Pharmacovigilance Review

Elisabethann Wright of Hogan & Hartson discusses the need to revise the current EU pharmacovigilance provisions

On 10th December 2008, the European Commission published its long-awaited proposal for a review of various aspects of the current EU legislation governing the authorisation of human medicinal products. The proposal includes propositions to revise the existing pharmacovigilance system. These elements of the proposal followed a detailed consultation procedure carried out by the European Commission. The replies to the consultation process demonstrated that a significant number of respondents felt that the current system was in great need of review. It was considered to be overly complex, with the available resources not always used to the best advantage. Such resources were often focused on meeting bureaucratic requirements, rather than proactively gathering data and information about the safety and risks of medicines. A need for rationalisation of the current system was also underlined.

The European Commission itself acknowledged that the present EU legislative framework governing pharmacovigilance provided only high level principles for pharmacovigilance, with the detailed procedures being left to the community guidance found in the 'Notice to Applicants'. One consequence of this was to leave the national authorities of the EU Member States with significant scope to elaborate what have become divergent legal and administrative practices. As a result, national authorities have imposed varying obligations on marketing authorisation holders (MAH), including, in some instances, the requirement that the MAH's qualified person be resident on their territory, rather than on EU territory as provided by the Community Code. One consequence of this flexibility granted to the national authorities of EU Member States is to impose a significant administrative burden on MAHs without necessarily leading to added value in terms of health protection.

Lack of a clear division of roles and responsibilities between key responsible parties and a lack of clear obligations against which they perform their roles has, the European Commission believes, resulted in poor compliance with pharmacovigilance rules. Furthermore, decision-making on drug safety issues has been slow, particularly for nationally authorised products, and has combined with frequent disharmony in action taken by the Member States.

The importance of a robust and effective pharmacovigilance system is demonstrated in the statistics provided by the European Commission regarding the financial consequences of adverse events related to human medicinal products. The Commission calls attention to the fact that between 0.12 and 0.22 per cent of hospital admissions result in death due to an adverse drug reaction (ADR). This corresponds to 100,800-197,000 deaths annually in the EU. Furthermore, between three and 10 per cent of hospital admissions are caused by ADRs (corresponding to between 2.5 and 8.4 million annually in the EU), while 2.1 to 6.5 per cent of hospitalised patients suffer an ADR, corresponding to 1.8 to 5.5 million cases annually in the EU. The Commission considers that an eye-watering €79 billion is a reasonable estimate of the total cost of ADRs occurring in the EU.

The European Commission therefore acknowledges that new measures are necessary to improve the way that the EU rules operate on the pharmacovigilance of medicinal products. The proposed modifications seek to change the Community Code on medicinal products and the EMEA Regulation governing pharmacovigilance so as to better protect public health, ensure proper functioning of the internal market and simplify the current procedures.

With admirable honesty, the European Commission also acknowledges that some of the pharmacovigilance changes introduced in the Community Code as adopted in 2001 have significantly increased administrative burden on MAHs without necessarily improving public health protection. Perhaps the best example of this is the introduction of the requirement for submission of a detailed description of the company pharmacovigilance system at the time of authorisation which then needs to be kept up to date with regulatory scrutiny (with payment of related 'variation fees' for each minor improvement to the company system).

In a manner that can sometimes be ambiguous, the European Commission also underlines the fact that there is an obvious link between the robustness of pharmacovigilance and innovation. While it is unquestionably true that investor confidence in funding pharmaceutical R&D can be linked to

Table 1: Incidence and prevalence of adverse drug reactions reported in literature (2)

