

# 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

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## 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
  - ...

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## 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"

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## 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 then 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

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## 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

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## 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
  - ...

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## Good Clinical Practise - GCP

- GCP as first regulatory requirements for
  - Planning
  - Conducting
  - Analysing
  - Reporting
  - Archivingof Clinic Trials
- Although only “soft law” major driving force for clinical trials
  - GCP compliance required for marketing authorisation

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## Soft law: Good Clinical Practice (GCP)

- United States of America
  - 1977 FDA-GCP
- EU-GCP
  - 1989: EU-GCP Note for Guidance
  - 1991: Directive 91/507/EEC
- ICH-GCP
  - 1996 ICH E6

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## 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 and Contents of Study reports)
  - Dose Response
  - Ethnic factors / acceptability of foreign clinical data
  - Good Clinical Practice
  - Drug Development (General Considerations on CTs)
  - GCP
  - ...

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## European Harmonisation: Directive 2001/20 “Clinical Trial Directive”

- 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
  - Labelling
  - Verification of compliance of investigational medicinal products with good clinical and manufacturing practice
- Notification of adverse events

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## 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

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## National Implementation

- 12<sup>th</sup> Amendment of the German Medicines Act
  - Major implementation of 2001/20
  - §§ 4, 40-42a AMG, GCP-V
- 14<sup>th</sup> Amendment of the German Medicines Act
  - Implementation of 2005/28
  - §§ 13, 40ff, 72 AMG; §4 GCP-V
  -
- 15<sup>th</sup> Amendment of the German Medicines Act
  - Reconstitution, Manufacturing, Advanced Therapies
  - §§ 4, 4a, 4b, 13...

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## 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

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## 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

Dietrich ES & Zierold F: Evaluation of the Scientific Quality of Postmarketing Surveillance Studies in Germany. ISPOR, 9th Annual European Congress, 2006

Dietrich ES. Die meisten deutschen Anwendungsbeobachtungen sind zur Generierung wissenschaftlich valider Erkenntnisse nicht geeignet. *PharmacoEconomics* 2009;7(1):3-14"

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## 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

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## 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

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## 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?

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