The Changing Regulatory Requirements for Applied Human Pharmacology

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The Regulatory Past

• What was first
  – Rules for Marketing Authorisation – or
  – Rules for Clinical Trials?
Prussian Ordinance 1900

- 1900
  - No studies in minors or subjects not able to give informed consent
  - Informed Consent required
  - Studies must be conducted by the principal physician or special representatives
  - Fulfilment of all legal requirements must be documented in the patient files

Directive of the German “Reichsminister” 1931

- 31 statements on research treatments
  - Definitions
    - “neuartiger Heilbehandlung”, „Wissenschaftliche Versuchen“
  - Experiment must be scientific sound
  - Positive risk/benefit ratio
  - Informed consent
  - Precautions for minors
  - Abuse of financial distress prohibited
  - …
Nuremberg Doctors’ Trial

- 20 of 23 defendants were medical doctors
- 16 defendants were found guilty
- 7 sentenced to death

- The judges’ verdict of the Nuremberg Doctors’ Trial included 10 statements on research with humans later referred as “Nuremberg Codex” or “Nuremberg Code”

Declaration of Helsinki

- 1964 first issued by the World Medical Association (WMA) as ethical principles for biomedical research involving humans
- In most countries not legally binding, but with a high impact
  - especially in countries with no legislation on clinical trials
- In Germany highest influence until 1999, since than decreasing impact, due to
  - Conflict on the use of placebo in clinical trials
  - New regulatory requirements in Europe (CTD 2001/20)
- References
  - ICH-GCP (2.8, 4.8.1): dynamic but less precise
  - Directive 2005/28 (GCP directive): direct but only to the 1996 version
The German Medicines Act(s)

- AMG1961
  - Notification based
  - No authorisation procedures

- Directive 65/65/EEC
  - Marketing Authorisation required

- AMG1976
  - Principles of marketing authorisation – but
  - No Rules on Clinical Trials

Bekanntmachung von Grundsätzen für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln

- Bekanntmachung des Bundesministers für Jugend, Familie, Frauen und Gesundheit
  - Bundesanzeiger 243 vom 30. Dezember 1987

- Umfangreiche Vorgaben zu klinischen Prüfungen
  - Aufbau eines Prüfplans
  - Statistik
  - Prüfbögen
  - ...
Good Clinical Practise - GCP

• GCP as first regulatory requirements for
  – Planning
  – Conducting
  – Analysing
  – Reporting
  – Archiving
  of Clinic Trials

• Although only “soft law” major driving force for clinical trials
  – GCP compliance required for marketing authorisation

Soft law: Good Clinical Practice (GCP)

• United States of America
  – 1977 FDA-GCP

• EU-GCP
  – 1989: EU-GCP Note for Guidance

• ICH-GCP
  – 1996 ICH E6
ICH Process

- Harmonisation of the three major regions
  - North America
  - Japan
  - Europe

- Set of Guidelines on Clinical Trials
  - Number of patients / duration
  - Drug safety reporting
  - Reporting (Structure an Contents of Study reports)
  - Dose Response
  - Ethnic factors / acceptability of foreign clinical data
  - Good Clinical Practise
  - Drug Development (General Considerations on CTs)
  - GCP
  - ...


- Scope
  - Directive does not apply to non-interventional trials
- Definitions
  - CT vs non-interventional trial
- Protection of clinical trial subjects
  - Clinical trials on minors / incapacitated adults not able to give informed consent
- Ethics Committee
- Commencement of a clinical trial
  - Conduct of a clinical trial
  - Exchange of information
  - Suspension of the trial or infringements
- Manufacture and import of investigational medicinal products
  - Labeling
  - Verification of compliance of investigational medicinal products with good clinical and manufacturing practice
- Notification of adverse events
Additional Directive: 2005/28
“The GCP Directive”

- Good Clinical Practice (GCP)
  - Ethics Committee
  - Sponsors
- Investigator’s Brochure
- Manufacturing or import authorisation
  - Exemption for Hospital & Health Centres and Reconstitution
  - Conditions of Holding a Manufacturing Licence
- The trial master file and archiving
  - Format of Trial Master File
  - Retention of Essential and Medical Records
- Inspectors
  - Inspection procedures

National Implementation

- 12th Amendment of the German Medicines Act
  - Major implementation of 2001/20
  - §§ 4, 40-42a AMG, GCP-V

- 14th Amendment of the German Medicines Act
  - Implementation of 2005/28
  - §§ 13, 40ff, 72 AMG; §4 GCP-V

- 15th Amendment of the German Medicines Act
  - Reconstitution, Manufacturing, Advanced Therapies
  - §§ 4, 4a, 4b, 13…
Next Steps?

• EU Level
  – Pharma-Package
    • Counterfeit
    • Patient information
    • Pharmacovigilance
      – Centralisation
      – Authorisation of Safety Studies
  – Review of the Clinical Trials Directive
    • Move towards centralisation?

• National Level
  – Authorisation process for clinical trials with medical devices
    • Combined trials

Scientific Analysis of Postauthorisation Surveillance Studies by a German Health Insurance Provider

• A sample of 118 postauthorisation surveillance studies notified to the National Association of Statutory Health Insurance Physicians (July-Dec. 2005) was analyzed with respect to scientific quality
• Data published


Were Postauthorisation Surveillance Studies only Marketing Instruments in the Past?

Implications?

Changes for non-interventional PAS

• Notification of the Competent Authority
  – Objectives, Time, Duration, Protocol

• Doctors which participate are potential targets for surveillance of the Association of Statutory Health Insurance Physicians (“KV“)

• First legal requirement that reimbursement for PAS must not be “a Booster” for prescription
The Future for Observational Studies

- Discussion in the light of the “Pharma Package”
  - PASS might be subject of an approval procedure?
  - PASS might be subject of review procedure?
  
  - Discussion is still ongoing

Conclusion

- Clinical trials were and are subject of increasing regulation measures

- Soft law has been replaced by a mixture of “hard law” and “soft law”
  - CT may be in accordance with legal requirements but still not accepted for marketing authorisation
  - Driving force: EU Commission

- Is centralisation the best way of harmonisation?