Federal Agency for Medicines and Health Products (FAMHP)

Clinical Trials in Belgium
The Role and Function of the National Competent Authority in a EU environment

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Head of R&D
1: Innovation in drug discovery and development: Participation of ALL stakeholders

- Healthcare professionals
- Research Based Pharma
- Academia
- Patients
- SME’s
- YIC’s
- Regulators
- Policy makers
- MS Policy makers
2: EU Legal Framework

- EU Directive 2001/20
- EU Directive 2003 / 94 (GMP guidance)
- EU Directive 2005/28 (GCP inspections)
- Eudralex, Volume 10 Notice to Applicants
  - Applications for a clinical trial
  - Safety monitoring and reporting of adverse events
  - Quality of IMP
  - Recommendations on inspections
  - Additional info (IMP - non commercial trials)

Website ec.europa.eu/enterprise/pharmaceutical/eudralex
2: EU Legal Framework: Directive 2001/20/EC

- Provisions for the conduct of clinical trials on human subjects involving medicinal products
- Compliance to the international recognised ethical and scientific quality requirements (GCP) is mandatory
- Exclusive non-interventional trials

- Protection of clinical trial subjects
  - positive Benefit/Risk balance at any time
  - rights of the subject to physical and mental integrity, privacy and protection of data
  - informed consent (minors, incapacitated adults)

- Clinical trials can only start after positive opinion of the Ethics Committee and when there is no major objection raised by the Competent Authority (Be)
2: EU Legal Framework : Directive 2001/20/EC

* Suspension of trial / infringements

* Manufacturing, import and labelling of IMP’s

* Verification of compliance with GCP/GMP

* Notification of serious adverse events (SUSAR’s)
3: National Legal Framework

- Law 7 May 2004
- RD 15 July 2004 (fees)
- RD 30 June 2004 (executive measures)
- Circular Letter October 2004 (some clarifications)
- Law 17 November 2004 (assessment of preclinical data to be performed by CA)
- Law 30 December 2005 (recognition of EC’s postponed till 1 September 2006)
- RD 18 May 2006 (GCP inspections)
- Law June 2006
- Law 13 December 2006 and Law 27 December 2006
- Circular Letter January 2007

www.fagg.be (Geneesmiddelen / Humaan Gebruik / Onderzoek en Ontwikkeling / Klinische studies)
3: National Legal Framework

* Law 7 May 2004: larger scope than EU directive
  all experiments in human where subjects are selected in function of future observations

* Main duties for the Ethics committee (relevance of the experiment / protocol / qualification of investigator and facilities / informed consent / ..)

* Main duties for the Competent Authority (evaluation of chemical-pharmaceutical and pre-clinical data / compliance check with GCP / evaluation of SUSAR’s / ..)
The Clinical Task Force is the Steering Committee assuring and surveilling the adequate implementation of the law related to experiments on human beings.

(7 May 2004)
4: Clinical Task Force

Different stakeholders represented:

- Core team:
  Representative of the Minister of Public Health
  Pharmaceutical Industry
  Ethics Committees
  Competent Authority

- On ad hoc basis:
  Academic Researchers
  Phase I units
  ...

4: Clinical Task Force

Strategic meetings on monthly basis:

Strategic Objectives:
- Follow-up of activities of CA (R&D department) and EC’s
- Fostering an optimal coöperation between CA and EC’s
- IT-strategy
- Troubleshooting

Organisation of scientific/technical workshops
Communication via website
www.fagg.be
Exchange of Scientific/Technical Info (not-dossier related)

CA  Key EC’s  Other EC’s

Clinical Trial Facilitation Group (HoA)
EC: Ad hoc working group
GCP: Inspectors meeting
EMEA ...
New initiatives from EU Ad Hoc Group CT

- NfG Ethics for clinical trials with children: released for public consultation

- Recommendations for early phase development CT with high risk compounds (application form; time of assessment, need of opinion from Expert Advisory Group)
  CHMP FIM guideline comes in operation 1 September 2007

- Recommendations for optimising the cooperation between EC’s and CA

- Recommendations related to the adequate treatment of reported SUSAR’s
Clinical Trial Facilitation Group

- Workgroups on IMPD, GMP, SUSAR’s: outcome to be reported next meeting
- Systematic discussion of EudraCT Alerts (lack of efficacy ..)
- Recommendations for early phase development CT: Sharing assessment reports for early phase development CT
GCP-inspectors group

- SOP’s of GCP inspections on behalf of EMEA :
  - will be published on their website
  - will be used as start for writing the SOP’s
    re NtoA Vol. 10