Outcome	Incidence/prevalence	Reference
ADR-related hospital admissions		
Drug-related admissions	4.2%	Einarson (1)
Drug-related admissions to an emergency department	5.7%	Dartnell *et al* (2)
Admissions associated with drug-related problems among children	3.4%	Easton *et al* (3)
Admission caused by ADRs	3.2%	Pouyanne *et al* (4)
ADR-related hospitalisation of the residents at a nursing facility (over four years)	15.7%	Cooper (5)
Patients with ADRs as reason for admission	7.2%	Lagnaoui *et al*(8)
ADRs in hospitalised patients		
Serious ADRs	6.7%	Lazarou *et al* (6)
ADRs during hospitalisation in a cancer institute	5%	Lapeyere-Mestre *et al* (7)
Number of ADRs per 1,000 patient-days in a medical ward	10.1 cases	Lagnaoui *et al* (8)
Number of ADRs per 1,000 patient-days in an internal medicine department	5.6 cases	Moore *et al* (9)

pharmacovigilance, the claim that "regulatory authority decision-making when authorising products is directly linked to the robustness of post-authorisation safety monitoring (pharmacovigilance)" is less clear (1). In the Commission's view, if regulators are confident in the pharmacovigilance system and aware that post-authorisation safety studies will be conducted, then they will be more likely to allow a product onto the market. While the Commission's conclusion – that this is of crucial benefit to patients with unmet medical needs – is unquestionably true, it must be questioned how far this approach dictates the decisions of competent national authorities in other circumstances.

The European Commission's proposal to revise the current pharmacovigilance structure includes some welcome practical modifications of existing EU legislation. These include a clarification of the roles and responsibilities of the key responsible parties, rationalisation of EU decision-making on drug safety issues, strengthening companies' pharmacovigilance systems, and ensuring the collection of high quality data.

One of the proposals that may have both positive and negative consequences (if adopted in its current form) is the suggestion that additional stakeholders would be involved in pharmacovigilance. This would include direct patient reporting of suspected adverse reactions. While there are undoubtedly benefits to be gained from receipt of ADR reports from as wide a variety of sources as possible, including the patients themselves, the framework that would be required to ensure that such a system functioned in practice may result in the imposition on MAHs of an even greater administrative burden than that which they currently face.

The suggestion in the European Commission proposals that the current routine requirement for industry periodic reports (PSURs) for low risk, old and established products be terminated is very welcome to MAHs. However, closer scrutiny of the suitability of the related procedure to ensure adequate reporting of ADRs for these products can be expected.

The European Commission proposal that a clear EMEA committee structure for pharmacovigilance, scientific assessment and decision making coordinating activities be established may well provoke debate. The proposals include suggestions for a new EMEA pharmacovigilance committee structure to require submission and coordinate assessment of PSURs and make consequent recommendations for product labelling. The recent adoption of the Advanced Therapies Regulation and the Commission's proposed 'recast' of existing EU legislation governing medical devices have both provoked debate regarding the perceived extension of current EMEA powers to areas not within its original sphere of activity, an extension that not everyone welcomes or feels is appropriate. This part of the Commission's proposal would appear likely to add to current debate.

The sentiment behind the proposed revision to the pharmacovigilance provisions is to be welcomed. Few would deny that the current process is not always effective, and can impose disproportionate and cumbersome obligations. However, debates on the European Commission's proposals, particularly with the national authorities of the EU Member States, are to be anticipated.

Reference

1. SEC, 2670 Impact Assessment, 2008
2. Lundkvist J and Jonsson B, Pharmacoeconomics of adverse drug reactions, *Fundamental and Clinical Pharmacology* 18: pp275-280, 2004

About the author

Elisabethann Wright's experience in the area of European law has included periods in private practice and periods working with international institutions. She focuses on European Union (EU) law relating to life sciences, with particular emphasis on pharmaceutical law, medical devices, food law and the environment. Elisabethann has extensive experience in litigation before the European Court of Justice, the European Court of First Instance, and the European Free Trade Agreement (EFTA) Court. Her practice includes advising on the challenge ability of decisions of EU Institutions and the validity of EU legislation. Elisabethann also advises on issues of European government contracts and public international law.
Email: ewright@hhlaw.com