies. According to a study by Merck, KOL-led discussions with physicians provide a better return on investment compared to meetings with sales representatives (Scott & Martinez, 2005).

A. Key Opinion Leaders under Commercial Agreements

Pharmaceutical companies engage KOLs under formal commercial agreements to act as spokespeople in promoting their products. The level of transparency of this product endorsement may range from obvious promotion to subtle inclusion in presentations, public forums, discussions with regulatory authorities, peers and/or social media followers.

Under the so-called ‘**speakers’ bureau**’ system, healthcare professionals are recruited and trained by pharmaceutical, medical device and biotechnology companies to deliver product information to their peers in exchange for a fee. Recruitment and training of KOLs is also outsourced to independent firms (Reid & Herder, 2013; Sismondo, 2013).

A business intelligence report showed that in pharmaceutical companies of all sizes, the average fee paid to a doctor for a ‘scientific speech’ exceeds \$3000 (Cutting Edge Information, 2008; Moynihan, 2008).

The practice is reminiscent of tactics used by the tobacco industry in promoting the safety of smoking (**Figure 11**).

FIGURE 11. The “More doctors smoke Camels” advertising campaign (1940-49) by the R. J. Reynolds Tobacco Company, 1946



Source: Stanford School of Medicine, 2015

FIGURE 12. Dr Oz



Source: Garcinia Cambogia Where to Buy, 2015

Dr Oz is a well-known key opinion leader. From November 2013 to July 2014, he received \$1.5 million in payments from health technology companies, including payments for promotional speaking and other activities, as well as royalties (Pro Publica, 2015.) Visit the Dollars for Docs website, which provides information about industry payments to doctors based on the United States Government's Open Payments Registry.

B. Key Opinion Leaders as Educational Speakers

Expert clinicians, researchers and academics are often invited to share new clinical findings or a treatment pathway with peers at health conferences. Their audiences often assume they are being informed about the product in an impartial way, but this is unlikely in conference settings controlled by the industry (Boumil et al., 2012; Smith et al., 2013).

For example, often a scientific conference or CME event is sponsored by one or multiple pharmaceutical brands. By no coincidence, the treatment pathway to be presented will often involve, or be relevant to, a product these companies manufacture. This marketing strategy is particularly effective because presentations provided by peers are unlikely to be perceived as advertising by an audience, thus increasing attendees' susceptibility to the messaging.

The audience will draw a link, even subconsciously, between the KOL's credibility in the field and the product. Clearly, this positively influences the audience's opinion of the product. Marketing goals can be achieved without even mentioning the medicine if key messages relate to the fact that a specific disease is underdiagnosed, undertreated, or more serious than generally believed (Fugh-Berman & Melnick, 2008).

Speakers often receive reimbursement for their time, travel and accommodation and, potentially, a gift from the sponsor. Clinicians and academics are often seduced by these invitations due to their own desire for career advancement and to be seen as an expert in their field. Other motivations mentioned by KOLs include networking with peers, future opportunities for benefits from the company, learning about new products, and simply enjoying speaking (Sismondo, 2013).

Even if healthcare professionals believe that the product they are promoting is superior and useful, they may **underestimate the extent to which financial or material incentives have biased their judgement** (Smith et al., 2013). Speakers not only influence audience members' prescribing behaviour, but also become more convinced themselves of the benefits of the products they endorse (Sah & Fugh-Berman, 2013).

C. Positions of Influence and Authority

KOLs can also be those that hold positions of authority or influence. A 2004 survey of 125 medical schools and the 15 largest independent teaching hospitals in the US discovered that 60% of department chairs had some form of personal relationship with the pharmaceutical industry. This included serving as a consultant, member of a scientific advisory board, paid speaker, officer, founder, or a member of the board of directors (Campbell et al., 2007).

Other influential stakeholders that pharmaceutical companies try to infiltrate include patient and healthcare professional advocacy groups—key stakeholders in health policy debates. **Pharmaceutical industry sponsorship to these organisations is common.** Concerns have been raised about the extent to which these groups may represent the interests of their corporate sponsors, even unintentionally, to the detriment of the interests of the constituency they represent. A study from Health Action International, which evaluated the impact of financial sponsorship from the pharmaceutical industry to patient organisations, revealed an association between receiving sponsorship and supporting the expanded role of the pharmaceutical industry as an information provider about its medicines (Perehudoff & Leonardo Alves, 2011).

