Impact of Clinical EU Directive on the implementation of Early development studies in Europe

Alain Patat, M.D.
Translational Development
Wyeth Research
Paris, France

AGAH-Club Phase 1 1st Syposium
Strasbourg 17-18 March 2005

Content

- Clinical Trial Directive (CTD) 2001/20/EC: Objectives
- Changes for early development studies
- Clinical Trial Application (CTA)
- Conclusion

Directive?

European derivative law…

Legally binding :

- *Regulations* – directly applicable and binding in all EU member states
- *Directives* – binding member states to common objectives to be achieved in a given timeframe. National authorities choose the means, i.e. national laws

« Soft law »

- *Guidelines*
- *Recommendations, Opinions, etc.*

Objectives of European Clinical Trials Directive 2001/20/EC

- To provide harmonization in the requirements for clinical trial authorizations and transparency in the authorization of clinical trials in Europe
- To establish legal basis for implementation of GCP and application of GMP to investigational products
- To establish legal basis for implementation of ICH E2 on monitoring and reporting of Adverse Reactions (EU-wide pharmacovigilance)
- To establish EU clinical trial database (trials content, initiation, termination)
- To reinforce the ethical principles of the Declaration of Helsinki on research on human subjects, ensuring and standardizing levels of protection for clinical trial subjects

Scope of European CT Directive

- All investigational medicinal products including cell and gene therapies
- All clinical studies
  - **Phase I, II, III and IV**
  - **Includes bioavailability and bioequivalence studies**
  - **National (one or more centers) or multistates**
  - **"Non interventional" studies are excluded**

    It is intended to exclude observational studies, where "no additional diagnostic or monitoring procedures are applied … and epidemiological methods are used for the analysis and collection of data"
- Industry-sponsored and academic clinical research
- Trials conducted in the EU Member states including those which joined on May 1st 2004 (25 states) and EEA (2)

Scope of European CT Directive

- IMP – Investigational Medicinal Product
  - Investigational product and comparator(s), placebo
  - Commercialized product
    - if used or assembled in a different way
    - if used in unauthorized indication
    - if used to gain more information

Main Changes

- Clinical Trial Applications
  - **Max 60 day Agency review time**
  - **Max 60 day EC/IRB review time (single opinion)**
  - **Parallel submissions**
  - **May be extended to 90 days for gene / cell therapy and genetically modified organism**
- Clinical Trial Authorization
  - **Per study, not per product**
- Legal basis for: GCP, GMP and Pharmacovigilance
  - **Enforceable**

Main Changes

- Community-wide databases
  - **All trials registered in new EMEA database (« EudraCT »)**
  - **All suspected, unexpected SAEs registered in EudraVigilance CT module**
- « Substantial amendments »
  - **All significance changes have to be submitted for approval**
  - **Increased administrative burden**

Directives and Guidances

Published:

Clinical Trials Directive EC/2001/20

GMP Directive 2003/94/EC

- GMP guideline: Annex 13
- Applications to Ethics Committees
- Applications to Competent Authorities
- EUDRACT clinical trials database
- Adverse event reporting
- EU database for reporting of SUSARS (suspected, unexpected serious adverse reactions)

Pending:

Final EU GCP Directive

What's in the GCP Directive?

Draft version (July 2004):

- Trial Master File and Archiving
  - 3+ years EC:s
  - 5+ years Sponsors and investigators
- Manufacturing an/or import authorization obligatory
  - Total or partial manufacture, dividing up, packaging or labeling
  - MS must provide within 90 days of application
- GCP inspections
  - Minimum qualifications of GCP inspectors defined
  - MS obligation to set up GCP inspection groups and procedures
- Reference to ICH GCP
  - Rights and safety of trial subjects prevail, trials must be scientifically and ethically sound, involved personnel must be qualified

National Implementation Status

- Implemented in May 2004
  - Austria
  - Belgium
  - Czech Republic
  - Denmark
  - Estonia
  - Finland
  - Greece
  - Hungary
  - Ireland
  - Italy
  - Latvia
  - Lithuania
  - Norway
  - Poland
  - Slovenia
  - Slovakia
  - Spain
  - Sweden
  - UK
- Germany (08/04)
- Portugal (09/04)
- Late starters
  - Netherlands (Q205)
  - France (Q2-Q3/05)
  - Malta (2006)

