International Clinical Trials

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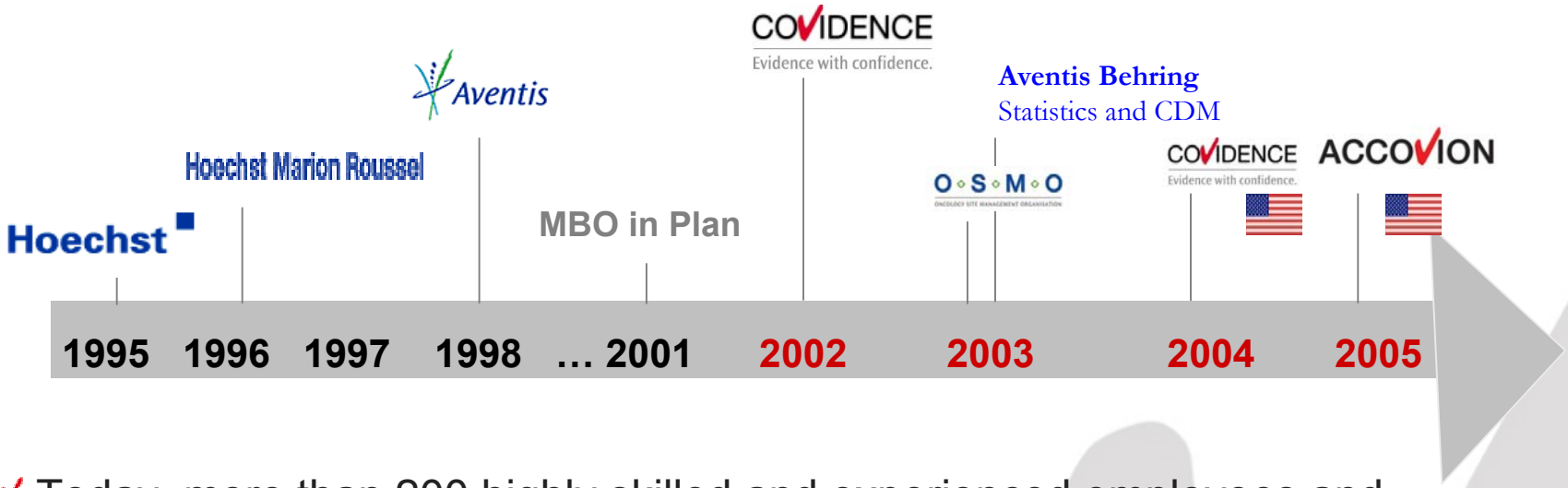
Based on "EU Legislation" by Regina Freunscht, Head QA, Accovion

Origins of Accovion

- Accovion is a clinical development service organization formed from the global clinical research, medical writing, pharmacovigilance, biostatistics and data management departments of Aventis (Hoechst) Pharma in Frankfurt.



- Today, more than 200 highly skilled and experienced employees and a network of more than 180 regional study monitors are working on regional and global projects ranging from phase I to IV studies and global submissions.

The European Union

- A family of democratic European countries, committed to working together for peace and prosperity
- Not “Unites States of Europe” or “Commonwealth of Europe”
- The historical roots of the European Union lie in World War II
- Economic and social solidarity
- Up to Today:
  - 25 Member States
  - ~ 475 million people
  - 20 official languages

ACCOVION

Bulgaria (2007)

Estonia

Latvia

Lithuania

Malta

Poland

Romania (2007)

Slovakia

Slovenia

Czech Republic

Hungary

Cyprus

The European Institutions

- ✓ European Parliament
  - Elected by the peoples of the Member States
- ✓ Council of the European Union
  - Representing the governments of the Member States
- ✓ European Commission
  - Driving force and executive body
- ✓ Court of Justice
  - Ensuring compliance with the law
- ✓ Court of Auditors
  - Controlling sound and lawful management of the EU budget