IN BRIEF: MARKETING TECHNIQUES

- As a healthcare professional, you are surrounded by pharmaceutical company messages that use subtle social psychology techniques to influence the way you perceive a product and the way you perceive your own behaviour.
- Promotional materials and presentations will never provide you with the full story. You must look beyond what is easily accessible to what the evidence really is and who generated the evidence.
- Not all research is good research. False academic authorship and selective reporting often masks the commercial objective to promote and positively position the product in your mind.
- With the rapid development of mobile health technologies and the growth of the internet as a source of medical information, pharmaceutical companies will have direct access to patients. Amongst other implications, this might involve misinformed self-diagnoses and increased demands from patients to healthcare professionals for specific treatments.

ACTIVITY 2

Make a List

As a group, list the ways you have been, or may be, exposed to these pharmaceutical promotion techniques. Discuss how these situations might look and feel, and how you might respond.



What Protects Healthcare Professionals from Unethical Behaviour by Pharmaceutical Companies?

What Protects Healthcare Professionals from Unethical Behaviour by Pharmaceutical Companies?

Laws on pharmaceutical promotion exist to ensure commercial interests do not override the values of good clinical care, individuals and society. However, legislative frameworks are often not robust enough and rely too heavily on self-regulation.

The EU pharmaceutical industry operates under three key regulatory arms:

1. The EU legislative framework;
2. Individual national laws incorporating EU provisions; and
3. Voluntary codes of conduct (self-regulation).

Ultimately, the existence of legislation and voluntary codes of conduct is irrelevant if not adequately monitored and enforced. Globally and across the EU, the resources allocated to control pharmaceutical promotion vary greatly between countries and implementation may be erratic.

Provisions of European Union Legislation

Throughout the EU, the advertisement of medicinal products for human use is governed by Directive 2001/83/EC. Within this Directive, 'advertisement' is understood as:

"Any form of door-to-door information, canvassing activity, or inducement designed to promote the prescription, supply, sale, or consumption of medicinal products."

This includes:

- advertising to the general public and persons qualified to prescribe or supply medicinal products;
- the provision of inducements to prescribe or supply medicinal products;
- visits by sales representatives;
- the supply of samples; and
- sponsorship of promotional meetings and scientific congresses.

Accordingly, there are some key provisions within the Directive that shape national regulations on pharmaceutical promotion:

1. Advertising must be consistent with the approved product information.

Upon market approval, pharmaceutical products are accompanied by approved product information that specifies the product use or uses (indication), dosage and administration, precautions and warnings, and information on contraindications, adverse effects and interactions with other medicines. The advertising of a medicinal product must be aligned with the corresponding approved product information.

2. Advertising must not be deceptive or inaccurate.

This provision pertains to the use of exaggerated claims and/or misleading information regarding a product.

3. Advertising of prescription-only medicines (and those containing substances defined as a psychotropic or narcotic) must not be direct to consumer.

Direct-to-consumer advertising of prescription-only medicines is banned in the EU. In addition, Member States can ban the advertising of medicinal products included in the national pharmaceutical reimbursement scheme. The advertising of over-the-counter (OTC) medicines to the general public is, however, allowed under some conditions. For example, the promotional material must be presented in a way that clearly shows the message is an advertisement. The ad must contain information for the correct use of the medicine and it cannot, for example, suggest that the medicine is unaccompanied by adverse reactions or superior to another treatment. Furthermore, ads cannot be directed exclusively or principally at children and/or refer to a recommendation by persons who, because of their celebrity, could encourage consumption of the product.

In comparison with other jurisdictions, like the US, this is a major advance. However, EU legislation allows for some flexibility, such as delivering 'information relating to human health or diseases' to the general public by pharmaceutical companies as long as no reference, even indirect, to medicinal products is made. Companies can also carry out campaigns to encourage vaccination as long as these are authorised by the competent authorities of the Member States. As we have seen, such campaigns are often of poor information quality, prompting patients to make specific medication requests to their doctors and increasing prescription rates for the sponsor's product.