EU CTD: Article 1 – Scope of the CTD

All clinical trials will be designed, conducted and reported in accordance with the principles of Good Clinical Practice

- ← GCP becomes a legal requirement
- ← GCP inspections of investigational sites mandated

Impact on Phase I in Europe

- ← Minimal, as GCP already implemented in Phase I Units (even required by law in some countries i.e. France)

EU CTD: Article 2 - Definitions

- A clinical trial is any investigation in human subjects intending to discover or verify the clinical, pharmacological, and /or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.
- Investigator - A doctor or a person following a profession agreed in the Member State for investigations, because of the scientific background and experience in patient care it requires. The Investigator is responsible for the conduct of the trial at the trial site.

Impact on Phase I in Europe

- Investigators are already Medical Doctors (MD) in most cases.

EU CTD : Articles 3-5 – Protection of trial subjects

- Subjects should have an interview with the Investigator or his designee prior to study start
- Rights to privacy and to the protection of the subject's data in accordance with Directive 95/46/EC
- Provision for insurance and compensation from Sponsor
- Medical supervision and care of subject under the responsibility of an appropriately qualified doctor
- Subject provided with a contact point to obtain further information

Impact on Phase I in EU

- Minimal as these procedures are already in place

EU CTD : Articles 6-8 – Ethics Committee

- Legal regulation for constitution and operation of Ethics Committees (EC)
- Legal requirement for Ethics Committee favorable opinion prior to the commencement of the trial
- Review period - up to 60 days for most products, may be extended to 90 days for gene/cell therapy and genetically modified organisms
- Defines the scope of information to be reviewed
- Single opinion per country in multicenter trials
- Applicant : Sponsor or investigator
- Extended responsibilities

EU CTD : Articles 6 - 8 Ethics Committees

- **Extended responsibilities of Ethics Committee**
  - Relevance of trial and design
  - Anticipated risks and benefit
  - Qualification of Investigator and involved staff
  - Qualification of trial site
  - Adequacy and completeness of IC information and justification for persons incapable of given consent
  - Indemnity or insurance
  - Amounts (arrangements) compensating investigators and trial subjects and arrangement with site
  - Arrangements for recruiting subjects
  - Notification of Adverse Events

Impact on Early Development Studies: Ethics Committees

- Ethics Committee approval procedures already in place, and even if not required by law, positive opinion of EC required by ICH
- Situation in France: Ethics Committee composition, procedures and favorable opinion, single opinion for multicenter trials and evaluation of site and investigator qualification already required by law since 1988.
- Situation in Germany: EC approval already required by law.
- Situation in the UK:
  - Ethics approval became a legal requirement.
  - Research Ethics Committees (REC) are regulated by the United Kingdom Ethics Committee Authority (UKECA).
  - Research Ethics Committees have been accredited by the Central Organization for Research Ethics Committees (COREC)

EU CTD : articles 9-11 – Conduct of Clinical trials

- Competent Authority (CA) authorization required for each trial and from each Member State involved in the trial
- Submission to CA & EC in parallel or sequential
- Review period - up to 60 days for most products, may be extended to 90 days for gene/cell therapy and genetically modified organisms
- Substantial protocol amendments (likely to have significant impact on subject's safety, scientific value , conduct or management of the trial, and quality or safety of the IMP) to be submitted for EC and regulatory review, with a review period up to 35 days
- Each trial will be assigned a EUDRACT number
- Sponsor should notify CA and EC of the end of a clinical trial within 90 days . If trial is ended early, this period shall be reduced to 15 days and reasons clearly explained.

CA Review

- Check for non-acceptable risks caused by the IMP (insufficient quality, toxicity, insufficient non-clinical or clinical investigation) or the protocol

Impact of EU CTD on Early Development studies

- No change e.g. Sweden: Regulatory approval already required for all trials.
- Notification procedure will change to regulatory review and authorization e.g. France, Germany
- Regulatory authorization required for Phase I studies for the first time e.g. UK

EU CTD : article 13-15 – Investigational Medicinal Products (IMP)

- IMP includes active compound, placebo and comparator
- EU Manufacturers or Importers must hold an **authorization** for these activities
- Have **Qualified Person** (QP)
  - Ensure each batch manufactured according to the principles of GMP (Directive 2003/94/EEC) and Annex 13 of the EC guide to GMP with new labeling requirements
  - Ensure that each batch imported has a certificate indicating it meets the above or has undergone relevant analysis, tests to confirm quality
  - Release all batches manufactured in or imported into the EU
- Manufacturing / Importing sites for IMPs may undergo regulatory GMP inspections