The Legislative System

- Regulations
  - Citizen
  - Directly binding
- Directives
  - Member States
  - Transition into national law
  - Binding to the citizen
- Guidelines (Note for Guidance)
  - Basically for competent authorities, but for citizen as well
  - Recommendations at high expert level
  - Deviations possible, with good scientific reasons

The Marketing Authorisation System

- ✓ Centralised Procedure
  - European Medicines Agency
    - → Committee for Human Medicinal Products (CHMP)
      - One representative of each MS + Iceland and Norway
      - Provides scientific expertise
      - Working parties: Quality, Biotech, Efficacy, Safety
    - → Committee for Veterinary Medicinal Products (CVMP)
    - → Committee for Orphan Medicinal Products
- ✓ Mutual Recognition Procedure
- ✓ National Procedure

Directive 2001/20/EC

of the European Parliament and of the Council

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Scope and Objectives

- ✓ Basis for the conduct of clinical trials
- ✓ Harmonisation between the member states in entire EU
- ✓ All clinical trials (phase I to IV), except non-interventional trials
- ✓ Industry and Academia sponsored trials
- ✓ Protection of human rights
- ✓ Special protection for minors and persons incapable of giving legal consent
- ✓ Rules for protection of personal data
- ✓ Declaration of Helsinki, version 1996
- ✓ Still in accordance with ICH-GCP

Scope and Objectives

- ✓ Ethical Committees, rules and single opinion
- ✓ Member States' competent authorities, implicit authorisation
- ✓ Information on content, commencement and termination of clinical trials
- ✓ Monitoring and reporting of adverse reactions (Pharmacovigilance)
- ✓ Manufacture, labelling, import and shipment of IMP (GMP)
- ✓ Verification of compliance / inspections
- ✓ Exchange of information (EudraCT & EudraVigilance DB)

Detailed Guidance documents

- ✓ Clinical Trial Application
- ✓ Ethical Committee Opinion
- ✓ Adverse Reaction Reports
- ✓ EudraCT Database
- ✓ EudraVigilance Database

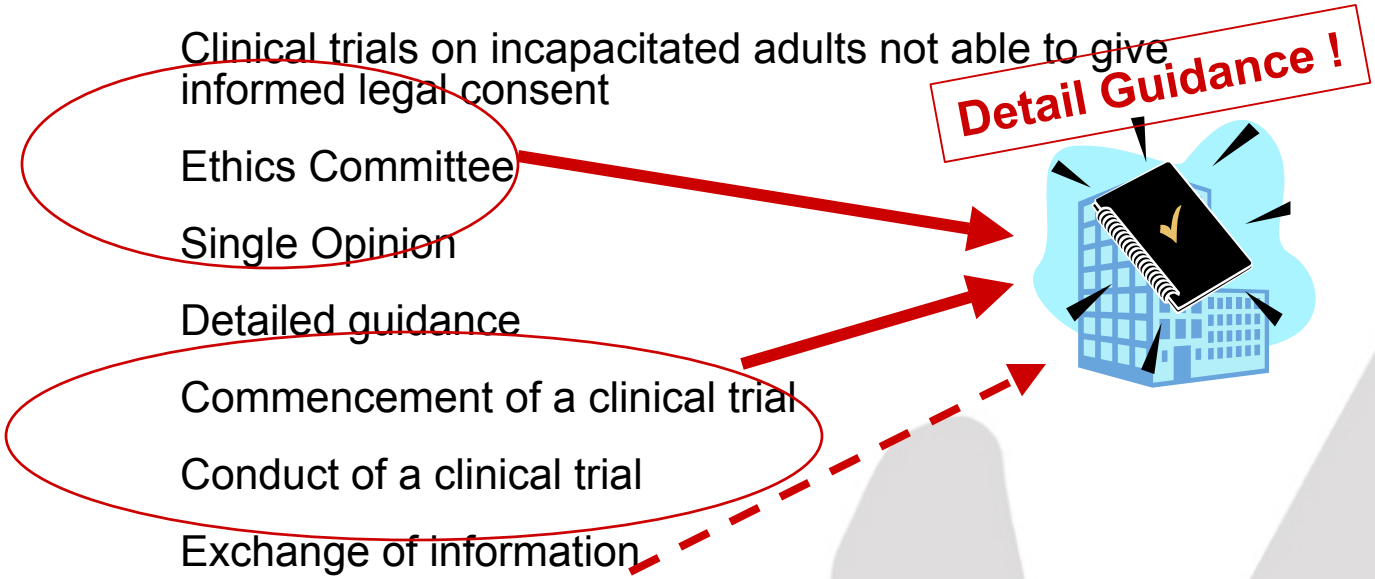
Final !!!