4. Advertisement to healthcare professionals.

Directive 2001/83/EC (European Commission, 2012) provides that:

- healthcare professionals may receive gifts, pecuniary advantages or benefits-in-kind, providing that they are "inexpensive and relevant to the practice of medicine or pharmacy"
- pharmaceutical companies may also offer hospitality at sales promotion events and for "purely professional and scientific purposes".
- healthcare professionals can be visited by sales representatives.
- product samples can be supplied to prescribers in limited volumes per year. The supply of samples must be in response to written requests by prescribers. Member States may place further restrictions on samples at their discretion.

Clearly, EU regulations aim at framing, rather than banning, situations that have been shown to undermine medical practice and prescribing habits.

5. Member States shall ensure adequate monitoring, but a system of prior vetting is not compulsory.

EU provisions state that national competent authorities shall ensure that there are effective methods to monitor the advertising of medicinal products, which may be based on a system of prior vetting. They shall also determine what penalties shall be imposed in case of non-compliance with the law.

6. Compliance/monitoring activities by competent authorities do not preclude voluntary control of advertising by self-regulatory bodies.

In addition to judicial or administrative proceedings put in place by competent authorities, it shall be possible to bring proceedings before self-regulatory bodies performing control on advertising of medicinal products on a voluntary basis.

Self-regulatory bodies are delegated, to a greater or lesser extent, monitoring and enforcement responsibilities by the national regulatory authority. For example, in the United Kingdom (UK), the Association of the British Pharmaceutical Industry (ABPI) is delegated responsibilities by the Medicines and Healthcare Products Regulatory Agency. This can vary significantly between countries. Self-regulation is often associated with weak monitoring and enforcement.

BOX 6

Examples of Poor Regulatory Enforcement at the National Level

Example 1

In 2004, the Institute for Evidence-based Medicine analysed 175 medicine advertisements received by 43 doctors in Germany. Of these advertisements, 94% were not supported by scientific evidence. Unsupported claims included benefits not mentioned in scientific papers, false descriptions of trial designs, wrongly cited figures and omitted adverse effects (Tuffs, 2004).

Example 2

According to EU regulations, advertising of a medicinal product cannot be directed exclusively or principally at children. The example below from Latvia shows little monitoring by national competent authorities (Health Projects for Latvia, 2014).



FIGURE 13. Television advertisements by Takeda for Ibuprofen (ibuprofen).³

Source: YouTube, 2015

The content of these videos was amended following a complaint by the non-governmental organisation, Health Projects for Latvia, to the Latvian Health Inspectorate. A sentence was added at the end of the advertisement warning parents to keep medicines out children's reach.

3 Video links to advertisements are available here: <http://bit.ly/TakedaTVads>.

BOX 7**Examples of Best Practice Regulation by EU Member States**

France was one of the first EU Member States to implement, by law, a 'Sunshine Act'. The so-called 'Loi Bertrand' (Law n° 2011–2012 on the Strengthening of Health Protection for Medicinal and Health Products) and complementary rules mandated health product companies to publish information about benefits to healthcare professionals, medical students and professional associations as of 1 January, 2012. The scope of the transparency requirements covers agreements and in-cash or in-kind benefits of €10 or more. Non-compliance by companies with disclosure obligations is subject to penalties; failure to comply carries fines of up to €225,000 and additional sanctions, which may include the suspension of business activities.⁴ Find out more about 'Sunshine Acts' in the 2018 paper, 'Sunshine Policies and Murky Shadows in Europe: Disclosure of Pharmaceutical Industry Payments to Health Professionals in Nine European Countries', published in the International Journal of Health Policy Management.

Although transparency of conflicts of interest should not be considered as an end in itself, Sunshine Act initiatives can enable patients and consumers to make more informed decisions about their medical care. It can also deter healthcare professionals from engaging in conflicting situations.

Industry Codes of Conduct

In EU Member States, the regulation of pharmaceutical promotional activities is entrenched in law, but governments have more or less handed control of promotional activities to industry associations. Under self-regulation, pharmaceutical industry associations or multi-stakeholder organisations (representing a group of affected sectors) develop their own codes and put in place procedures to respond to complaints about advertising. The problem is that self-regulatory codes are not technically part of the law. Although governments can intervene in case of a serious violation, it is rare (WHO & HAI, 2009).

Key industry codes of conduct applicable to the promotion of medicines include the Code of Practice of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the codes from the European Federation of Pharmaceutical Industries and Associations (EFPIA).

A study of the self-regulation of anti-depressant advertising in Sweden concluded that self-regulation had failed to protect doctors from unreliable information on antidepressants.

