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Policing the European pharmaceutical market’s priorities

Received: 4 January 2000 / Accepted: 14 April 2000

Key words Debate · Europe · Pharmaceutical market

“In order to promote the protection of human... health and of consumers of medicinal products”, states article 51 of the Regulation establishing the European Agency for the Evaluation of Medicinal Products (EMEA), “...the Agency [will] provide... the institutions of the Community with the best possible scientific advice on... the quality, the safety, and the efficacy of medicinal products...” [1]. Experience to date suggests that the proposed means are not sufficient to fulfil this commitment. These notes aim at illustrating some of the limitations of the rules governing the pharmaceutical market and make some suggestions for getting around them.

Not meeting the needs

As in other areas, the pharmaceutical market seldom succeeds in meeting real needs. It often addresses minor needs or even induces false ones that are easier to fulfil and more remunerative. Sometimes companies have no interest in developing innovative products according to acceptable standards, even those that would be promising for orphan therapeutic areas and therefore of major importance in terms of public health [2].

This is the case, for instance, with drugs for rare diseases, or for extension of indications to other diseases (e.g. a different tumour) or other patient populations (e.g. children). The safety documentation may be inadequate or the proof of efficacy based only on small phase-II studies. Patients would probably benefit from such drugs; the regulatory authority has almost all the information needed to approve them, but what is missing is essential. The company, however, sees no economic return from further investment in their development. Whatever decision the agency takes is wrong, as it means either denying needy patients a potential benefit or exposing them to a possible risk.

Since its commitment is “to promote the protection of human health”, the regulatory authority should be enabled to promote the pre-clinical study or the clinical trial(s) needed to complete the outstanding safety or efficacy profiles, regardless of the manufacture’s willingness to do it. The EMEA should be provided with the power and support needed to tackle this. The agency should be enabled to acquire the rights on drugs abandoned by industry because of the lack of commercial interest despite their clinical importance. It should be able to complete the development of these products and sell the licence to companies willing to market them as generics.

This implies enlargement of its tasks, duties and rights listed in article 51 (a)–(f), and provision of funds to cover independent research in the interest of public health. The financial provisions of the regulation [article 57(2)] do not seem to exclude this approach, as the agency’s expenditures include, besides staff, administration, etc., “operational expenses and expenses resulting from contracts entered into with third parties”. Alternatively, the agency could refer these cases to the European institution which, it is hoped, will be established to meet the need for independent clinical research, as outlined by the EUTERP Pilot Study Group [3].

Meeting no needs

Innovation is a challenging enterprise, whereas copycatting what is already available is much easier and less risky. The market is already there: one has only to be satisfied with a bit of it. Among the 126 products (98 substances) granted a positive opinion by the EMEA up to the end of 1999, about half (66 products, 48 substances) can be considered copies or me-too drugs.
According to the rules of market competition, the more options available, the greater choice one should have. In actual fact, however, neither patients nor national health services (NHS) really exploit this flood of clinically unjustified copies. These products have often been approved simply because they are “equivalent” to their comparators. Differences are hard to pick out from their Summary of Product Characteristics (SPC), so it is impossible to make a rational choice based on their risk–benefit profiles.

A catalogue of good quality products as such is time-wasting for the agency and useless for public health. It may provide the NHS with “the best possible scientific advice on the quality, the safety, and the efficacy” of single products, but fails to “promote the protection of human health and of consumers”, as it offers no means of selecting the best.

Clearly, the regulation is not intended to “affect the powers of the Member States’ authorities as regards...inclusion of medicinal products...in the scope of the social security schemes”, as stated in its first article. However, member states should be enabled to exercise such powers and select, from equivalent drugs, the one with the best benefit–risk profile or the most advantageous cost-effectiveness ratio.

To meet its institutional commitment, EMEA should be required to identify any qualifying advantage of a new product over existing ones, including cost. Lower costs in maintaining the present standard of public health would allow resources to be redirected to unmet needs. Therefore, the agency must know the costs, so they enter into the central evaluation of the product, together with quality, safety and efficacy.

Assuming that equivalence really does identify situations in which two drugs are very close in efficacy and safety (rather than simply not showing any obvious difference, as often appears), it is still mandatory to assess the better safety or ease of use, or cheapness. As SPC do not allow for comparisons of drugs of the same class or for the same indication [4], it is pointless – besides being scientifically [5] and ethically [6] inappropriate – to approve drugs on the basis of questionable clinical equivalence to others already on the market. In the interests of public health, products promising nothing better than those already on the market should not be approved. If this policy is not considered acceptable in the defence of interests other than people’s health, the lack of advantage offered by these new authorisations should be clearly stated as to avoid the absence of benefit turning out to be a risk or actual harm.

Meeting only some needs

“The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community”. The rule laid down in article 12 (2) of the regulation with regard to the centralised procedure is cancelled out by the alternative standard evaluation procedure, known as mutual recognition. Pharmaceutical companies wishing to market a drug in the community may ask member states to recognise the authorisation previously applied for in and already granted by one member state. “Save in the exceptional case... [of a risk to public health], each Member State shall recognise the marketing authorisation... within 90 days...” says article 9(4) of the directive [7]. However, if “...Member States have not reached agreement ... they shall forthwith refer the matter to the Committee [for Proprietary Medicinal Products, CPMP, the scientific organ of EMEA]” (article 10). Once it has become a decision of the Commission, the CPMP opinion is binding on all member states [article 14(4)].

The procedure seems to meet the general purpose of the directive [7], which is “...to facilitate the adoption of common decisions... on the authorisation of medicinal products... on the basis of scientific criteria...” as stated in article 8(1), which continues “...and to achieve thereby the free movement of medicinal products within the Community”. This latter objective rightly appears to be the main purpose of the overall legislation, considering that companies may withdraw the application in any member state at any time during the evaluation phase of the procedure. In other words, contrary to what is established for the centralised procedures, companies trying to achieve the largest market possible for their drugs may in the end decide simply to hang on to whatever they can get by eliminating member states whose objections might lead to referral, a negative opinion and no market anywhere in the European Union (EU). In the EU, a double procedural standard leading to different outcomes in different member states should not be admissible. The recommended “adoption of common decisions” can only be achieved if the mutual recognition procedure offers a methodological, not a substantial alternative to the centralised procedure. Whenever a member state raises a major objection against the documentation submitted on the quality, the efficacy or the safety of a new product, the matter should be referred to the CPMP and arbitration should be mandatory.

Meeting only someone’s needs

Since the medicinal market is quite different from markets for any other goods, it requires clear-cut priorities. The only – or at least the primary – objective must be the interest of consumers, i.e. people’s health. No other purpose, not even defending jobs, can claim higher priority. Therefore, drug evaluation should ultimately lead to approval only of products useful to the public health, enabling the NHS to identify the most effective or safest, tolerable or practicable or, at least, the best value for taxpayers’ money.