European Society of Radiology

Vienna, September 10, 2010

Contribution of the European Society of Radiology (ESR) to the Public Consultation on the European Commission document entitled "Draft detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ('CT-3')"

The ESR generally agrees on the content of the CT-3 document, and in particular on:

- The legal framework for reporting serious adverse events arising during clinical trials of an investigational medical product by the investigator to the sponsor, including the timelines defined for immediate reporting;

- The legal framework for reporting suspected unexpected serious adverse reactions (SUSARs), including those occurring after the end of the trial, by the sponsor to regulators (the Ethical Committee issuing the single opinion and, up until today, the relevant national competent authority);

- The role of the Eudravigilance Clinical Trials Module (EVCTM) and its enhanced functionalities.

The ESR suggests to initially adopt the direct reporting to the EVCTM as unique way or to define a pathway towards the generalized adoption of the direct reporting to the EVCTM, in order to make the role of the European structure stronger in its relation with Member States. This is proposed considering the need of fast management of information regarding SUSARs related to investigational medical products all over the European Union.

Moreover, the ESR pays attention to the problem of "causality assessment" as it is addressed in this CT-3 document and in the ICH E2A, Chapter 3A.
In fact, a "reasonable casual relationship" between the serious adverse event and the investigational medicinal product may be very difficult to be defined in case of late events. In the radiological world, the recent experience of the nephrogenic systemic sclerosis (NSF) created a concern about possible hidden adverse reactions to radiological contrast materials. NSF is a very rare consequence of the administration of gadolinium-based contrast materials for magnetic resonance imaging in patients with acute kidney disease or severe chronic kidney disease (i.e., with estimated glomerular filtration rate <30 ml/min x 1.73 m^2). It was firstly reported in 1997 as a scleromixedema-like disease in renal-dialysis patients which warranted its designation as a new clinic-pathological entity [1], but the association between the intravenous administration gadolinium-based contrast materials and the development of NSF was firstly hypothesized only in 2006 [2]. Notably, the interval between contrast administration and disease onset ranges from a few days to more than 6 years [3]. This episode poses more problems related to pharmacovigilance as set out in Directive 2001/83/EC than those related to the Directive 2001/20/EC (and ICH E2A and CT-3 documents), but the issue of late SUSARs with uncertain causal relationship could be specifically addressed also for reporting in the context of clinical trials of investigational medical products.

References:

1. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant. 2006; 21(4):1104-1108.
2. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet. 2000; 356:1000-1001.
3. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. Clin J Am Soc Nephrol 2007;2:264-267