- ✓ Trial Master File and Archiving
- ✓ GCP ..... → **Commission Directive on GCP Currently in Final DRAFT Status**
- ✓ Inspection Procedure
- ✓ Qualifications of Inspectors

Inspection Section of the EMEA

Content of Directive 2001/20/EC

- ✓ Art 1 — Scope
- ✓ Art 2 — Definitions
- ✓ Art 3 — Protection of clinical trial subjects
- ✓ Art 4 — Clinical trials on minors
- ✓ Art 5 — Clinical trials on incapacitated adults not able to give informed legal consent
- ✓ Art 6 — Ethics Committee
- ✓ Art 7 — Single Opinion
- ✓ Art 8 — Detailed guidance
- ✓ Art 9 — Commencement of a clinical trial
- ✓ Art 10 — Conduct of a clinical trial
- ✓ Art 11 — Exchange of information
- ✓ Art 12 — Suspension of the trial or infringements



Content of Directive 2001/20/EC

- ✓ Art 13 — Manufacture and import of investigational medicinal products
- ✓ Art 14 — Labelling
- ✓ Art 15 — Verification of compliance of investigational medicinal products with good clinical practice

GMP

- ✓ Art 16 — Notification of adverse events
- ✓ Art 17 — Notification of serious adverse reactions
- ✓ Art 18 — Guidance concerning reports
- ✓ Art 19 — General provisions
- ✓ Art 20 — Adaptation to scientific and technical progress
- ✓ Art 21 — Committee procedure
- ✓ Art 22 — Application
- ✓ Art 23 — Entry into force
- ✓ Art 24 — Addressees

Detail Guidance !

Definitions from the Directive 2001/20/EC

Non-interventional Trial

a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data

Investigational medicinal product

a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form

Definitions from the Directive 2001/20/EC

Sponsor

an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial

Investigator

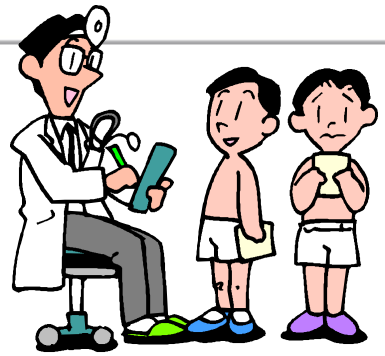
a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator

Inspection

the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's facilities, or at other establishments which the competent authority sees fit to inspect

Protection of clinical trial subjects

- Foreseeable risks and inconvenience must be weighted against the anticipated benefit for the individual trial subject and other present and future patients
- Anticipated therapeutic and public health benefits justify the risks
- Trial subjects must understand the objectives, risks and inconvenience of the trial <= prior interview with the investigator
- Right to withdraw from the trial at any time without detriment
- Physical and mental integrity of subjects
- Privacy and protection of data according to Directive 95/46/EC
- Insurance or indemnity to cover liability of investigator and sponsor
- Medical care and decisions made only by an appropriately qualified doctor
- Contact point for further information



Clinical trials in minors

- IC of parents or legal representative
- Should receive information acc. to its capacity of understanding from experienced staff
- Explicit wish of a minor must be considered by the investigator
- Some direct benefit for the group of patients, related directly to a clinical condition
- No incentives or financial inducements
- Follow corresponding guidelines from agencies
- Constant monitoring of risk threshold and degree of distress
- EC with paediatric expertise