Specifically, self-regulatory bodies repeatedly failed to challenge inflated claims of antidepressant efficacy, suggesting lax oversight. They also found there was an average of 15 weeks between printing and censure of a wrongful claim and, in 25% of cases, more than 47 weeks elapsed.

Source: Zetterqvist & Mulinari, 2013

⁴ Visit the centralised transparency portal at www.transparence.sante.gouv.fr/flow/main?execution=e4s1.

CASE STUDY

Self-regulation in the UK and Sweden

A study by Zetterqvist et al. (2015) examines the evidence for promotion and self-regulation in the UK and Sweden, two countries frequently cited as examples of effective self-regulation. The regulatory arrangements in these countries are 'delegated'. That is, the national regulatory authorities have delegated a significant part of their defined statutory responsibility to the industry trade groups. The respective groups are the Association of the British Pharmaceutical Industry (ABPI) in the UK and its Swedish counterpart, the Läkemedelsindustriföreningen (LIF). Tables 1 and 2 summarise the key findings.

The study recognises that the analyses done (for the 2004 to 2012 period) is a gross underestimate of industry misconduct due to the exclusion of violations that go undetected, unrecorded or unpunished by self-regulatory bodies.

The prevalence and severity of breaches illustrates the gulf between the ethical standards reported in industry codes of conduct and the actual conduct of the industry.

The authors propose several improvements to current regulation, including intensified pre-vetting and active monitoring of promotion, along with larger fines and giving greater publicity to breach rulings. However, they also note that there are additional layers of industry bias that cannot be addressed only with increased oversight and penalties, such as biases in the design and reporting of clinical studies. Charges levied by regulatory authorities could be used to fund independent research and information on treatment (Zetterqvist et al., 2015).



Table 1: Recorded code breaches between 2004 and 2012 in Sweden and the UK

| | Sweden | UK (not including OTC medicines) |
|--|------------|----------------------------------|
| Recorded breaches between 2004–2012 | 536 | 597 |
| Complaints | | |
| • Active monitoring | 47% | 0.2% |
| • Industry | 28% | 26% |
| • Healthcare professionals | 7.4% | 40% |
| • Other individuals | 3.7% | 21% |
| • National Authority Group | 11% (MPA) | 0.8% (MHRA) |

Source: Zettergvist et al., 2015

Table 2: Summary of key findings

| | Sweden | UK (not including OTC medicines) |
|---|--|----------------------------------|
| Highest number of violations | 58% misleading claims 23% failure to comply with undertakings (from prior breach) 23% pre-licensing and off-label promotion 15% promotion to the public | |
| Number of companies in breach | 27 | 36 |
| | 46 in breach across both countries 7 in breach more than 10 times each | |
| Average fines collected for breaches per year * | €447,000 | €765,000 |
| Percentage of annual sales revenue paid in fines * | 0.014% | 0.0051% |
| Particularly serious breaches | 17% | 16% |