- Certification of phase 1 units performing CT with high risk medicinal products

- Increased coördination of GCP-inspections within EU and especially in 3th countries

- Impact of negative GCP inspections
5: Scientific - Technical board Key EC’s-CA

Mandate:

To assure the quality of the decision making process with regard to the authorisation and the follow-up of clinical trial applications in Belgium.
To optimise the scientific / technical interactions between the Ethics Committees and the Competent Authority

Core composition:

Representatives of the Key EC’s (KUL, RUG, UCL, UIA, ULB, ULG, VUB), from AdvComBioEth, from FPHS and from FAMHP.
5: Scientific - Technical board Key EC’s-CA

Activities:

- QA of the decision making processes (alerts, divergent opinions etc)
- Organisation of scientific/technical workshops: for 2007:
  with Rapporteurs designed from different Key EC’s in tandem with the CA

- Paediatric Regulation
- Compassionate Use and Medical Need Program
- Safety reporting
- Exploratory CTA’s
- Non-commercial trials
- Substantial amendments
- Medical devices
- Non-interventional CT
6: Current situation in Belgium Realisations: R&D

- **Budget**: from 500 € / full application to 1350 € / full application
- **Recrutement**: 80 % roll-out versus original plan

- Assessment of pre-clinical data included in the Law
- Amendment of the Law by RD for the implementation of GCP-inspections
- Enhanced activities in function of the cooperation with EC’s:
  - IT project interactive website EC’s-CA
  - Infosessions with 35 EC’s (fully recognised)
    - (minimal performance criteria linked with remuneration)
  - Scientific / Technical Board Key EC’s-CA
- FAQ’s and Workshops (published on website www.fagg.be)
- KPI’s: 95 % of the CTA applications treated within legal timelines (risk management approach)
6: Trends

1: Increased amount of CTA-applications:
- 2007: 95 applications / month (50% amendments)
- 2004: 50 applications / month (20% amendments)

2: Increased % Phase 1 trials (FIM):
- 2007: 26%
- 2004: 17%

3: Increased % non-commercial trials:
- 2007: 8%
- 2004: 3%
6: Trends

4: Start of exploratory CT applications in Belgium

5: Increasing demands for regulatory advice for innovative trials (Paediatric Investigation Plans, Advanced therapies, ..)

6: EU legal framework (Volume 10 EudraLex) and EC/EMEA working groups installed...
   -> harmonisation process still needs further optimisation
   -> TGN case UK → FIM guideline released by CHMP
   -> Reflection on 2001/20/EC at EU level:
      3 October 2007
6: Workplan 2007 GCP- inspections

- Preparing the design of the Inspection plan 2008: Q3 2007

- Installation of a minimal QA system in function of conducting GCP - inspections in coöperation with P&D department:
  -> minimal set on SOP’s
  -> Peer review related to gradation of findings
  -> Defining sanctions for non-compliance at macro-level
  Q3-Q4 2007

- Development of a training program for certified GCP inspectors
  Q3 2007

- Preparative steps for the integration in the new structure early 2008?
6: National Guidance on Exploratory CT

• Answer specific questions about the potential usefulness of substances or the validity of certain targets to treat human disease

• Questions and program should be adequately defined

• Limited exposure (time, dose, number of participants)

• Limited testing

• Limited amounts of substance synthesised
6: National Guidance on Exploratory CT

Presubmission

- Different substances involved or innovative targets involved: more time needed and involvement of experts

- EC should be involved (delegation of expert)

- Written procedure, electronic, teleconference, formal meeting
6: National Guidance on Exploratory CT

- Quality requirements defined
- Preclinical requirements defined:
  - Pharmacological inactive dose (microdose approach)
  - Pharmacological active dose
  - Overage approach

in cooperation with Key EC and Research based Pharma
- Guidance published: June: pilot phase 6 Months
- Guidance presented at CTFG, at PEI/Bfarm Mid September 2007
6: CHMP FIM guideline

- Triggered by TGN case UK
- Draft CHMP guideline will come into operation
  1 September 2007
- Critical points:
  - Definition of high risk substances
  - MABEL approach for starting dose if high risk compound
  - Protocol and infrastructure should be adapted to high risk
7 : The way forward ...

- Optimisation coöperation with EC’s on permanent basis :
  → Interactive website EC-CA : preparing phase 2

- From Risk management approach to project management of development programs (clinical trials) :
  Permanent Risk/Benefit monitoring

- Strengthen the scientific expertise (EMEA think-thank group on innovative drug development)

- Strengthen the position of Belgium at EU level
  Importance of Early Phase Development in Be

- National Reflection Day Law 7 May 2004 : Mid September 2007
Many thanks for your attention