Clinical trials on incapacitated adults not able to give informed consent

- ✓ IC of legal representative
- ✓ Persons not able to give IC must have received information acc. to his/her capacity of understanding on the trial, risk & benefit
- ✓ Investigator must consider explicit wish of the subject if he/she is capable to build an opinion
- ✓ No incentives or financial inducements
- ✓ Must directly relate to a life-threatening or debilitating clinical condition
- ✓ Constant monitoring of risk threshold and degree of distress
- ✓ EC with expertise in the related disease and concerned patient population
- ✓ Benefit to the patient should outweigh the risks

Ethics Committee

- ✓ EC shall give its opinion before a clinical trial commences
- ✓ Consider:
  - Relevance of the trial and design
  - Benefits and risks
  - Protocol
  - Suitability of investigator
  - IB
  - Quality of facilities
  - Adequate and complete written information and the procedure to be followed
  - Provision for indemnity or compensation
  - Insurance or indemnity to cover the liability of investigator and sponsor
  - Any financial agreements (investigators, trial subjects, sponsor <>site)
  - Arrangements for recruiting subjects

Ethics Committee

- EC has max. 60 days from the date of receipt of a valid application to give reasoned opinion
- EC may request additional information within that period => clock stop
- Gene therapy, somatic cell therapy, GMOs
  => 90 days with option of further 90 days in event of consultation of a group or a committee is needed
- Xenogenic cell therapy => no time limit

Commencement of a clinical trial

Parallel Process for EC opinion & CTA

- EC has given favourable opinion
- CTA was requested at CA of concerned MS
- Max. 60 days after receipt of a valid request
- Implicit authorisation, but CA can notify sponsor before end of this period that there are no grounds for non-acceptance
- If MS provides grounds for non-acceptance, the sponsor may amend the content – only 1 occasion !
- If the sponsor fails to amend, the CTA will be considered rejected and the trial may not commence

Written explicit authorisation

- Gene therapy, somatic cell therapy, GMOs
  => 90 days with option of further 90 days in event of consultation of a group or a committee is needed
- Xenogenic cell therapy => no time limit
- Part A of the annex of Directive 2309/93:
  - Recombinant DNA technology
  - Controlled expressions for genes coding for biological active proteins in prokaryotes and eukaryotes including transformed mammalian cells
  - Hybridoma and monoclonal antibody methods
- Biological products of human or animal origin (active substances, ingredients, components, needed for manufacturing process)

Conduct of a clinical trial

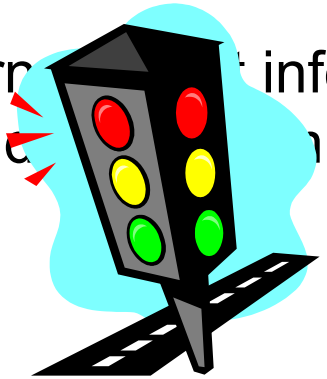
- Sponsor may change or amend any information as submitted within CTA or EC opinion request
- Notify CA and EC in case of substantial amendments
  - Safety of subjects
  - Scientific value of trial
  - Conduct or management of trial
  - Quality or safety of IMP

Any Change on information of CTA:
- Adding new trial sites
- Change of PI
- Change of CRO

- EC have max. 35 days after receipt of proposed amendment
- No time period mentioned for CA
- Urgent safety related measures to protect subjects against immediate hazard => inform CA and EC ASAP
- End of trial notification to CA and EC within 90 days
  if early termination, notify within 15 days and give reasons

Suspension of the trial or infringements

- CA of MS may suspend or prohibit the clinical trial in case of
  - Conditions of CTA are not longer met
  - Information raising doubts about safety or scientific validity
- If not imminent risk, the MS must ask sponsor and/or investigators for their opinions, which must be delivered within one week
- The CA concern[illegible] inform all other involved CAs, ECs, EMEA and [illegible]ission of their decision and give reasons



