Chapter 5
Europe

The major pharmaceutical markets are the US, Europe (where the UK, Spain, France, Italy and Germany are the major players), Japan and the rest of the world. As I explain in the section on industry, the US comprises about 40–50% of the market, Europe with 20%, Japan with 10% and the rest of the world at 20%. As the US share drops because of the recession and increasing competition and health care reform, the emerging markets like China, India and others are taking up the slack. Europe, nevertheless remains an important market. They have a complex regulatory environment and tough pricing policies. Europe has been ahead of the curve in recognizing the perfect storm afflicting antibiotics. Whether they will actually act in accordance with their published analyses and resultant recommendations for dealing with the storm remains to be seen.

As part of the formation of Europe as a common market, the European Medicines Agency (EMEA) was established as the regulatory body for the group of nations. Prior to this, sponsors had to submit a separate dossier of data to each of the national regulatory agencies within the European block to obtain marketing approval for each individual country. This approach is still possible. But with the establishment of the EMEA, sponsors now have the option, and for some drugs the requirement of submitting a single dossier to Europe (Centralized Procedure) and gaining marketing approval for the entire block of nations. The actual opinions of the EMEA are provided by the Committee for Medicinal Products for Human Use or CHMP. Within the CHMP are Scientific Advisory Groups which provide advice to both sponsors and the CHMP regarding products in key areas. There is a specific advisory group for anti-infectives (antibiotics and anti-fungal compounds). The approval by the EMEA with all its CHMP caveats must be followed by a negotiation with each individual country as to the terms under which the product can be marketed within that nation. Each country maintains a national negotiation for establishing conditions of marketing and product price. This is a completely different situation than that found in the US where there is no national negotiation at all. There are large blocks of patients that negotiate price, such as the Veterans Affairs administration and others, but there is no truly national price negotiation. This accounts for the fact that drug prices in the US are consistently higher than they are in other countries.

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Europe also has much tighter controls on how antibiotics are used. Each country sets criteria under which the use of an antibiotic is reimbursed either to the hospital or to the patient. Any use outside of these pre-set criteria means that the government is no longer obligated to pay for the prescription. This system gives the European nations much more control to prevent abuse of antibiotics and, accordingly, it limits the market for antibiotics. Thus, while Europe has 30% more population than the US, its pharmaceutical market is smaller – partly because of price and partly related to marketing restrictions within each of the member nations.

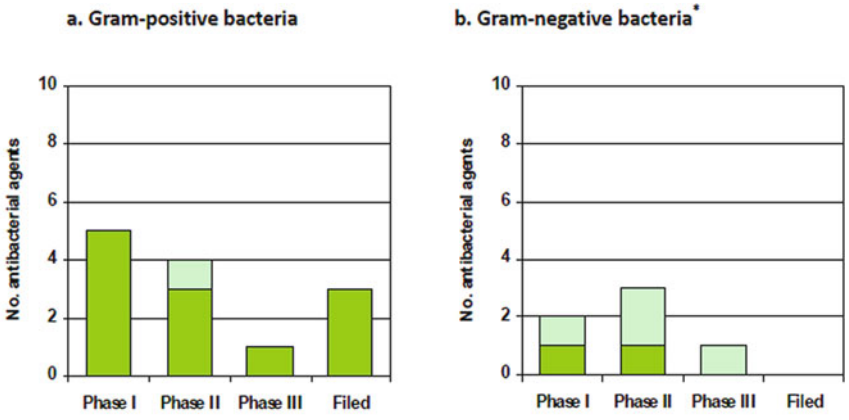
One of the great advantages of the FDA is that it is easy to speak with them throughout development starting at the earliest stages and going all the way through to post-marketing activities. Europe is not constructed that way. To speak to the EMEA, you must apply for scientific advice. In this case, the Scientific Advisory Group is convened and the sponsor's questions are dealt with in a formal meeting. This meeting takes around 12 weeks to set up. The responses by both sponsor and EMEA are said to be binding. But, like many binding contracts, if things change, which they often do, the agreements are less solid. Nevertheless, the EMEA has been in general more bound by these agreements than the FDA. The FDA has made it clear in recent years that it no longer feels bound by such agreements and they frequently change their goalposts in mid-stream. Europe seems still much less likely to do that. Nevertheless, speaking to Europe is much more cumbersome. One option for sponsors is to speak to different national authorities like the UK, France or Germany. I personally prefer this to the formal advice route with the EMEA. The disadvantage to this is that you are not speaking to the group to whom you will ultimately submit your dossier.

