The 90s – the completion of the single market for pharmaceuticals and the establishment of the EMA

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An important harmonization effort in the first 30 years

Medicinal products for human use were amongst the first consumer goods that attracted the attention of the European legislator in the early days of European integration, second only to foodstuffs. Directive 65/65/EEC, Directive 75/318/EEC, Directive 75/319/EEC and Directive 83/570/EEC all represented important milestones in this respect.

In 1985, when the completion of the internal market became the primary objective of the European Commission lead by Jacques Delors, the pharmaceutical sector again received particular attention, as no less than 13 of the 300 steps identified in the *White Paper on Completing the Internal Market* (COM(1985) 310 final) as necessary for the establishment of a functional internal market concerned medicinal products.

Six Directives were promptly adopted at the end of 1986, including Directive 87/21/EEC (introducing a simplified registration procedure for generic products on the one hand, and 6 or 10 years of data exclusivity for the innovator on the other hand) and Directive 87/22/EEC (establishing the so-called 'concertation procedure').

Only three years later, in 1989, a second package of Directives extended Community pharmaceutical legislation to: official preparations and products for research or export (Directive 89/341/EEC), vaccines (Directive 89/342/EEC), radio-pharmaceuticals (Directive 89/343/EEC), and blood and plasma products (Directive 89/381/EEC).

The outstanding measures envisaged in the *White Paper* were eventually adopted in a third wave, in 1992. They dealt with: the wholesale distribution (Directive 92/25/EEC), the legal status (Directive 92/26/EEC), the labeling and leaflet (Directive 92/27/EEC), and the advertising (Directive 92/27/EEC) of medicinal products. Add, for good measure, Directive 92/73/EEC on homeopathic medicinal products.

The fragmented EU pharmaceutical market in the early 90s

Yet, despite this important harmonization effort, at the beginning of the 90s the European pharmaceutical market remained more fragmented, along Member States boundaries, than any other market for consumer products. There were several reasons.

Firstly, the granting of marketing authorizations remained entirely in the hands of Member States. Mutual recognition, which was at the core of the new strategy highlighted in the *White Paper*, is inherently ineffective in a sector where public health concerns, the ultimate tool to decline recognition of decisions reached in other *fora*, is the very name of the game. The 'multi-state procedure', introduced by Directive 83/570/EC, and the 'concertation procedure', introduced by Directive 87/22/EEC, certainly improved goodwill and sowed seeds of cooperation within the Committee for Proprietary Medicinal Products, but they failed to produce an operative mechanism either for the recognition of national decisions or for the adoption of coordinated Community marketing authorization decisions respectively.

Secondly, Member States maintained tight control on all things economical about medicinal products on their market, at least for those eligible for reimbursement under the national health system. Many price control schemes had been introduced at times of double-digit inflation in the 70s, but were maintained long after for failure of any exit strategy, and eventually morphed into actual price-fixing mechanism in some Member States. If that was not enough, squeezing prices could be achieved almost effortlessly at the time of admitting products for reimbursement by social security paymasters eager to contain the drug bill. Perhaps as painful as the price-squeeze itself was the excruciating time taken by all but a few Member States to pronounce on the pricing and eligibility for reimbursement of newly authorized medicinal products.

The Commission had, in the 80s, asked the Court of Justice on a number of occasions to review the compatibility of some Member States' cost-containment measures with the Treaty provision on the free movement of goods. However modest the results, they were consolidated into the so-called 'Transparency Directive' (Directive 89/105/EEC) which laid down minimum transparency standards and maximum

deadlines for Member States decisions on the pricing and reimbursement of medicinal products.

Autonomous price control and cost-containment policies, aggravated by currency fluctuations, lead to price differences, and price differences lead to parallel imports. Both the Commission and the Court Justice offered unconditional protection to parallel traders, unabatedly ignoring the fact that, in this case, price differences between Member States were induced by factors beyond the control of the producers concerned, and the circumstance that what was little else than arbitrage did not result in any savings for final consumers or for the national health service in the Member State of importation, as parallel importers and pharmacists would just split the price difference between themselves. Needless to say, pharmaceutical companies were not amused, and more than a few elected to take the opportunity of the natural market segmentation resulting from unconnected national marketing authorizations to even accentuate product differentiation.

Thus, the very same medicine would be marketed in different Member Sates under different brand names, different colours, different pack sizes; the same pill was to be taken before breakfast in one Member State, after lunch in another, before going to bed in a third… Whether these differences reflected different medical traditions in the Member States, or different reimbursement policies by national health system paymasters, or deliberate practices by producers, one thing was clear: a single market, there was not.

Most worrying however was the considerable time taken for new medicinal products to reach the European market, depriving European patients from the benefits of pharmaceutical innovation and preventing pharmaceutical companies from reaping the benefits of their research and development. Regulation (EEC) No 1768/92 introduced the 'supplementary protection certificate' (SPC) for medicinal products which was making up for the long time needed to obtain regulatory approval by extending the patent protection for a maximum period of 5 years. However important for the industry, it was addressing the symptoms of the problem rather than its cause, and did not do anything to bring innovation closer to the patient.

A new European authorization system for pharmaceuticals

In November 1990, the Commission had proposed to Council and Parliament a major overhaul of the European authorization system for medicinal products. This was providing for the introduction of a 'centralized' Community authorization procedure for technologically advanced medicinal products, in particular those derived from biotechnology. The 'centralized procedure' would also be available, on a voluntary basis, to for all products containing new active substances.

