The patient, their doctor, the regulator and the profit maker: conflicts and possible solutions

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The dilemmas and conflicts between industry, who develop and market antibiotics and the regulators who are responsible for regulating their use to preserve efficacy are explored. Despite regulations, the industry remains profitable and should concentrate more on development of innovative products which readily gain market share without excessive marketing. Various aspects of regulations are discussed as they influence the prescriber and the patient.

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In the community, use of antimicrobials can result from prescription of antimicrobials by a general practitioner (GP) or over-the-counter (OTC) delivery of antimicrobials by a pharmacist, both of whom possibly being influenced by demand from the patient. Some of the factors that influence such prescription, demand and delivery are summarized in Figure 1. They can be grouped into two major activities, i.e. education and regulation, which, besides patients, GPs and pharmacists, involve pharmaceutical companies and public healthcare systems.

In primary healthcare, there is a possible conflict between patients and GPs concerning the demand for antimicrobials. Probably because of increasing access to information, patients are more aware of health issues and have become more questioning and challenging. Education of the general public has been and is still in practice in Denmark to inform about situations where antimicrobials are not needed. Such a campaign has recently been launched in Belgium [1] and preliminary results show that it resulted in a substantial reduction of antimicrobial consumption in primary healthcare in that country (Isabelle Bauraind, personal communication). In some countries, patients can ‘shop’ among an unlimited number of GPs until their demand for antimicrobials is satisfied and still get reimbursement for the consultation. Such systems clearly promote competition for patients among GPs. Healthcare systems in which patients only get reimbursed for consultations with a single GP, with whom they must be registered, and where appointments with other GPs are not easily accessible, generally report lower antimicrobial consumption levels.

Conflicts between GPs and the pharmaceutical industry have already been discussed at length in this issue [2]. Unfortunately, there is clearly a blurred boundary between the educational information delivered by pharmaceutical representatives and the marketing practices of that industry. Despite the publication of a European Code of Practice for the Promotion of Medicines [3], there is evidence that this code is often not respected in the physician’s office and improvement is needed in this area [4]. One should also be very cautious about information available on the Internet and available to both prescribers and patients. For example, the home page of LIBRA, an initiative launched by Bayer to ‘preserve antibiotic effectiveness for public protection’, listed quinolones as narrow spectrum antimicrobials (accessed 15 May 2001 – this information has since been deleted) [5]. Although true for early quinolones used to treat urinary tract infections, this information is not correct for fluoroquinolones because they are active on both Gram-positive and Gram-negative bacteria, and they have proven negative effects on the normal flora [6,7]. In the section ‘News’, the same home page presents a press conference promoting LIBRA with reference to abstracts from peer-reviewed scientific articles.

Because of financial and time constraints, GPs often rely on pharmaceutical companies for their information. Friis et al compared the effect of information about prudent use of antimicrobials delivered during lectures arranged by the local clinical microbiology laboratory with that delivered by a pharmaceutical company, and demonstrated the absence of change in practices in the latter group [8]. GPs also report

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difficulties with keeping up-to-date with an increasing number of professional guidelines. In Denmark, access to national guidelines has been facilitated by the yearly publication of the ‘List of Pharmaceuticals’ by the Danish Medical Association. It is sent free-of-charge to every physician in the country and includes, among others, national recommendations for the treatment of infectious diseases [9]. In the various Danish counties, local clinical microbiologists organize educational sessions and audit GPs on their rational use of antimicrobials. Another approach could be to establish an educational task force of public health physicians in charge of the ‘academic detailing’ of antimicrobial guidelines directly in the GP’s office, thus balancing the influence of promotional activities by pharmaceutical companies. Although costly and time-consuming, this approach deserves to be tested. In hospitals, similar conflicts occur between hospital prescribers and the pharmaceutical industry [10].

Finally, there is a conflict between pharmaceutical companies selling antimicrobials and agencies that implement drug regulations. An argument generally pushed forward by the pharmaceutical industry is that increased regulation will necessarily decrease investments into research and development (R & D) of new drugs. As already mentioned in this issue of the journal, a lot of money is invested into R & D by the pharmaceutical industry [11]. However, what proportion of the revenues of pharmaceutical companies does R & D represent? And how does R & D compare with other expenses such as marketing and profits? To answer these questions, we analysed data abstracted from the 2000 annual financial reports of the top 10 pharmaceutical companies worldwide, as ranked in a recent article [12]. This analysis confirmed that more than $26 billion was spent for R & D in 2000, which corresponded to an average 14.1% of revenues of these companies. However, it also revealed that, during the same year, these companies devoted 35.1% of their revenues to selling, general and administrative expenses – which, for a large part, are represented by marketing, and 19.1% to profits. When considered separately, eight out of these top 10 pharmaceutical companies allocated more of their revenue to profit than to R & D. Moreover, these top 10 companies reported an average 12.8% increase in global sales between 1999 and 2000, while the fraction of revenues invested in R & D decreased from 14.3% to 14.1% and the fraction allocated to profit increased from 15.8% to 19.1%.

