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EDITORIAL

EMA and national drug agencies: cooperation or competition?



Contribución de la Agencia Española de Medicamentos y Productos Sanitarios al Comité Europeo de Evaluación de Medicamentos de Uso Humano

Since 1995, the European Medicines Agency (EMA) has adopted the centralized procedure to grant marketing authorizations across all its Member States.¹

This attempt to harmonize the drug regulation procedure in Europe, of which the centralized procedure is a major expression, goes back well beyond the creation of EMA. In 1965, the first European legislation in the pharmaceutical sector clarified what a “medicinal product” was considered to be and established that a drug would only be approved for marketing if its safety, effectiveness and therapeutic value were documented.² Ten years later, two Council Directives introduced common rules to standardize tests and trials involving medicinal products in the European Community³ and a multi-state mutual recognition procedure.⁴ Though these represented the first steps toward a single evaluation and decision, the final responsibility for decision at that time still rested with the Member State concerned.

The first real “coordinated procedure” for highly innovative medicinal products was introduced in 1987 and differed from the multi-state procedure as it was applicable prior to any national decisions. This procedure became a standard with Council Regulation EEC/2309/93, which established the European Medicines Evaluation Agency (EMEA, now EMA) and its Committee on Proprietary Medicinal Products Committee (CPMP, now Committee on Medicinal Products for Human Use, CHMP).⁵ This Regulation clarified the differences between the Centralized Procedure, which would be supported by the new Agency, and the Decentralized and Mutual Recognition procedures, under the control of national agencies. It also stated that decisions on the authorization of medicinal products should be based on their quality, safety and efficacy and not on economic or other considerations.⁵

Most observers consider the EMA a success story, as it introduced harmonized evaluation criteria by establishing

a homogeneous regulatory policy throughout the European Union (EU). It also served to optimize the evaluation process and the use of the human resources and expertise devoted to the same objective, saving time and effort by the Member States but also time and financial resources by the companies. The Member States hampered the Commission’s effort at harmonization, fearing a loss of sovereignty in a common drug market. This led to a model where, while the pivotal role of the EMA as the engine of the European pharmaceutical regulatory system is evident, the roles of national competent authorities remain equally important.⁶

The EMA was never meant to be a European equivalent of the US Food and Drug Administration. It acts as a highly-specialized secretariat and has to be responsive to national authorities’ demands. The European Union regulatory network consists of 31 national authorities who are each responsible for regulatory tasks in their country’s system^{7,8} and provide technical and scientific expertise to the EMA through membership of its scientific committees, such as the CHMP. As pointed out by Alonso-Gutierrez and colleagues⁹ the EMA contracts out the scientific evaluation of products in the centralized procedure to a handful of national authorities (Rapporteurs and Co-Rapporteurs). The appointment of the Rapporteurs usually starts seven months before the intended submission date of the application, with the actual appointment taking place one month later. It is said to be based on “objective criteria”, namely to “allow the use of the best and available expertise” on the relevant scientific area.¹⁰ During the assessment procedure, the necessary scientific work to evaluate the quality, efficacy and safety of a new medicinal product does not take place in London, where the EMA is located, but in the offices of the Agency of the Rapporteurs’ Member States.

The wide variability between EU Member States in contributing to the Centralized Procedure is well known and

documented. This variability does not seem to correlate with the countries' populations and the older, better-structured EU countries most often candidate themselves and are appointed as Rapporteurs. Countries that joined the EU later (and have lower economic resources) are also those in which the level of evaluation and uptake of new medicines is low. In fact, despite harmonization of the marketing authorization process in Europe, innovative medicines are not equally available to all citizens in the EU in a timely and equitable manner.¹¹

The differences in the uptake of medicines between EU Member States seems to reflect their economic situation and resource possibilities of these countries. In some countries like Portugal and the Baltic States over 40% of the centrally authorized medicinal products were not available even five years after the formal EU market authorization.¹¹ Reimbursement, pricing and formulary policies, and competence of each national government strongly influence the uptake of new medicines in clinical practice. Moreover, after the licensing of a new medicinal product the national authorities or other governmental agencies usually do a health technology assessment (HTA) to evaluate the medical, social, ethical, and economic implications of the implementation, distribution, and use of a health technology, including cost-effectiveness analysis. These evaluations are tailored for national health policy stakeholders and intended to bridge the gap between research data and health policy decision-making. Here again, even though licensing is harmonized throughout the EU, evaluation of the relative effectiveness and place in therapy of a new drug relies on the national governments. This task is even more complicated by the lack of a robust evidence package on the comparative efficacy and safety of drugs at the time of approval. How can new drugs be assessed in regard to the existing therapeutic options in the absence of data from adequate comparative trials? The evidence gap is usually filled by contextual national pressures, e.g. from politics, finance, society and media, increasing the differences in decision-making, hence also in the uptake of new medicine.

In its Roadmap to 2015, the EMA proposed better alignment of regulators' and HTA bodies' evidence requirements and a constant dialogue throughout the whole medicinal product's life-cycle.¹² This dialogue should be enriched by close liaison with academic research, which plays a key role in producing evidence on the value of drugs in clinical settings, and with patients and citizens who should always be the focus of drug development. All these expectations can only be fulfilled if transparency is guaranteed, from the data and documents that form the basis of the evaluation to the decision-making itself.

A first step in the collaboration between EMA and the European network for Health Technology Assessment (EUNetHTA) regarded evaluation of the usefulness of information reported in the European Public Assessment Report (EPAR).¹³ Though important, the EPAR represents only the tip of the iceberg of the knowledge needed to establish the efficacy and safety of any new drug. The path toward more harmonized drug access for European citizens should start from a more robust licensing process,¹⁴ aimed at assessing the real added value of new medicinal products and not only their innovative pharmaceutical features. This

would also assist the Member States in their HTA and in the negotiation of sustainable prices.

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