Federal agency for medicines and health products

A critical review of the proposed EU Clinical Trial regulation

Walter Janssens – Kristof Bonnarens – April 2013

famhp

.be

CT regulation - general

- **Commission adopted the proposal on 17th of July**
- **Discussions at the EU Parlement & Council started**
- **Aim = Adoption before next EU elections (2014)**
- **In the meantime it is only a proposal !**
- **Interventional clinical trials only**

CT regulation - Autorisation process : overview

- **Autorisation process :**

  - **Submission of the application**
  - **Assessment**
  - **Decision**
  - **Other issues**

CT regulation - submission (1)

- **Process only defined to member state level – roles EC / NCA not defined**

- **All submissions through one single EU portal (web)**

- **No difference between :**
  - **multinational / mononational trials**
  - **commercial / non-commercial trials**

- **One submission dossier for the EU, requirements described in the annexes of the regulation (CT-1 + CT-2)**

CT regulation - submission (2)

- **Sponsor choses reporting memberstate (must be concerned and in case of monocentric trial or multicentric trial in only one memberstate this is thus the memberstate where the trial will be conducted)**

- **Other concerned memberstates can take over if mutually agreed**

- **Assessment of two parts :**

➢ **Part I by reporting memberstate (with input from other memberstates)**

➢ **Part II by every memberstate**

CT regulation

- **A clinical trial may be conducted only if**
- **the rights, safety and well-being of subjects are protected and**
- **the data generated in the clinical trial are going to be reliable and robust.**

CT regulation - assessment (1)

- **Part I = « harmonised advice » by reporting MS**
- **Anticipated therapeutic and public health benefits :**

  – the characteristics of and knowledge about the investigational medicinal products;

  – the relevance of the clinical trial, taking account of the current state of scientific knowledge, and of whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products;

  – the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial and methodology (including sample size and randomisation, comparator and endpoints);

CT regulation - assessment (2)

- **Part I = « harmonised advice » by reporting MS**
- **The risks and inconveniences for the subject:**

  – the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;

  – the characteristics of the intervention compared to normal clinical practice;

  – the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;

  – the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated

CT regulation - assessment (3)

- **Part I = « harmonised advice » by reporting MS**
- **Compliance with the requirements concerning the manufacturing and importation of investigational medicinal products and auxiliary medicinal products set out in Chapter IX;**
- **Compliance with the labelling requirements set out in Chapter X;**
- **The completeness and adequateness of the investigator's brochure.**

CT regulation - assessment (4)

- **Part I = « harmonised advice » by reporting MS**
- **Until the assessment date, any Member State concerned may communicate to the reporting Member State any considerations relevant to the application.**
- **The reporting Member State shall take those considerations duly into account.**
- **The reporting Member State, and only the reporting Member State, may, between the validation date and the assessment date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 5.**

CT regulation – assessment (5)

- **Part II = Each Member State concerned shall assess, for its own territory:**
- **(a) compliance with the requirements for informed consent as set out in Chapter V**
- **(b) compliance of the arrangements for rewarding or compensating investigators and subjects with the requirements set out in Chapter V**
- **(c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V**

CT regulation - assessment (6)

- **Part II = Each Member State concerned shall assess, for its own territory:**
- **(d) compliance with Directive 95/46/EC;**
- **(e) compliance with Article 46;**
- **(f) compliance with Article 47;**
- **(g) compliance with Article 72;**
- **(h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.**

CT regulation : decision

- One single decision per memberstate with principle of tacit approval
- Involvement of laymen and patients obligatory
- Opting out possible (but limited)
- (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice
- (b) infringement of the national legislation referred to in Article 86.

CT regulation : decision

- **Adding of memberstates – reporting MS remains**
- **Substantial amendments – reporting MS remains**
- **Disconnect between part I and part II possible**

CT regulation - risk-adaption (1)

- **Principle of « low-intervention trials »**

  → Adaption of timelines (shorter) and damage compensation

- **Safety reporting :**

  - **normal pharmacovig for low-intervention trials**
  - **Expedited reporting / development safety update report remains**
  - **all safety reporting via EudraVigilance-CTM**