* Data from 2009-2012

Source: Zettergvist et al., 2015

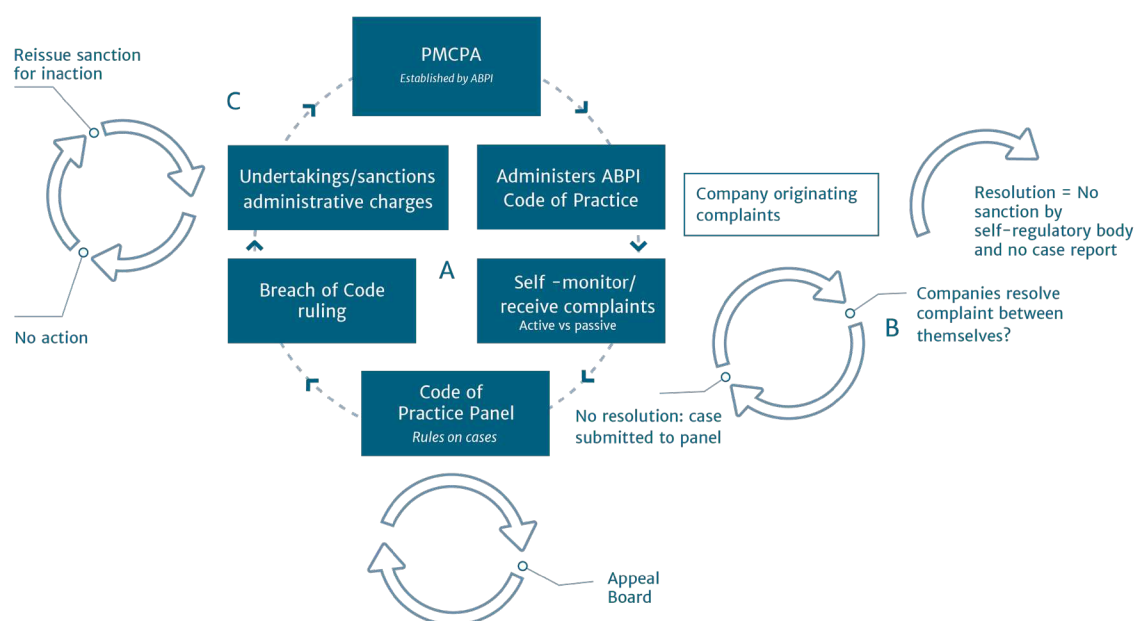
Why Self-Regulation Does Not Work

Without sound monitoring and legal enforcement of codes, the control of pharmaceutical promotion will have limited effects. Self-regulation by the pharmaceutical industry is not sufficient for the protection of public health because:

- **it is a conflict of interest.** Codes are created and administered by those who have commercial motivations.
- **it is voluntary and not entrenched in law.** 'Opt in' mechanism. Not automatically applicable to the whole industry but to industry association members.
- **it occurs too late.** Pre-vetting mechanisms are generally lacking and monitoring is not proactive enough. Breaches are spotted when consumers and healthcare professionals have already been exposed to its impact. It lags behind societal expectations of timely sanctions.
- **economic sanctions are too mild.** Evidence shows that charges equate to less than 1% of annual sales revenues. They also contribute to the costs of administering the self-regulatory system rather than providing compensation for damages caused by illicit promotion and acting as a dissuasive measure.

Figure 14 outlines an example of self-regulation under the ABPI process. ABPI develops the Code of Practice for the Pharmaceutical Industry in the UK (2015) and has established the Prescription Medicines Code of Practice Authority (PMCPA) to administer the ABPI Code.

FIGURE 14. The Association of the British Pharmaceutical Industry's self-regulation process



This diagram shows the process that breaches follow before resulting in any sanctions or public record. This is a basic representation of the ABPI process. Each self-regulatory system may differ in the way it operates. A) Alleged cases of non-compliance are identified through a submitted complaint or, less commonly, through self-monitoring; B) A number of industry-originated complaints may never progress to become established cases, usually because the inter-company resolution process allows companies to rectify the misdemeanour; C) Violations that result in sanctions do not necessarily result in immediate withdrawal or correction of the issue. In the study from Zettergqvist et al. (2015), this is evidenced by the significant number of breaches for “failure to comply with undertakings”; D) Administrative charges paid by companies contribute to financing the self-regulatory system.

IN BRIEF: REGULATION

The pharmaceutical industry in the EU operates under three key regulatory arms:

1. The EU legislative framework;
 2. Individual national laws incorporating EU provisions; and
 3. Voluntary codes of conduct (self-regulation).
- The EU legislative framework for advertising to healthcare professionals is fairly permissive. EU regulations aim at framing, rather than banning, practices that can undermine clinical practice.
 - National regulatory authorities delegate responsibilities to self-regulatory bodies. The process of self-regulation is inherently flawed.
 - Legislative changes are needed at the EU and national levels to ensure regulatory frameworks on medicine information put patients' safety at the forefront. This should include pre-vetting and active monitoring of advertising materials.
 - Unethical practices are common across the EU. Without proper enforcement of pharmaceutical promotion rules, regulation will continue to have limited impact.





Conflicts of Interest

Conflicts of Interest

The key ethical basis for any interaction that healthcare professionals have with the pharmaceutical industry is the understanding that the values of clinical care—of the welfare of society and of science—should prevail over the commercial imperatives and monetary concerns (World Medical Association, 2013).

According to the US Institute of Medicine (2009):

A conflict of interest is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.

Healthcare professionals have subscribed to a high level of ethical conduct. They have committed to putting the health of patients first and are therefore required to disassociate themselves from situations where their clinical judgments can be influenced by secondary considerations that may be in conflict with patients' best interests.

