What's next for the EU Clinical Trials Directive

The European Commission will soon issue its legislative proposal to revise the *EU Clinical Trials Directive (2001/20/EC)* after years of negotiations that have included a multitude of stakeholder meetings and two public consultations.

Although this will mark the beginning of a potentially lengthy legislative process, industry, regulators, academia, patients' organisations and other stakeholders see the revision as a unique opportunity to establish a clinical trials framework that is fit for purpose, and in turn, to revitalise declining investment in European research.

The objectives of the Clinical Trials Directive are to provide greater protection to subjects participating in clinical trials, ensure quality of conduct, and harmonise regulation and conduct of trials throughout Europe. However, there is widespread stakeholder dissatisfaction with the legislation. Its shortcomings – which largely focus on unnecessary administrative burdens and a lack of harmonisation in applying the law across EU member states – are well documented.

Each stakeholder group has its own agenda, but most, if not all, agree that costs associated with conducting clinical trials have risen exponentially since *Directive 2001/20/EC* entered into force in 2004. Many believe that this has been a contributing factor in the overall decline in trials conducted in Europe.

There is general consensus about which parts of the law are flawed. The Commission aims to address these in its upcoming proposal, due to be presented to the European Parliament in mid-2012, and ideally reaching first reading agreement before parliamentary elections in 2014.

Whereas the Commission launched an initial consultation in 2009 to assess the impact of the revision and identify the key areas of contention, its second consultation[1] in February 2011 attempted to come up with concrete solutions. These are still under negotiation, although the formal consultation is now closed.

Application process

One of the main complaints about the Directive is that sponsors of multinational trials have to submit an application in each member state concerned. This creates unnecessary administrative costs because largely identical information has to be sent to several different member states. To address this, the Commission has suggested that an EU portal be created where both commercial and non-commercial sponsors (eg academia) can file a single submission.

Although the portal would be challenging to set up, there is broad support for this concept. Some stakeholders such as the European Association for Bioindustries (EuropaBio) have stressed, however, that a single clinical trial application would need a common standardised format that reflects the requirements in current European Commission guidelines.[2,3] In other words, a harmonised dossier would not be a cumulative list of all the country-specific requirements.

Efpia, the European Federation of Pharmaceutical Industries and Associations, also supports the single EU portal concept. "It would avoid the first divergence of requirements with some very detailed, very specific local requirements...and ultimately submitting the same set of data would mean the evaluation process itself would be streamlined," the federation's regulatory affairs director Isabelle Clamou told *MedNous*.

Harmonised assessment

Divergent assessment processes across member states are an even greater hurdle. Currently, national competent authorities in member states have different processes for carrying out reviews as well as different documentation requirements. Respondents to the Commission's latest consultation emphasised that regulators' expectations varied with regard to the content of the documentation, rather than the documentation itself.[4]

To further complicate the situation, the remit of the competent authorities and the ethics committees also varies from country to country, said Mrs Clamou. "There are certain parts of clinical trials applications that are reviewed by the national authority in one member state, while they are reviewed by the ethics committee in another member state. The most known case is the Netherlands, where the ethics committee has a scope of review which is extremely broad compared with other member states," she explained.

The Commission has not addressed the role of ethics committees in its consultations, however, because this is considered a national competence. "The Commission says it has limited flexibility" in this regard, according to Mrs Clamou.

She said that Efpia would "see value with a pan-European [scientific] assessment", despite the Commission and other stakeholders believing that a centralised assessment option would be unworkable.

In its 2011 consultation, the Commission sought input on whether a separate national assessment (as now), a centralised assessment (similar to the centralised marketing authorisation procedure) or a co-ordinated assessment procedure ('CAP', modelled to some degree on the decentralised procedure for marketing authorisations) would be the best way forward. Many stakeholders, as well as the Commission, feel that complete centralisation of the process via, for example, a super committee with representatives of all the member states, is an unrealistic option.

According to the Commission, a centralised assessment would not take into account ethical, national and local perspectives, nor would this approach be flexible enough to handle the large quantity of multinational trials that take place each year. At a meeting hosted by Efpia and Roche on 7 March, European commissioner for health and consumer policy John Dalli said that "a central bureaucracy would lead to uncompetitive timelines, and to inflexible and disproportionately expensive mechanisms".[5] (Please see page 11 for a synopsis of his comments).

Mr Dalli said that the legislative proposal would instead introduce an assessment procedure that had a "mechanism

of co-operation" between member states. To avoid any conflicts of interest, this procedure would be strictly separate from the scientific advice process, which gives guidance on what clinical data are desirable in a future marketing authorisation application. The implication is that the European Medicines Agency would not be involved in any assessment of clinical trials applications.