Indeed, with an 18.6% return on revenues in 2000, the pharmaceutical industry was once again rated by Fortune Magazine as the most profitable sector of the US industry and has been consistently ranked as number one or two over the
past few decades [13]. Other sources have reported a 16% increase in sales forces among the top 40 US pharmaceutical companies between 1999 and 2000 [14] and a 14.3% increase in total US pharmaceutical company promotional spending directed toward physicians and consumers [15]. In Europe, purchases at retail pharmacies of drugs overall and of anti-infectives alone increased by 8% and 4%, respectively, among the five leading countries, i.e. Germany, France, Italy, Spain and the UK, between 1999 and 2000 [16]. An analysis of the 2000 annual financial reports of the top 10 European-based pharmaceutical companies yielded figures similar to those of the top 10 worldwide, i.e. a 17.6% increase in global sales, a decrease of the fraction invested into R & D from 17.1% to 16.6%, and an increase in the fraction allocated to profit from 13.4% to 19.2% between 1999 and 2000. A subsequent analysis of data from Handelsblatt and Wall Street Journal’s ‘Europe 500’ database confirmed these results and showed that a group of nine companies among the top 10 European-based pharmaceutical companies (data for one company were not available) reported an average 45% increase in profits between 1999 and 2000, ranking the pharmaceutical industry increase in profits 19th out of 51 sectors of European industry [17]. One should also be aware when considering these statistics that a substantial fraction of R & D corresponds to marketing research studies and research to develop similar drugs, or nearly similar, to existing drugs also known as ‘me-too’ drugs. The latter do not correspond to real innovation and need increased promotion to gain their share of the market. Conversely, experience shows that, because of the necessity to treat patients infected with multidrug-resistant micro-organisms, antimicrobials that represent real innovations, e.g. imipenem, vancomycin or more recently linezolid, are readily accepted by hospital prescribers and naturally gain market shares.

It is only normal that pharmaceutical companies, like other industries, return profits to their shareholders. We are grateful to pharmaceutical companies for developing new classes of antimicrobials, and excessive regulation should not prevent such innovation. However, the data presented above show that, although public health systems are increasingly taking their share of responsibility in controlling antimicrobial overuse and misuse, the pharmaceutical industry is still a very profitable business. The so-called ‘R & D Scare Card’ is therefore not justified.

Our intention is not to exacerbate the debate over the control of costs of medicines that are reimbursed by public healthcare systems, such as the one presently taking place in the US [18]. When considering antimicrobials, especially in Europe, the debate should mainly focus on the ecological consequences of overuse and misuse of antimicrobials, i.e. antimicrobial resistance. When dealing with antimicrobials, pharmaceutical companies are accountable, not only to their shareholders, but to the society at large and should understand the need for public health authorities to implement regulation when these drugs are overused or misused. Even innovative antimicrobials must be used cautiously. Resistance to imipenem or vancomycin emerged after several years of use and has now become a problem in numerous hospitals. The recent report of the first linezolid-resistant Staphylococcus aureus only came to remind us that, sooner or later, resistance to all new antimicrobials will emerge as a consequence of antimicrobial use [19].

Because antimicrobials are societal drugs that affect not only the microbial ecology of the patient receiving the drug but also bacteria in his environment and possibly other humans, they should be regulated accordingly. There are very few scientific arguments against regulation of antimicrobials for use in primary healthcare. In Denmark, specific rules such as differential subsidization have been used successfully to control overuse of antimicrobials with known negative ecological effects and have resulted in decreasing prevalence of resistance [20,21]. Controlled registration of ‘me-too’ antimicrobials is likely to result in limited market competition and consequently a lower use of a class of antimicrobials. Control of antimicrobial use in hospitals must be considered with caution since it might affect adequate inpatient care. However, specific subsidization rules to prevent overuse of antimicrobials for surgical prophylaxis are acceptable and have contributed to the proper use of antimicrobials in this indication in Belgium [22]. By making antimicrobials a legal exception among commercial drugs, we should be able to preserve the activity of valuable antimicrobials.

Opinions on the various points mentioned above have been expressed in this special issue of the journal, including the minimum antibiotic stewardship measures from the European Study Group on Antibiotic Policy (ESGAP)[23], and in other publications such as the Position Paper on Containment of Antibacterial Resistance of the European Federation of Pharmaceutical Industries and Associations [24]. Despite obvious areas of conflict, we hope that this symposium has established a platform for dialogue, which should result in a better definition of the responsibilities of each party involved.

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