Pharmaceuticals

This section updates readers on the latest developments in pharmaceutical law, giving information on legislation and case law on various matters (such as clinical and pre-clinical trials, drug approval and marketing authorisation, the role of regulatory agencies) and providing analysis on how and to what extent they might affect health and security of the individual as well as in industry.

Simple, Safe And Transparent(?): Preliminary Reflections on the Proposal for a New EU Regulation of Clinical Trials

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A significant reform is currently under the scrutiny of EU institutions in the field of pharmaceutical risk regulation. With its proposal dated July 17th 2012[1], the Commission seeks to modernise the legal framework of clinical trials by addressing a series of shortcomings ascribed to the current regime governed by Directive 2001/20/EC (to be repealed by the new legislation). The iter of the reform is proving to be complex and lengthy, the first vote having been delayed to March 2014. While a comprehensive account of such a detailed proposal would defeat the scope of this short report, the analysis will focus on some of the most salient features of the proposed regulation, and attempt to situate them in the international context of pharmaceutical regulation.

I. Background and Salient Aspects of the Proposal

The major flaw of the current regime, under Directive 2001/20/EC[2] (hereinafter "the Directive"), is identified by the Commission in the costly burdens to multinational trials due to differences in application dossiers requirements across Member States: evidence of this include (a) the 25 % drop in applicants for clinical trials in the short time lapse between 2007 and 2011, as sponsors have moved increasingly to emerging countries; (b) the 98 % boost in administrative costs due to administrative requirements set by the Directive, coupled with an unsustainable 800 % increase in insurance fees; and (c) the 90 % increase (to 152 days) in the average delay in launching clinical trials. While this trend is hardly imputable to the Directive alone, the Commission nonetheless considers that the existing provisions "appear to have hampered the conduct of clinical trials in Europe", and aims, through this reform, to restore the EU's attractiveness for clinical research: a much needed intervention to reverse a trend of "dire economic consequences". It is also a means to promote the advance of medicine, academic research, and both patient safety and transparency, the lack of which has been one of the most acutely perceived and widely discussed issues in pharmaceutical regulation[3].

The proposal is essentially equivalent in scope to the Directive it is set to replace. The foremost anticipated advantage of the replacement instrument is its nature as a Regulation rather than a Directive. Discrepancies in national implementations of the Directive are the key factor in rendering cross-border trials economically burdensome and difficult to structure. The adoption of a Regulation will simplify the existing legal framework, ensuring consistency in the

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1 Commission Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, COM(2012) 369.

2 Council Directive 2001/20/EC on good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ 2001 L 121/34.

3 Peter C. Gøtsche, Anders W. Jørgensen, "Opening up Data at the European Medicines Agency", *BMJ* (2011), 342:d2686

application of a Europe-wide single regime. In this sense some of the innovations proposed in the reform have been widely welcomed by all stakeholders, four in particular:

- The harmonisation of the application dossier for the initial authorisation, set out in Art. 5 and Annexes 1 and 2 of the proposal, shall rationalise the existing cross-border diversities through a codification of the existing Commission guidance guidelines.
- The creation of a single "EU portal", in Arts. 77 and 78 of the proposal, through which applications to conduct clinical trials will be submitted is indeed a significant simplification, requiring the submission of one uniform application regardless of the Member State (or States in case of multi-state trials) in which the trial is to be carried out. The registration through a single portal of all clinical trials is also meant to facilitate public access to information on all trials data submitted for application (with 3 general exceptions: protect personal data, protect commercially confidential information, ensure effective supervision of the trial by Member States).
- The substantial simplification of rules governing clinical trials involving authorized medicines and/or low-intervention procedures also responds to a rational and much needed urge for simplification. The lower degree of risk a patient is exposed to when a solid body of prior knowledge exists on the investigational medicine involved in the trial justifies an increased flexibility in the rules, overcoming the Directive's rigidity, where the same criteria would always apply.
- The creation, by Art. 73 of the proposal, of national indemnification funds for cases in which clinical trials pose additional risks to patient safety, compared to treatment in normal clinical practice, is meant to help and encourage non-commercial sponsors, for whom the Directive's regime of "obligatory insurance/indemnity" has been particularly problematic due to the often unsustainable costs of coverage.