For the most part, if healthcare professionals clearly understood the extent to which exposure to pharmaceutical promotion can compromise the integrity of their clinical decision-making, they would not participate in these activities. As Michael Rawlins, chair of the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and former chair of the National Institute for Health and Care Excellence (NICE), pointed out:

"...few doctors accept that they, themselves, have been corrupted. Most doctors believe that they are quite untouched by the seductive ways of industry marketing men [and women]; that they are uninfluenced by the promotional propaganda they receive; that they can enjoy a company's 'generosity' in the form of gifts and hospitality without prescribing its products. The degree to which the profession, mainly composed of honourable and decent people, can practice such self-deceit is quite extraordinary. No drug company gives away its shareholders' money in an act of disinterested generosity." (1984)

Indeed, many healthcare professionals sincerely believe they are unaffected by gifts and other forms of pharmaceutical company influence. However, as we have seen, there are a number of published studies that demonstrate otherwise. Bias is not necessarily conscious. Many instances of bias occur due to compounding factors, such as time and workload pressures, and lack of timely access to objective information. However, this is also what pharmaceutical companies rely upon.

The behaviour is also learned. Industry influence has become a social norm in healthcare. That is, the behaviour of accepting gifts and receiving promotional messages from industry has been modelled as an acceptable behaviour for decades. It is natural for us to look to our peers for social validation of our own behaviour—and even to rationalise behaviour where we may identify a conflict of interest (Sah & Fugh-Berman, 2013). For example, healthcare professionals may feel uncomfortable about meeting with sales representatives or receiving gifts, but because a mentor or colleague does so, it negates the perceived conflict.

Change Starts with You

Medical students and healthcare professionals must identify ways to acknowledge and circumnavigate industry influence that can negatively impact clinical decision-making. If a critical mass of healthcare professionals avoids being indebted to companies and if academic prestige equates to an arm's-length relationship with the industry, "a new social norm may emerge that rejects transactions fraught with conflicts of interest" (Sah & Fugh-Berman, 2013). That norm would promote, rather than undermine, patient care and scientific integrity. HAI's online toolkit includes expert webinars to help facilitate change. Visit the website: www.haiweb.org/what-we-do/pharmaceutical-marketing/

The 'Front Page' Test

A useful ethical analysis tool is the 'front page' test. It requires asking yourself: How would I feel if the course of action I am considering was reported on the front page of the local newspaper? What would people think about the reported facts of the situation? How could my actions be perceived?

If you would be at all uncomfortable, or you feel the facts have the potential to be misconstrued, the best course of action is to not do it.

This test is analytically useful because it encourages people to think about how their actions may look to the outside world. People tend to rationalise their actions, usually by starting their analysis with what they want to do and then reasoning backward to justify that course of action.

Best Practice Prescribing

Patients have a right to good care. Providing it should be the aim and responsibility of all healthcare practitioners. Above all, patients have the right to be protected from unnecessary harm. For this reason, prescribing and dispensing must always balance the potential for benefit against the possibility of harm.

"It is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them."

— Philippe Pinel, 1745–1826

Healthcare professionals should always strive to make informed treatment decisions based on high quality, unbiased information on medicines. In addition to regulatory information, checking independent evidence (like systematic reviews) can aid in understanding a treatment's effects. (See the **Annex** for examples of independent sources of information.)

IN BRIEF: CHANGING BEHAVIOURS

- Healthcare professionals have subscribed to a high level of ethical conduct. They are therefore required to disassociate themselves from situations where their clinical judgments may be influenced by secondary considerations that may be in conflict with patients' best interests.
- The 'front page test' is a useful tool in understanding how one's actions may be perceived to be in conflict with your duties as a health professional.
- Good medical practice relies upon:
 - the ability to recognise and take account of the effects of misleading promotional material and activities;
 - an understanding of the commercial biases; and
 - relying on unbiased, high-quality evidence on the effects of medicines.

ACTIVITY 3

The Change Starts Now

As a group, develop **your own charter for behaviours that you will live by**. This should include:

- **Three core principles that you will subscribe to** in your dealings with the pharmaceutical industry.
- **Six actions you will undertake** to enable you to live up to these principles.

Share group members' charters and consolidate them into one charter for the group. Print the final charter and post it where you can see it.