For already authorised medicinal products, a series of mechanisms were proposed, under a so-called 'decentralized procedure', whereby a company could ask for the recognition of the authorization issued by a Member State in one or more of the other Member States. If one or more of the other Member States considered that there were grounds for supposing that the authorization of the medicinal product concerned could present a risk to public health, the matter would be referred to the appropriate committee and a decision would be taken at Community level which would be binding on all Member States. This kind of 'Community arbitration' would also be available whenever divergent decisions had been taken by two or more Member States, and it was felt that there was a Community interest in settling the matter.

Whilst most stakeholders, and notably the research-based pharmaceutical industry, strongly supported these proposals, there was considerable opposition from a number of Member States, in particular in respect of the centralised procedure, as this was actually transferring a major competence from the Member States to the Community.

The creation of the European Medicines Agency

To support the operation of the new European authorization system, the Commission had proposed to set up a 'European Medicines Evaluation Agency' (EMEA).

Under the 'centralized procedure' the application for the authorization of a new technologically advanced medicinal products would be submitted directly to the EMEA, which would provide a scientific evaluation of the highest possible standard of the quality, safety and efficacy of the product. In the case of a positive EMEA opinion , the Commission would grant the marketing authorisation if this was also supported

by a qualified majority of Member States under the 'comitology' procedure applicable at the time.

The proposal to lay down a centralized procedure and to establish the EMEA provided for passionate debates. Although both contributed to the completion of the single market beyond any possible doubt, the Council did not accept the legal basis proposed by the Commission (Article 100A EEC) and considered the proposal under Article 235 EEC instead. Unlike Article 100A (decision by qualified majority), Article 235 notably required unanimity for a decision to be taken. With hindsight, this may have been a blessing in disguise, as it was much better for the new authorization system and the EMEA to be endorsed by all Member States, as it eventually was, rather than by a majority of them, not to mention the overwhelming support of Parliament.

Regulation (EEC) No 2309 (establishing the centralized procedure and the EMEA) was thus adopted unanimously by the Council in July 1993, only one month after Directive 93/39/EEC (decentralized procedure) had also been adopted, by qualified majority. It was soon after decided that the EMEA would have its seat in London (and not Barcelona, as was widely expected). The EMEA was inaugurated on 26 January 1995, and on 20 October 1995, the Commission granted the first Community marketing authorization, following a positive EMEA opinion for Gonal-F, an infertility medicine.

The centralized procedure was an instant success, as it effectively allowed access to the entire EU market in little over a year, closely matching the mean review time of the U.S. FDA. Previously, it took on average 6 years for a new medicines to be authorised in a significant number of Member States.

After a slow start, use of the decentralized procedure also increased significantly, in sharp contrast with the very modest results of its predecessor, the 'multi-state procedure'. They weren't many referrals, though: the mere threat of a binding arbitration proved a sufficient deterrent in all but exceptional cases. Member States were obviously eager to prove the inherent value of the decentralized procedure and to maintain it as an attractive alternative to the centralized procedure in all cases were the use of the latter was not compulsory in view of the nature of the product.

The EMA: the hub of a network of national administrations

The success of the new authorization system for pharmaceuticals established in the 90s owed a lot to the structure of the EMEA, or EMA as it has been renamed in the meantime. Far from being an isolated European agency, the EMA is actually the hub of a network of national administrations and agencies.

This is first and foremost reflected in the organs of the EMA. The management board, which oversees the operations of the agency, is essentially composed of representatives of the Member States, with the addition of two representatives each for the European Parliament and the Commission. The Member States also appoint the members of all scientific committees operating within the Agency, and propose experts to serve on the working parties and scientific advisory groups.

Secondly, upon receipt of an application for a Community marketing authorization, the EMA committees actually delegate the assessment of the medicinal product concerned to one or two of their Members, acting as rapporteur and co-rapporteur as the case may be. About one half of the fees paid by applicants is actually transferred to the Member States national agencies by way of remuneration for the services thus provided to the EMA. In general, Members of the committees and experts responsible for evaluating medicinal products rely on the resources available to the national marketing authorisation bodies which appointed them.

Thirdly, as it does not have its own inspectors, the EMA relies on the Member States' competent authorities to inspect manufacturers, whether they are established in the EU or in a third country. Such an inspection may be necessary, for instance, for the purpose of assessing an application for a Community marketing authorization.

Conclusion

Under the centralized procedure, new innovative medicines were reaching the entire EU market at the end of the 90s in a fraction of the time that was needed a decade earlier. In turn, the decentralized procedure proved much more resilient than many had expected, and provided a real alternative to the centralized procedure.

Admittedly, new difficulties arose, notably in terms of availability and delays to market in some Member States. Towards the end of the 90's, Commissioner Martin Bangemann convened a series of Roundtables in an effort to engage the research and development-based part of the pharmaceutical industry and its regulators on how to address the pressures growing in the pharmaceutical market in ways that would allow Member States to maintain control over aggregate expenditure on pharmaceuticals whilst creating an economic framework that would stimulate the development of the competitiveness of the European aspects of this important industrial sector.

The outstanding cooperation between the Commission, the EMA and the Member Sates, allowed the EU to affirm its leadership on the international scene, notably in ICH, which was about to embark on an ambitious project to develop a common application dossier to facilitate global developments of medicinal products. Strong ties were built with the candidate countries of central and eastern Europe, which would prove essential for the subsequent enlargement of the EU a few years later. At home, EMA set up new standards in matters of communication, public consultation, access to document and reaching out to stakeholders. In less than a decade, the EU regulatory system for pharmaceuticals had transformed itself into the world-class operation which it is still today.