Assessing the European Commission’s Proposal to Revise the Clinical Trial Directive (2001/20/EC)

A six-step process on how life sciences organizations can be better prepared for impending legislation that will overthrow regulatory requirements for clinical trials.

Executive Summary

There is a significant amount of focus on research and clinical trials/development (R&D) for improving the delivery of better healthcare, a development which would undoubtedly improve the commercial prospects of life sciences organizations. In 2011, PhRMA member companies alone invested $49.5 billion in R&D to bring forth new and powerful medical products to fight disease.1 While R&D investments are increasing (almost doubling during the last decade), regulatory agencies are working hard to put appropriate checks and balances in place to ensure human rights are protected.

Once such major regulation is the Clinical Trials Directive (CTD) of the European Commission (EU), 2001/20/EC, which was issued in May 2001. Its aim was facilitating quality research by companies seeking to bring affordable and life-saving products to local markets. Industry leaders see the €20 billion annual average clinical trial investment by global companies as vital to the growth policy of the EU 2020 agenda. While the CTD has brought significant improvements in the practice and compliance of drug research within EU states, the regulation has been subject to serious criticism for deficiencies in its operating framework and nonuniformity in trial procedures across European states.

On July 17, 2012, the EU commission adopted a historic proposal for a regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and revised the previous directive 2001/20/EC to make it less stringent. The legislative proposal is expected to go into effect in the 2016 session of the EU parliament and the council. The new objectives and policies in the proposal are expected to work in conjunction with other relevant EU regulations like Risk Management Plan (RMP), Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) and Identification of Medicinal Products (IDMP) for an improved regulatory framework and better clinical outcomes.

This white paper provides a granular understanding of the constructs behind the revision of the main CTD and presents our point of view on how life sciences organizations can be better prepared for the upcoming changes.
Aim and Scope of the EU Clinical Trials Directive, 2001/20/EC

Adopted in 2004, the EU CTD’s fundamental aims were to:
• Protect the rights, safety and well-being of clinical trial participants.
• Simplify and harmonise the administrative provisions governing clinical trials.
• Establish a transparent procedure to harmonise the conduct of clinical trials in Europe and ensure the credibility of research results.

Shortfalls of the EC Clinical Trial Directive 2001

The EU Clinical Trial Directive, 2001/20/EC, through lack of implementation of trial directives uniformly amongst member states and inattentive operating procedures, has caused business deceleration in clinical research in the EU member states. Data from the EudraCT database proves the uninterrupted decline of clinical trial activities within the last five years. What follows are the contributing factors for legislation proposing the revision of the CTD.

High Clinical Trials Conduct Cost

One of the major reasons for the proposal of a new directive is that the then-current Clinical Trial Directives policies were unable to normalize administrative and clinical trial conduct costs. Due to the increasing staff requirements and administrative burden, the need for a new directive will surely be a boon to the discontented clinical trial space stakeholders, especially noncommercial sponsors such as academics, foundations, hospitals and research networks. The impact of the current directive has resulted in high costs for the pharmaceuticals industry.

Decline in Applications for Clinical Trials in the EU

In the EU/EEA, approximately 4,400 clinical trials are applied for every year. This equals approximately 10,000 applications in the member states (as one clinical trial can mean up to 27 clinical trial applications). Approximately 60% of clinical trials are sponsored by the pharmaceuticals industry and 40% by other stakeholders, such as academics. According to the official EU database for clinical trials (EudraCT), since 2007 the number of clinical trials applied for in the EU has fallen by 25% to ~3,800 in 2011.

There are various reasons for the decline of clinical trials in the EU:2
• An increase in administrative costs up to ~98%.
• National differences in fees levied on noncommercial sponsors range from €0 to €2,500 for an initial ethics committee application and from €0 to €1,000 when submitting a substantial trial amendment.
• Fees paid to competent authorities range from €0 to €4,000 for an initial application and from €0 to €1,500 for a substantial amendment with waivers for noncommercial sponsors.
• Staff requirements for sponsors to conduct clinical trial authorization process have doubled to ~107%.
• In the safety reporting zone of clinical trial regulations, the number of employees required by pharmaceuticals companies increased by 85%.
• Insurance fees have drastically jumped, up to 800%, for industry sponsors.

Delays for Launching a Clinical Trial

The current CTD has limitations in handling protocol updates or amendments. Since more than one member state is involved in large clinical trials, there exists the need for amendments, updates to the documentation to ensure data reliability and similarity in understanding of the protocol. Due to this, study timelines are affected since there is a delay between the study startup phase (final protocol) and the study conduct phase (first patient visit). This was widely observed as a major reason for the decline in clinical trials and also the biggest concern for the clinical space in Europe. Note the following statistics:
• The average delay between finalization of the protocol and the “first patient in” has increased by 90%, to 152 days.²
• Sweden reported a decrease of 25% in submissions.
• Ireland reported a decrease of 40% in submissions, with a drop of 60% from noncommercial sponsors.
• According to Cancer Research UK (a charitable organization) the number of clinical trial applications was down by approximately 50% in the UK.
• The European Organization for Research and Treatment of Cancer (EORTC) saw its research activity drop from 23 new studies in 2007 to 10 studies in 2010.²

Complex Legal Landscape Within Each Member State

Due to the directive’s complexity, its transposition imposed a new legal landscape consisting of 27 frameworks at the EU national level. Although
the directive set out to introduce a single set of principles and procedures, EU member states have implemented it in different ways. Countries differ notably in their interpretation of the sponsorship rules, the complexity of the procedures for ethics approval and the level of detail required for drug safety reporting (see Figure 1).