A further aspect worth mentioning is the content of Chapter 8 of the proposed Regulation, on the conduct of trials. The intended effect of the articles contained in this chapter is to bring together the rules provided by Directive 2005/28/EC,[4] laying down principles and guidelines on good clinical practice, and the Commission guidance documents on the topic. Rather than detailing such principles and guidelines on the actual trial conduct, the proposal refers explicitly to ICH guidelines on the matter (ICH guideline E6 more specifically), and in substance focuses on a series of provisions on monitoring of trials sites, suitability of patients, and duties (Arts. 44–56), *de facto* acknowledging an established trend that upholds the higher suitability of policy documents vis à vis hard law instruments in governing such highly technical (and therefore constantly evolving) issues.

II. Criticisms and Major Amendments

The proposal has been generally welcomed for its efforts towards a rationalisation and simplification of the rules on trials application and approval, making them more uniform across Europe. This notwithstanding, heavy criticisms have been raised by several stakeholders on diverse aspects. In response to pressing demands for revision of the proposal, in June 2013 the Committee on the Environment, Public Health and Food Safety (ENVI) adopted a wide range of amendments to the Commission's text, backing up proposals made by rapporteur Glenis Willmott[5]. Major contentious areas have been addressed by ENVI's report with a prevalent focus on patient safety and transparency.

1. Ethics Committees & Approval Timelines

A first issue addressed by ENVI relates to the exclusion from the Commission's proposal of any provision on Ethics Committees (ECs), which represents a significant departure from the rules laid down by the Directive. The intent of the proposal was to leave Member States free to define their own organisational set-up to comply with the authorisation procedure of the Regulation, and to organise internally the attribution of tasks to different bodies involved in such procedure. Therefore, the choice was to exclude pro-

4 Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practices, OJ 2004 L 136/34.

5 Report on the Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, ENVI, A7-0208/2013. Articles cited in the section are referred to this document.

visions on the harmonisation of the exact functioning and means of cooperation of ECs. This choice has been strongly criticised as it has the potential to jeopardise the independence of reviewing bodies and, as a consequence, patient safety. As acutely observed by concerned stakeholders, the deletion of ECs annuls the differentiation between these and the Competent Authorities in Member States, despite the "conflict of interest of drug regulatory agencies when assessing trials applications for which they provided scientific advice"[6]. On a broader level, ECs have been long recognised at an international level as a key instrument in the protection of patient safety (for example in the Declaration of Helsinki). The ENVI report addresses these issues by reintroducing ECs through a number of amendments to the Regulation, sanctioning their role in authorising trials and guaranteeing patient safety (ammended Art. 4a), and proposing a Europe-wide network of cooperation among Committees through a platform to be set by the Commission (ammended Art. 4a.2).

The issue of ECs, crucial *per se*, gained a lot of attention when considered alongside the new stringent timelines the Regulation is set to establish (e.g. Art. 7 limiting to 10 days the time for Member States to produce their assessment reports on ethical aspects). While ENVI's amendments have focused on the introduction of clear rules governing the ECs, the deadlines set out in the Commission's proposal, although perceived as ambitious and very stringent, have been left substantially untouched (on the premise that they are based upon European best practices). This is because the Directive's long approval timelines are among the principal factors in the growing costs of conducting trials in the EU. To this end, both the Commission and ENVI rely heavily on the idea of tacit approval. It remains however unclear whether such tacit approval is to be limited to purely administrative matters *after* the approval of a trial by an EC, or if it expands to a tacit approval *of the trial* by the EC.