Manufacture, import and labelling of IMP

- MS must ensure the manufacture and importation of IMP is subject to the holding of authorisation
- The holder of authorisation must have permanently and continuously at his disposal the services of at least one qualified person
- Annex 13 of GMP provides guidance on evaluating products and releasing batches
- No further checks for drug import, if IMP was manufactured acc. to GMP and the qualified person has signed the batch release certifications
- Qualified person must certify that each production batch fulfils requirements, records must be kept up-to-date and available for at least 5 years
- Labelled with at least the official language of the MS on the outer packaging of the IMP acc. to Annex 13 of GMP
- If MA exists in MS, separate labelling for clinical trial is not necessary if no changes to SMPC and MA (indication, dosing, etc)

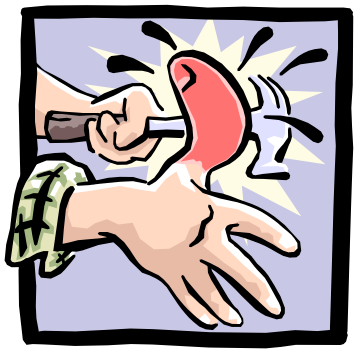
Compliance with GCP and GMP

- MS appoint inspectors to inspect the
  - Investigational sites
  - Manufacturing sites
  - Laboratories
  - Sponsor / CRO premises

- Inspections will be coordinated by the EMEA
- Inspection report will be made available to the sponsor while safeguard confidential aspects
- Results will be available to all other concerned MS, ECs and EMEA on reasoned request

Notification of Adverse Events

- AEs and laboratory abnormalities, if defined in the protocol as critical, must be reported to the sponsor
- Sponsors must keep detailed records of all AEs



Notification of Serious Adverse Reactions

- Investigators must report all SAEs immediately to the sponsor, followed by a written report
- In case of death of a subject, the investigator shall supply sponsor and EC with additional information on request
- Sponsor must ensure expedited reporting of SUSARs to CA and EC according to ICH E2 a + b
  - Within 7 days in case of death or life-threatening, follow-up within further 8 days
  - Within 15 days for all other SUSAR cases
- Sponsor shall also inform all investigators
- Once a year sponsor must submit a Annual Safety Report (listing of all SARs and a report of subjects safety) to all concerned CAs and ECs

General provisions

- The sponsor or a legal representative of the sponsor must be established in the Community !

- IMPs and devices used for their administration shall be made available free of charge by the sponsor

Examples for country specific implementation:

- ✓ The Netherlands
  - Contact person for participating subjects must be an independent physician
  - Review by CA: AEs, Inspection reports, Compliance to GCP
  - Review by Ethic Committee: Clinical Protocol, IB, minimal IMPD, Subject Information and Consent form
- ✓ Belgium
  - Labels on study medication in three national languages: Dutch, French and German
- ✓ Denmark
  - Provides training and help to hospitals and medical agencies
  - University hospitals have established GCP units
  - Website (in Danish only) allows downloading SOPs and information about the implementation of the new legislation

Examples for country specific implementation:

- Italy
  - 11 additional documents on functioning of ECs and modalities for application to EC & CA
  - For multi center studies -> multiple CAs :
    - → General Director of local health facility (“ordinary” IMPs, after Phase I)
    - → Instituto Superiore di Sanità (new chemical entities – Phase I)
    - → Ministery of Health for biotechnological products, biological products and / or component (human or animal origin), gene therapy, somatic cell therapy, drugs containing GMOs
  - Sanctions (Section 22), examples:
    - → Commencement of trial without obtaining favorable opinion by the competent EC 100.000 to 500.000 €
    - → Continuation on the basis of substantial unauthorized amendments 100.000 to 500.000 €
    - → Notification of serious adverse reactions: failure in reporting and recording 50.000 to 250.000 €