The Impact of the Proposed Regulation

We believe that the new proposal for legislation will not only have a positive impact on the industry, but will subsequently confer advantages to subjects/patients as well. Investments in clinical trials in the EU will provide better efficiencies using procedural incentives, overhead reductions and IT rationalization.

The new directive will have direct impact on people, processes and technology. Figure 2 summarizes the potential strategic changes, the possible policy changes and the anticipated advantages/outcomes.

So how does a life sciences organization prepare for the upcoming change? For an organization to adapt to the new directive, we believe that the strategy can be logically constructed using a six-step process (see Figure 3).

Step One: Form a Core Group
- Create a group comprising personnel from regulatory affairs, clinical operations, technical architects, etc. from various departments.
- This group will be responsible for tracking the discussions, participating/creating a group that works with EMA throughout the process of defining the legislation.
- Prepare the organization to adopt the change from people, processes and technology.

Step Two: Determine Adoption Goals
- The directive will not only have impact on your internal environment, but will also extend to the external environment.
- Based on your organizational strategy, determine the adoption goals of the upcoming directive change. For example, if your organization sources the majority of its clinical development and safety work, it may want to deal with CROs, which means it should engage them early on in the process.
- Determine your exact priorities and budgeting.
- If need be, identify partner(s) whom you can trust in formulating adoption strategy and hand-holding throughout implementation. The partner(s)
can support you from legal, regulatory as well as techno-functional perspectives.

- Continue to monitor the progress of the directive’s definition.

**Step Three: Impact Assessment**

- Once the directive is ready for public review, conduct an impact assessment before you implement a solution to comply with the new directive.
- Based on your adoption criteria, identify what business units/processes, user communities, geographies, ongoing/upcoming molecule submissions, etc. will be impacted.
- Prioritize the impacted business units/processes based on the following criteria: patient safety, product quality, patent protection, market share protection, top-line/bottom-line impact, etc.
- Determine a phased rollout of the adoption for each impacted business process based on the above prioritization.

**Step Four: Pilot Roll Out**

- Out of the prioritized business units/processes, identify a business process where a pilot for the adoption can be carried out.
- Define specifications and anticipated outcomes.
- Determine the right IT systems required for the new processes.

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### New Legislation’s Potential Impact

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<th>Strategic Objectives</th>
<th>Possible Policy Changes</th>
<th>Advantages</th>
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<tbody>
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<td>A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials, taking into account the multinational research environment.</td>
<td>Single submission with joint assessment by member states of issues not related to ethical aspects. Replacement of the directive by a regulation.</td>
<td>Reduction in overall timeframe of clinical trial applications, marketing authorizations, etc. Direct time, effort and cost savings due to reduced administrative costs and burdens created by multiple submissions. Unlike a directive, which only binds member states to the result sought while leaving to them the choice of form and methods, a regulation would obviate the need for national transposition measures.</td>
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<td>Regulatory requirements that are adapted to practical considerations, constraints and needs, without compromising the safety, well-being and rights of participants in clinical trials and without compromising data robustness.</td>
<td>The removal of regulatory requirements on the basis of the knowledge of investigational medicinal products. Insurance or optional “national indemnification mechanism” for assuring compensation to damaged clinical trial participants.</td>
<td>This policy option would remove regulatory requirements for clinical trials with authorized medicinal products used for the authorized indication or with medicines used in a well-known manner. This would reduce the regulatory burden and thus costs, thereby contributing to the operational objective. Under this policy option, member states would set up a national indemnification mechanism that provides for a sum of money paid in compensation for loss or injury for clinical trials performed in their territories. Such mechanism would greatly facilitate assuring insurance coverage, and costs for this coverage would be limited to the costs caused by actually occurring damage. Administrative burdens and other compliance costs would be reduced.</td>
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<td>Addressing the global dimension of clinical trials when ensuring compliance with GCP.</td>
<td>Increase GCP compliance. Increased transparency on trials conducted outside member states (third-party countries).</td>
<td>Obligation to register publicly all clinical trials whose results are used subsequently in an application for marketing authorization for a medicinal product. Until now ClinicalTrialsRegister.eu was used only for trials conducted in at least one EU member state, but now it will open up for all trials that are performed exclusively in third-party countries. A system will be installed to inspect third-party countries’ regulatory systems that are referred to in seeking marketing authorization in the EU to ensure principles equivalent to EU CTD were practiced in conducting the trial.</td>
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Figure 2
Six Steps to Directive Compliance

- Determine the change in IT systems required or any new systems required.
- Avoid a “big-bang” approach.
- Conduct the pilot and establish the plan to roll out to all other departments/countries.

**Step Five: Harmonise Other Impacted Business/IT Practices**
- Once the final directive is out, harmonise other impacted business/IT processes.
- Establish a user group, complete training and define a governing body for a group of mutually exclusive impacted business/IT processes.
- Each harmonisation effort can be a project/program.

**Step Six: Steady State and Continuous Monitoring**
- The core group and the “governing” body should communicate/meet on a regular basis to monitor the adoption as well as to continue monitoring future CTD trends.
- Capitalise the time, effort and money spend on this adoption to enhance your brand value.

In order to do this, participate in DIA/CDISC and other industry forums, publish articles in journals, etc.

**Conclusion**
Revision of the CTD is a definite positive recommendation put forth by the European Parliament to simplify reporting procedures, add transparency and allow the European Commission to conduct controls in member states and other countries to make sure the rules are being properly supervised and enforced.

However, the preparations to be ready for CTD by 2016 also need to be seen in conjunction with other relevant EU regulations like Risk Management Plan (RMP), Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) and Identification of Medicinal Products (IDMP) in 2015. This will make the most out of investments and bring synergistic alignments of all stakeholders involved in regulatory compliance, thereby resulting in better health outcomes and confidence in products in which the industry is investing.

**Footnotes**
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