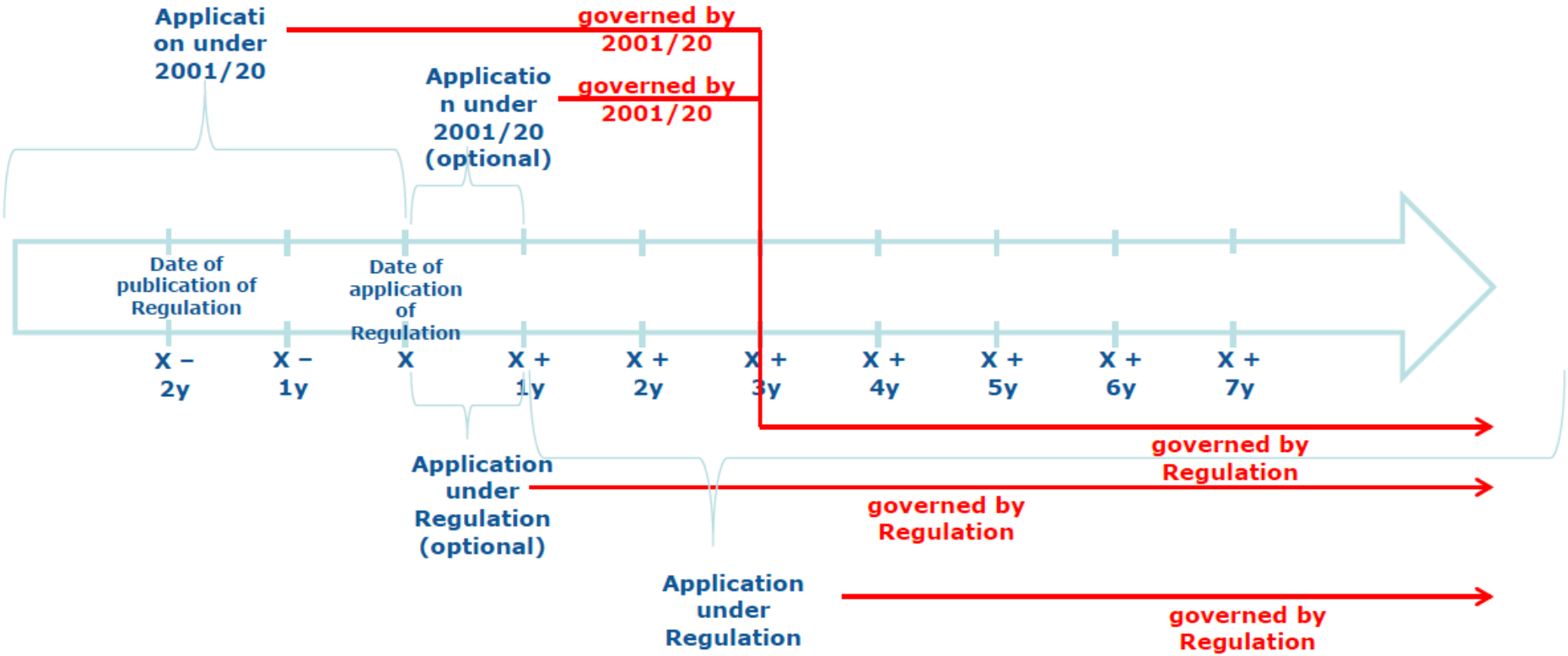
CT regulation - risk-adaption (2)

- **Simplified rules for IMPs and Auxiliary MP's (ex-NIMP) for manufacturing and labelling**
- **Autorisation for manufacturing required, but exceptions remain**
- **Magistral / officinal preparations can be used**
- **Authorised products in open label trials : easier labelling**

CT regulation - changes

- **Insurance mechanism to be set up by MS**
- **Cosponsorship possible**
- **Contact person within the EU obligatory**
- **CTFG → CTAG (presidency & secretariat by Commision)**

CT regulation – transition



Main discussion points at the EU Council

- **The Portal : Functional analysis and User Acceptance testing by MS .**
- **Tacit approval : is not acceptable in combination with short timelines for most memberstates**
- **Selection of Reference Memberstate**
- **Definitions and new concepts :**
  - **Low-interventional**
  - **Legal representative**
  - **Minor / incapacited subject / emergency trials**
- **Clearer collaboration mechanisms needed between memberstates in the part I assessment**
- **Ethical assessment**
- **Timelines**

Draft report of the Rapporteur

- **Ambitious timeframe for treatment in the EU Parliament**
- **Introduction of "ethics committees" and references to Declaration of Helsinki in the text**
- **Facilitation of cooperation between ethics committees on a European level**
- **After marketing authorisation, data from a clinical trial will be fully accessible**
- **EUguidelines on informed consent**
- **Introduction of "clinical study report" as an obligation**
- **Unnecessary duplication between the EU Portal,EudraCT and the EudraVigilance database shall be avoided**

Changes with regard to Phase I trials

- **More transparency: publication of trials and reports, public availability of raw data.**
  - **Await final Regulation for further details**
- **Timelines will be uniform throughout EU**
  - **Maximal time alloted for evaluation is defined and will be longer than currently in a number of Member States**
  - **Can still be shorter, depending on interaction with Ethics Committee and therefore time actually needed does not necessarily become longer**
  - **Principle of tacit approval: await final Regulation**
- **Implementation of GMP**
  - **Legal requirement**
  - **Should be feasible (e.g. circular letter 596 in Belgium)**
- **One portal for submission and one opinion per Member State**
  - **Will have little impact for monocentric studies**

Contact

Federal agency for medicines and health products - famhp

Place Victor Horta 40/40
1060 Bruxelles

tel. 0032 2 524 80 00
fax 0032 2 524 80 01
e-mail welcome@fagg-afmps.be

www.afmps.be

Your medicines and health products, our concern

famhp

.be