Legislative Framework

Directive 2001/83/EC

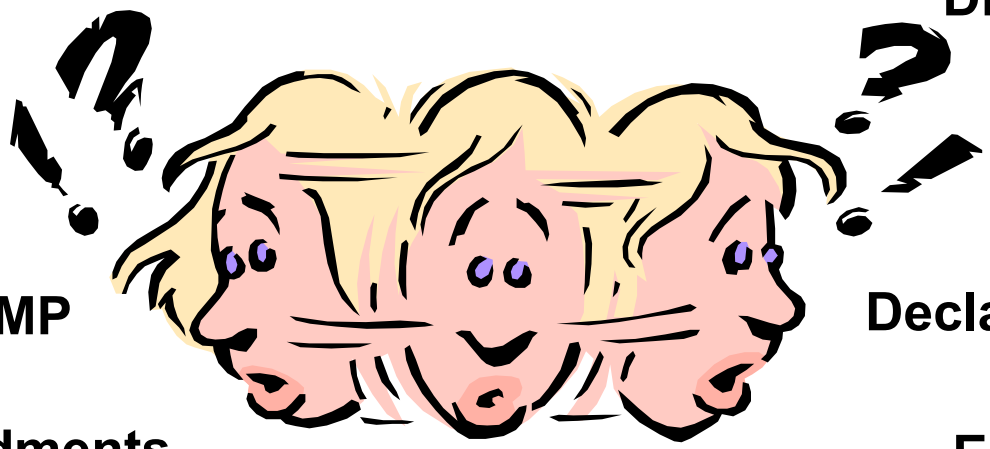
Directive 2001/20/EC

Directive 2003/63/EC

Directive 95/46/EC

Directive 2003/94/EC

eCTD



ICH E6: GCP

ICH E2 A+B

Annex 13 of GMP

Declaration of Helsinki

CTA, amendments
& EoS declaration

EudraCT db

Eudravigilance db

Ethical Committee opinion

DRAFT on TMF and Archiving

Adverse Reaction reports

DRAFT annex on inspectors qualification

DRAFT annex on inspections

Directive **95/46/EC** EU Parliament and Council	Protection of individuals with regard to the **processing** of **personal data** and on the free movement of such data
Directive **2001/20/EC** EU Parliament and Council	Provisions of the Member States relating to the **implementation of good clinical practice** in the conduct of clinical trials on medicinal products for human use
Directive **2001/83/EC** EU Parliament and Council	Community code relating medicinal products for human use *Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use*
Directive **2003/63/EC** Commission Directive	Documents accompanying an application for marketing authorisation (Table of content of **CTD**) Amending Annex 1 of Directive 2001/83/EC
Directive **2003/94/EC** Commission Directive	Principles and guidelines of **good manufacturing practice** in respect of medicinal products for human use and **investigational medicinal products** for human use
GMP **Annex 13** Commission Directive	Manufacture of investigational medicinal products

EUDRALEX **Volume 9**	**Pharmacovigilance**
Regulation 726/2004 EU Parliament and Council	Procedures for the **authorisation** and **supervision** of **medicinal products** for human and veterinary use and establishing a **European Medicines Agency**
CPMP/ICH/135/95 ICH Topic **E 6** EMEA	Note for guidance on **good clinical practice**
CPMP/ICH/377/95 ICH Topic **E2A** EMEA	Note for guidance on Clinical Safety Data Management: Definitions and Standards for **Expedited Reporting**
CPMP/ICH/287/95 modification ICH Topic **E2B M** EMEA	Note for guidance on Clinical Safety Data Management: Data Elements for **Transmission of Individual Case Safety Reports**

Useful Source of information

- Contact us — www.accovion.com

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European Pharmaceutical legislation	http://pharmacos.eudra.org
European Competent Authorities	http://heads.medagencies.org/
European Medicines Agency	http://www.emea.eu.int/
European Clinical Trials Database	http://eudract.emea.eu.int/
EudraCT Supporting Documentation	http://eudract.emea.eu.int/document.html
Pharmacovigilance	http://www.eudravigilance.org/
Inspections in the EU	http://www.emea.eu.int/Inspections/index.html
GMP, Annex 13	http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm
European Union	http://europa.eu.int/
EU Data Protection Directive	http://europa.eu.int/comm/internal_market/privacy/index_en.htm