Like Efpia, EuropaBio would still like to see a single scientific assessment to improve the approval of multi-state clinical trials, according to Christiane Abouzeid, who heads regulatory affairs at the UK's BioIndustry Association and is the topic leader of EuropaBio's Clinical Trials Group. "We want to see something that goes beyond CAP," Dr Abouzeid told *MedNous* in a phone interview. Both she and Mrs Clamou have acknowledged that a pan-European outcome is the way forward for industry.

This would require the integration of certain decisions, such as ethical aspects and local facilities approval – though made separately at national level – into the process for the authorisation of a clinical trial, said Dr Abouzeid.

Asked whether a system such as the Heads of Medicines Agencies' Voluntary Harmonisation Procedure (VHP) would be feasible, Dr Abouzeid praised the system, noting it was a first step in providing a harmonised regulatory decision across member states participating in multinational clinical trials. However, she said that it had its limitations as it is run on a voluntary basis and some member states have declined to participate. Mrs Clamou's comments were along the same lines.

At the Efpia/Roche meeting, Commissioner Dalli announced that the Commission would be proposing the revisions as a Regulation rather than a Directive. Though a Regulation may not guarantee uniformity, it would be less likely to result in a differing application of the law because it would apply directly in all member states. A Directive, on the other hand, could again lead to the transposition of similar but different national laws in each member state.

The Regulation will be subject to the ordinary legislative procedure, meaning both the European Parliament and the Council of Ministers will have to approve it.

Reducing the regulatory burden

To reduce the regulatory burden of the current framework and cut down on costs, industry and other stakeholders are also calling for risk-adapted rules for the content of applications and for safety reporting. There is general consensus that the existing one-size-fits-all system does not take into account trials where the risk to the patient is minimal.

The Commission has also recognised this and plans to address it in the legislative proposal. Industry has cautioned, however, that the definition of "risk" should be clearly defined and scientifically based.

Trials with already authorised medicines that may improve treatments – often conducted by academia – are prime examples of those where the risk to patients is relatively low. Professor Olivier Chassany, chairman of a French ethics committee in Paris, suggested at a December 2011 workshop that adaptations for minimal risk trials could include, for example, expedited reviews by the regulators and ethics committees.[6]

Another major area of contention with the current legislation is safety reporting requirements, particularly for suspected unexpected serious adverse reactions. Both EuropaBio and Efpia say that the safety reporting requirements need to be "meaningful and useful" and that quality is more important than quantity. There is criticism that the current system leads to the reporting of information that is not even relevant to maintaining patient safety, and moreover, that the volume of reports makes it difficult to discern which should be acted on.[7]

Clarification of scope and definitions is also sorely needed, most notably with the definition of 'investigational medicinal product' and 'substantial amendment'. According to Dr Abouzeid, there has been progress on reaching common ground on the latter and she is hopeful that the legislative proposal will reflect this.

Flexible and global

Mrs Clamou said that one of Efpia's key messages is that the revision must better reflect the global nature of the pharmaceutical industry and be ambitious enough to make the legislative process predictable for the next 10-20 years. Furthermore, she said that it should be flexible enough to adapt to new science and development pathways such as personalised medicine, where, for example, one would expect to see more clinical trials with fewer participants.

Indeed, there is a lot more riding on the outcome of this revision than merely achieving greater efficiency in the clinical trials review process. This 11-page piece of legislation has been blamed not only for contributing to the downward spiral in clinical trials carried out in the EU, but also for negatively influencing medical research at the global level.

To help reverse this trend and avoid future pitfalls, the Commission and EU legislators will need to be more forward thinking than they were with *Directive 2001/20/EC*. As Commissioner Dalli said on 7 March: "This time we have to get it right."

References: 1. European Commission, Revision of the 'Clinical Trials Directive' 2001/20/EC: Concept Paper Submitted for Public Consultation, 9 February 2011, http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm.
2. EuropaBio response to European Commission consultation, May 2011, www.europabio.org.
3. European Commission, EudraLex, Volume 10: Clinical trials guidelines, http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm.
4. European Commission, Summary of the replies to the public consultation on the 'concept paper', 7 July 2011, http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm.
5. Commissioner Dalli's participation at the joint Efpia/Roche event on 'The Revision of the Clinical Trials Directive', 7 March 2012, http://ec.europa.eu/commission_2010-2014/dalli/docs/speech_07032012_en.pdf.
6. EuropaBio, Workshop on the Benefits of a Simplified and Coherent Clinical Trials Framework in Europe, 1 December 2011.
7. Supporting research, protecting patients: Cancer Research UK's recommendations to reform the Clinical Trials Directive, February 2012, http://info.cancerresearchuk.org.

This article was written by Karen Finn, contributing editor to *MedNous*.