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EDITORIAL

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The European Directive 2001/20 for clinical research: friend or foe?

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In their contribution to *Intensive Care Medicine* Veelo et al. [1] show how a recent modification to the Dutch law on research humans will, or at least could, improve inclusions in clinical trials. The new provision allows family members to act as legal representatives for granting consent/assent in case the patient is himself incapacitated, whereas the previous legislation restricted that possibility only to the spouse. Such a strange limitation had raised an outcry in the medical community, as described in this journal by Kesecioglu et al. [2]. Apparently the lobbying by our Dutch colleagues toward their policymakers proved efficient, which is a good news to all the European investigators still fighting against inadequate, if not inept, provisions in their own national legislations. It is worth remembering that these new hurdles are not always imposed by the implementation of EU directives and other Brussels "guidance" but by national policymakers. The other important information in their contribution is that patients interviewed as to how they felt about their representatives gave them unequivocally good ratings. This confirms similar findings recently reported in this journal by British investigators [3].
In an accompanying contribution, van der Voort et al. [4], also from The Netherlands, comment on the same legislative move and add some information regarding other new important provisions. A rigid interpretation of directive 2001/20 has in some EU member states mandated that all sponsors, and not only the pharmaceutical industry, finance freely all trial drugs. Academic sponsors, especially those dealing with cancer research, such as the EORTC [5], have complained strongly, arguing that such a provision is most of the time absurd, for instance, when applied to trials comparing existing strategies or adding only a new compound to already marketed and widely used therapies. The Dutch regulation has been amended in such a way that other bodies are now allowed to fund clinical research, specifically permitting payment of already registered drugs. Similarly, in France an amendment to a law on research voted last April gave the same possibility to academic sponsors, ruling out a decree promulgated in 1990!
Where are we, 2 years after directive 2001/20 was implemented in all EU member States?

Some hot issues seem to have been somewhat adequately settled. The mysterious "legal representative" has some kind of existence in nearly all national laws [6]. When he/she is not a person designated in advance by the patient himself, he/she can be a member of the family, which is commonsense. In most European countries emergency research is now possible with a delayed consent, or a mere waiver. Directive 2005/28 seems to have confirmed that those countries such as Belgium, The Netherlands, and France were right in authorizing this possibility since 2004. Parliament in the United Kingdom is considering modifying its legislation to incorporate such a provision in 2007, which was initially denied [7, 8]. The process for trial authorization, submission to a Research Ethics Committee and declaration of adverse events to the competent authority

are currently being implemented in all EU countries, according to several Brussels "detailed guidance".
A key issue has always been that all regulations and laws concerning clinical research have been drafted and implemented in the context of the assessment and authorization of medical drugs [9]. The guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use on good clinical practices, right or wrong [10], have been so far the unique template for all types of research. After all, directive 2001/20 was produced by the Directorate General Enterprise of the EU Commission and not by other bodies focused on research, human rights or public health! Existence, legitimacy, and value of academic/noncommercial research have only recently been recognized. The lobbying capacities of Big Pharma and Academia are largely unequal. Obtaining recognition of the specificities of academic research is a long and painful process. However, gaining the regulatory network which allows performing that research is even more excruciating. The results are finally there. Academic/institutional sponsors were mentioned in Recital 14 of Directive 2001/20 as "non commercial" sponsors, and again in Directive 2005/28 (Recital 11). Moreover, a detailed guidance on the "specific modalities for non-commercial trials" has been drafted by the EU Commission
and is currently subject to public consultation (available at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm). Since 2004 the French law on clinical research entails several important provisions specifically directed to academic sponsors.
What still remains to be solved?
Van der Voort et al. conclude their article with a touch of anxiety as to the possibility for academic researchers to fulfill all the new obligations and survive the added red tape the directive now imposes, ignoring that most of the burden will actually fall on sponsors. Obtaining simplified and expedited ways to carry out research with no risks, however, becomes of paramount importance for academic investigators and sponsors, almost a matter of survival. There are actually two separate issues here: research on drugs, which is governed by Directive 2001/20, with all derived national regulations, and research on other topics, for instance, medical devices, surgery, pathophysiology, epidemiology.
Regarding research on drugs, there is no discussion that phases 1, 2, and 3 of drug research must comply with the common rules. Whatever its sponsor, such research is risky, as demonstrated by many previous ICU trials [11]; all relevant and indeed compulsory provisions must be implemented accordingly. However, applying such rules to phase 4 trials, when experimental drugs have been in the market sometimes for decades, makes no sense. These trials are badly needed today [12]. Yet, the current system of authorization and oversight is simply not applicable to them. A concerted action at the Commission level, jointly with other academic sponsors, scientific European societies and funding bodies should be able to convince European lawmakers that Directive 2001/20 must be revised to take in account this issue, totally missed when it was drafted.

Regarding research
not concerning drugs, some European countries, including France, The Netherlands, Belgium, and Germany, have extended their regulatory system to all types of research well beyond the realm of drugs. The United Kingdom is considering doing the same [8]. France now has a special set of regulations concerning research applied to "current care", in an expedited and simpler way. In addition
to the legal framework applied to drug research, other countries are still in a total legal vacuum. Specific and common rules need to be established for such research.

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