Europe has been much more forward thinking than the US regarding the dilemma now facing antibiotics and the pharmaceutical industry. With the caveat that thinking is one thing and acting is another, we should explore what Europe has been doing, as it could be a model for all of us. Sweden, which assumed the rotating European Presidency during 2009, has been particularly active in this regard and just held a large meeting on this subject in September where the Obama administration was represented. Three documents have been published and are available on the web for those that are truly interested; *Policies and incentives for promoting innovation in antibiotic research*, commissioned by the Swedish Government and written by Professor Elias Mossialos and his co-workers at the London School of Economics and Political Science on behalf of the European Observatory for Health Systems and Policies; and *The bacterial challenge: Time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents,* jointly written by two European agencies, the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMEA) in collaboration with the international network Action on Antibiotic Resistance, ReAct. The resulting report from the meeting held in Sweden in September, 2009 is also available. It is entitled, Innovation Incentives for Effective Antibacterials.

In the analysis by Europe, they estimated that 25,000 European patients died from an infection caused by one of the ESKAPE organisms noted in the Chapter 3.

They estimated that these infections led to 2.5 million additional hospital days and additional in hospital costs of 900 million Euro ($13.5 billion) per year. Overall, the additional costs to society of these infections was estimated at 1.5 billion Euro ($2.25 billion) per year. In their report, it was clearly stated that these figures almost certainly represent an underestimate since all costs, such as those attributed to intensive care for example, could not be taken into account in their model.

At the same time, as shown below (Fig. 5.1), they noted that there were only 15 antibiotics under development by pharmaceutical companies and biotech that might be useful in treating infections caused by the ESKAPE organisms. Of these, only eight were active against the Gram negative members of ESKAPE where there is the greatest perceived medical need. Of the total 15 compounds, three have already completed trials and have been filed – all active against Gram positives. Of the eight compounds active against Gram negative pathogens only four have survived to Phase II or later trials and none has yet been filed. Given the overall chances of being approved in our current times, it is likely that few of these products in development will make it all the way to market. The European analysts clearly recognize this risk.



Note: In vitro *activity based on actual data is depicted at the bottom of each column in darker colour. Assumed in vitro activity based on class properties or mechanisms of action (where applicable) is depicted in a lighter colour at the top of each column.*

** Two carbapenems have been omitted from Figure 4.4.5b since they are no more active than earlier carbapenems against Gram-negative bacteria. The relative novelty of these agents was based on a better profile of activity against antibiotic-resistant Gram-positive bacteria and are therefore included in Figure 4.4.5a.*

Fig. 5.1 New systemic antibacterial agents with a new target or new mechanism of action and in vitro activity based on actual data (*dark colour bars*) or assumed in vitro activity based on class properties or mechanisms of action (*light colour bars*) against the selected bacteria (best-case scenario), by phase of development ($n = 15$). From Mossialos et al. (2008), a publicly available report from the London School of Economics and the European Observatory on Health Systems and Policies

They also examined regulatory issues in antibiotic development in Europe. Key stumbling blocks were around clinical trial design – as they are in the US with the FDA – and drug pricing policies in individual member states. Although the regulatory authorities in Europe have said that they will be more flexible than their FDA colleagues, this has yet to be seen by the industry. Further, with the continued US dominance of the marketplace, if the FDA insists on infeasible trial designs, it might not matter what Europe does. Changing European regulatory guidelines to be more accommodating to antibiotic development in the absence of similar changes in the US will only work if the US market dominance recedes or if the FDA can be dragged along with the EMEA. It is not clear if the EMEA is actually in synch with the desires expressed in this regard by their EU Commission colleagues. For example, in the alterations to European guidelines for the development of antibiotics, it is clearly stated that they will also prefer placebo-controlled trials for self-limited infections such as otitis, sinusitis and bronchitis. Some European authorities with whom I have communicated state that they will be more flexible here than is suggested by the guidelines. But we will only know this if someone actually proposes a new trial in one of these indications. At this time, that seems highly unlikely given the written perspectives of Europe and the stated guideline in the US.

Europe also carried out a very detailed investigation of the economics of drug discovery and development in order to understand which incentives might work best for industry. These will be considered later in the Chapter 7. Nevertheless, the entire analysis was presented in international meetings on the antibiotic dilemma convened by Sweden in late 2009. The result of these studies and meetings was a recommendation to the Council of the European Union to develop and implement strategies as noted. The resulting resolution by the Council is cited in its entirety below. This result shows that Europe is very clearly ahead of the US and the rest of the world in its thinking on antibiotic discovery and development.