Annex

Useful Links and Contacts

Cochrane

International and independent organisation that carries out systematic reviews of health care interventions. Provides a database of systematic reviews.

www.cochrane.org

Community Catalyst

United States-based non-profit advocacy organisation that represents consumers' voices in health care. Published a series of toolkits for critical appraisal, Conflict of Interest Policy Guide for Medical Schools and Academic Medical Centers.

www.communitycatalyst.org/initiatives-and-issues/initiatives/prescription-reform/conflict-of-interest-policy-guide

Drug and Therapeutics Bulletin

Scientific journal that provides independent evaluations of, and practical advice on, individual treatments and the overall management of disease for doctors, pharmacists and other healthcare professionals. Member of the International Society of Drug Bulletins.

<http://dtb.bmj.com>

Formindep

French association of healthcare professionals, patients and concerned individuals that aims to provide independent medical training and information.

www.formindep.org

Geneesmiddelenbulletin

Independent Dutch medicines bulletin that promotes the rational use of medicines. Publications developed in consultation with experts and available on periodic basis. Member of the International Society of Drug Bulletins.

<http://geneesmiddelenbulletin.com>

International Society of Drug Bulletins

World-wide network of bulletins and journals on medicines and therapeutics. Financially and intellectually independent of the pharmaceutical industry. Membership is present in 14 European countries.

www.isdbweb.org

Healthy Skepticism

International non-profit organisation that aims to "improve health by reducing harm from misleading pharmaceutical promotion" by informing health professionals and the general public.

www.healthyskepticism.org/global

No Gracias

Independent civil society organisation that advocates for transparency, integrity and equity in health policy, healthcare and biomedical research. International movement includes Healthy Skepticism, No Free Lunch, No Grazie, Pago Io, Gezonde Sceptis and Mein Essen zahl ich selbst.

www.nogracias.eu

PharmAware

Network of health professionals, students and other interested individuals. Aims to improve health by reducing harm from inappropriate, misleading or unethical marketing of health products or services, especially misleading pharmaceutical promotion in the United Kingdom.

www.pharmaware.co.uk

PharmedOut

Georgetown University Medical Center project that advances evidence-based prescribing and educates healthcare professionals about pharmaceutical marketing practices.

www.pharmedout.org

Prescribers' Letter

Subscription service for prescribers that provides update on new developments in drug therapy. The service consists of a monthly letter, as well as 'detail-documents', available 24 hours a day. Free of advertising and other financial support from the pharmaceutical industry.

<http://prescribersletter.therapeuticresearch.com/home.aspx?cs=&s=PRL>

Prescrire

Non-profit continuing education organisation that provides independent information to healthcare professionals about medicines and therapeutic diagnostic strategies. Publishes a monthly journal in French and an international edition in English 11 times a year, plus a yearly supplement in French devoted to medicine interactions. Member of the International Society of Drug Bulletins.

www.english.prescrire.org

RxIsk

Independent website that enables patients, doctors and pharmacists to research prescription medicines and report medicine side effects.

www.rxisk.org

Therapeutics' Letter

Bi-monthly letter that identifies problematic therapeutic issues. Process involves a literature review and message development by different working groups of the Therapeutics Initiative from the University of British Columbia in Canada. Independent organisation, separate from government, the pharmaceutical industry and other vested interest groups. Member of the International Society of Drug Bulletins.

www.ti.ubc.ca/TherapeuticsLetter

The Medical Letter

Non-profit organisation that publishes critical appraisals of new prescription medicines and comparative reviews of medicines for common diseases in its newsletter. Solely supported by subscription fees and does not accept grants, donations or funding from any source. Does not sell reprints to industry for promotion and does not accept advertising in any of its publications.

<http://secure.medicalletter.org>

Universities Allied for Essential Medicines

Non-profit organisation rooted in a global movement of university students. Advocates for improved access to medicines and medical innovations in low- and middle-income countries, medical research that meets the needs of people worldwide, and the empowerment of students to respond to the access and innovation crisis.

<http://uaem.org>

Worst Pills, Best Pills

Independent expert 'second opinion' on more than 1,800 prescription medicines, over-the-counter medications and supplements. Project of Public Citizen's Health Research Group and a member of the International Society of Drug Bulletins. Takes no corporate or government contributions and accepts no advertising.

www.worstpills.org

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