2. Risk-Based Approach & Trials' Relevance

Two issues of great concern not sufficiently addressed by the original proposal are substantially amended. The first one is the precise definition of "low-intervention" clinical trials, allowing for speedier and less stringent requirements. ENVI proposes an interesting and sensible change of wording, switching to the term "low-risk" trial. As pointed out by Rapporteur Willmott, defining the type of research in terms of risk to the subject, abandoning the focus on the type of intervention, better fits the general aim of the proposed Regulation in establishing a risk-based approach. Through several amendments to Art. 2.2, ENVI purports to rationalise the idea of a low-risk clinical trial, better clarifying for example the level of risk in the use of authorised pharmaceutical products in clinical trials: "low-risk" only if the product is used within its licensed indication, "medium-risk" in case of off-label use, unless the trial treatment is only to compare standard practice treatment approaches (in which case the risk remains "low") (ammended art. 2.2 point 3a and b). Despite the significant improvements to the original text, ENVI's amendments are not as clear and explicit on whether or not post-marketing safety and efficacy studies fall within the scope of "low-risk" clinical trials.

A further issue not sufficiently covered by the Commission's proposal pertains to the relevance of clinical trials. Acknowledging that currently clinical trials are often conducted on populations that differ substantially from the target patient populations, ENVI proposes a number of amendments to tackle trials' relevance. Specifically, modifications to the proposal are meant to ensure that "groups of subjects participating in the trial represent the population to be treated, in particular with regard to *gender, age and other specific characteristics of the subject*, or if not, explanation and justification is provided" (ammended Recital 10 and Art. 6.1, emphasis added). This clarification is to be welcomed as a formal sanctioning of fundamental international standards.

3. Transparency Requirements – Applicability and Enforcement

As already observed, the creation of a "single EU portal" for registration of *all* clinical trials, regardless of their positive or negative result, has been unanimously welcomed as demonstrating significant progress towards simplification and transparency. This

6 AIM, ISDB, MiEF, WEMOS. Proposed regulation on clinical trials: joint analysis. <http://english.prescrire.org/en/79/207/46302/2507/2506/SubReportDetails.aspx> (last accessed November, 2013).

notwithstanding, ENVI proposes numerous modifications to the original proposal (in ammended Arts. 2 and 6), based on criticisms identifying two fundamental flaws in access to information. The requirement, set by the Commission, for sponsors to produce a summary of the trial's results, created by the Commission's original proposal, is considered insufficient as summaries are partial and often biased[7]. Therefore, the amendments focus on the necessity for sponsors to publish full clinical trial reports on the EU database. Such reports should include not only a simplified summary but also the complete results of the study, to be made publicly accessible. In order to guarantee the enforcement of such requirement, ENVI's amendments introduce a time limit of one year for sponsors to submit full reports to the database, and fines to be imposed by Member States in case of violations of the deadline. These provisions however are not meant to be retroactive, thus leaving clinical trials data which precede the adoption of the Regulation out of reach of the new requirement. For example, the new stringent definition of commercially confidential information provided by ammended Art. 78.3 will certainly represent a major step forward in transparency as it establishes a general principle of overriding public interest, but, in its current form, it is significantly weakened by its non-applicability to previous trial data. Independent research on pre-Regulation trials will therefore continue to suffer limited access to essential informations.

The European Federation of Pharmaceutical Industries Association (EFPIA) suggests that such measures are liable "to harm interests of innovators and individuals", as an indiscriminate approach to transparency may damage for instance non-patent-covered uses of marketed products (currently protected only by data-secrecy). ENVI however correctly shifts the focus to patients, emphasising how a decision to participate in clinical trials is aimed at helping "to advance medicine for themselves and other patients in their situation, not a particular company".[8]

4. Enforcement of Monitoring and Inspection Rules

A series of provisions in the Commission's proposal, substantially unaltered by ENVI's amendments, respond to the phenomenon of clinical trials' outsourcing to third countries, and especially developing countries. These provisions have two main goals. The first one (amended Art. 25.5) is to ensure that whenever a sponsor elects to use data gathered outside the EU, the clinical trials must have adhered to standards equivalent to those provided by EU law, together with international guidelines on ethics. Moreover, to ensure that third countries do effectively comply with EU standards in both practices and infrastructures, amended Art. 76.2 establishes that Commission officials may conduct inspections where it is considered necessary.