The Council of the European Union met on November 30-December 1, 2009 and adopted the following resolution for the European Union:

CALLS UPON THE MEMBER STATES TO

– develop and implement strategies to ensure awareness among the public and health professionals of the threat of antibiotic resistance and of the measures available to counter the problem;

– ensure the development and use of integrated strategies to diminish the development and spread of antibiotic resistance as well as healthcare-associated infections and their consequences, encourage healthcare institutions to have structures in place as well as ensuring effective coordination of programmes focusing on diagnosis, antibiotic stewardship and infection control;

– review and consider options to strengthen incentives to conduct research and development of new effective antibiotics within the academic as well as the pharmaceutical sector as a whole, taking into account the situation of small and medium-sized enterprises. These options and methods could include cost-effective

push mechanisms to remove bottlenecks in the early stages of research and development of new antibiotics and pull mechanisms to promote the successful introduction of new products.

15. CALLS UPON THE MEMBER STATES AND THE COMMISSION TO

– support the sharing of research infrastructures, recruitment of researchers, stimulation of and support for global research cooperation, increasing the spread of research results and knowledge through information exchange structures and considering existing and new financial instruments;

– explore ways to promote further public-private partnerships between industry, academia, non-profit organisations and the healthcare system to facilitate research into new antibiotics, strategies for use of currently available antibiotics and diagnostic methods;

– within the legal framework for market authorization of medicines, facilitate development of new antibiotics for which a particular medical need exists and when only limited clinical data can be submitted by the applicant for objective reasons, take full advantage of additional means of assessing safety and efficacy such as the utilization of preclinical assessment tools and pharmacokinetic data analyses;

– identify appropriate regulatory instruments to facilitate early approval for new antibiotics for which a particular medical need exists, in terms of providing continuous EMEA and national competent-authorities-assisted scientific advice, including strategies for adequate post-authorisation follow-up with an emphasis on safety aspects, including monitoring of antibiotic resistance;

– examine how to keep effective antibiotics on the market;

– while facilitating the development of new effective antibiotics, ensure prevention of healthcare-associated and other infections as well as the rational use of existing and new medicines;

– ensure that all actions are appropriately co-ordinated between different stakeholders from the sectors involved, such as health, finance, economic, legal and research.

16. CALLS UPON THE COMMISSION TO

– within 24 months, develop a comprehensive action-plan, with concrete proposals concerning incentives to develop new effective antibiotics, including ways to secure their rational use; and ensure that these proposals take account of the economic impact on the financial sustainability of healthcare systems.

– consider using experience regarding relevant procedures from previous specific EU legislation on orphan drugs and drugs for paediatric use to stimulate the development of new antibiotics for which a particular medical need exists;

– monitor and regularly report back to the Council on the public health need for new antibiotics, based on the emergence of antibiotic resistance, the characterisation of

new resistant pathogens and new antibiotic medicinal products and other methods to treat and prevent infectious disease in development as well as to propose further action when appropriate.

It is clear the Europe has expended an extraordinary amount of energy in their consideration of the problem of antibiotic resistance and the dry antibiotic pipeline. They have examined a range of solutions many of which are sensible. The problem is, that I do not see that they can be implemented in any kind of reasonable time horizon.

The economic solutions suggested consist of so called hybrid push pull mechanisms. For a detailed discussion of this issue, see Chapter 7. But, in brief, the example they give is one where a governmental body – Europe in this instance – purchases an "option right" to purchase a supply of a new antibiotic at some early stage in its development. This would be similar to the partnering activity that goes on now between small and large pharmaceutical companies where the large company purchases rights to market the small company's products in return from some monetary consideration and usually an obligation to pay for future development. In the case of the European Commission, the "option right" would provide funding for further development thereby reducing the risk for the company. This is the so-called push mechanism. The additional carrot, or "pull" mechanism, would be the obligation to purchase a certain amount of the product if the company is successful in winning marketing approval through the usual regulatory process. The problem I see with this is simply one of cost. The option right would cost on the order of $100 million to offset a company's development costs and risk. The guaranteed purchase would have to be considerable – on the order of $500 million or more. In return for this, the government realizes no monetary gain directly. On the other hand, they do save considerable money on health care overall if the antibiotic is active against resistant strains that are currently costing the governments on the order of hundreds of millions of dollars per year. While this kind of hybrid mechanism might work, the so-called wild-card patent extension discussed in more detail in Chapter 7 would probably work better.