While these measures are of great importance, and perfectly in line with both international guidelines and previous legislation (the power of inspection is clearly stated in the recalled Directive 2005/28/EC), the real concerns here are about the enforceability of the measures. A report published by the European Medicines Agency (EMA) in 2010 shows that only a very limited amount of trials are subject to inspection when carried out outside the EU. The countries with the highest number of inspections are the US (21.9 %) followed by Canada (5.7 %), India (3.9 %), Russia (3.5 %), China (1.8 %), Philippines (1.8 %), South-Africa (1.3 %) and Thailand (1.3 %, the percentages express the rate of inspected trials per total number of registered trials per region).[9] Therefore, in this case the issue is not so much one of law-making as it is one of enforcement. The major factor contributing to the low percentages achieved by the EMA is a lack of resources compared to the magnitude of the task. The material means of enforcement of the new rules will therefore play an essential role in ensuring the effectiveness of the proposed Regulation.

III. Brief Conclusions (in Context)

With the earliest vote on the proposed Regulation pushed back to March 2014, it becomes crucial to closely monitor the evolution of the debate and the fate of ENVI's amendments. As suggested throughout this short report, the Commission's proposal is

7 Peter C. Gøtsche, "Deficiencies in Proposed New EU Regulation of Clinical Trials", *BMJ* (2012), 345:e8522.

8 Report on the Proposal, *supra* note 5, p. 147.

9 EMA, "Clinical Trials Submitted in Marketing Authorization to Applications to EMA: Overview of Patients recruitment and the Geographical Location of Investigator Site", Doc. Ref. EMA/INS/GCP/154352/2010, 5 November 2010, available at <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf> (last accessed May 2013).

strongly focused on the simplification and harmonisation of the rules, while ENVI's amendments add more prominently transparency and patient safety. In this sense, the next steps in the legislative process leading to the approval and adoption of the new Regulation on clinical trials, call for an attentive examination of the context outlined in these concluding lines. Pharmaceutical risk regulation, and clinical trials regulation specifically, do not happen in a *vacuum*. The international regulatory framework is characterised by the prominent role of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an informal and public-private hybrid regulatory network issuing voluntary protocols on all major aspects of pharmaceutical regulation, systematically adopted and enforced by EMA through policy documents. The flexible nature of these documents, compared to "hard law" instruments, allows for speedier modifications and updating in the face of scientific or regulatory progress[10]. In this context, the adoption of a detailed Regulation, aimed at the consolidation and advancement of a Europe-wide harmonised legal framework, constitutes a significant exception to the general trend.

In attempting a contextual analysis, the contemporaneity between the clinical trials regulation debate and the negotiations on the Transatlantic Trade and Investment Partnership (TTIP) also provides interesting insights. The initial position paper of the Commission, of June 2013[11], contains, in its Annex III on Pharmaceutical regulation, a series of objectives substantially based on regulatory simplification and speedier mutual recognition agreements between the US and the EU. The original proposal of the Commission appears to be very much aligned with this line of policy goals. The forthcoming vote of the EU Parliament, in light of ENVI's amendments, becomes therefore crucial, as it could represent a significant and defining normative moment in the shaping of not only European but western pharmaceutical regulatory attitudes.

10 Ayelet Berman, "The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of the ICH" in J. Pauwelyn, R. Wessel, J. Wouters (eds.) *Informal International Lawmaking: Mapping the Action and Testing Concepts of Accountability and Effectiveness* (Oxford: Oxford University Press, 2012)

11 EU Commission, "Note for the attention of the Trade Policy Committee – Annex III Initial Position Paper on Pharmaceuticals", 20 June 2013, available at <http://www.iatp.org/files/TPC-TTIP-non-Papers-for-1st-Round-Negotiatons-June20-2013.pdf> (last accessed November 2013).