Impact on Early Development studies: IMPs

- Phase 1 units required partial manufacturing authorization for packaging and labeling activities
- Sponsor's QP will release of IMP from Sponsors.
- GMP inspections will take place at the trial site, manufacturing site, any analytical site and the Sponsor's premises, whatever their location.
- Source reference products from EU (with a marketing authorization number) when possible

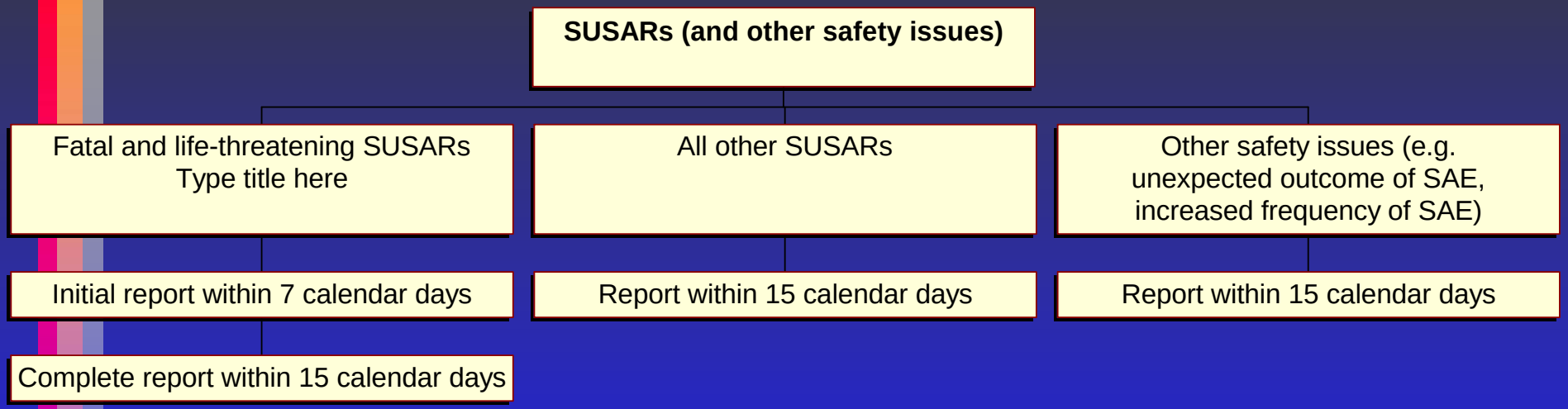
EU CTD : Article 16-18 – Adverse Events / Serious adverse events

- Defines the notifying person and his responsabilities
- Notification to CA:
  - all SUSARs (Serious Unexpected Suspected Adverse Reactions)
  - Timelines for reporting SUSARS: 7 to 15 days
  - EUDRAVIGILANCE database
  - Annual Safety reports required from 2005
- Notification to EC :
  - SUSAR and annual Safety report

Impact on Phase I in EU

Minimal as reporting procedures are already in place

Expedited Reporting Requirements



Send to:

- Competent Authorities of concerned MS, concerned ECs, EMEA Eudravigilance module
- …but individual investigator letters not obligatory

EU CTD: article 19
General Provisions

- Sponsor or a legal representative of the Sponsor must be established in the EU

Impact on Phase I in EU

- Sponsor has an office in EU

or

- Sponsor to define legal representative

Clinical Trial Application (CTA)

- Eudract Number ,Covering Letter and Application Form
- Protocol, any substantial amendment and Investigator's brochure
- IMP Dossier / Simplified IMPD for known products in EU / SmPC for marketed products in EU
- Importer 's authorization if applicable , Manufacturer's authorization or QP declaration of GMP equivalent to EU GMP
- Sample of IMP label
- EC opinion when available
- Letter from sponsor identifying the legal representative if sponsor is not based in EU

Format of IMP Dossier

- Summaries on quality, manufacture and control of any IMP
- Non clinical data
- Clinical data (where applicable)
- Tabular format where possible
- Use Common Technical Document format
- Guidance provided by UK (www.mca.gov.uk) and France (www.afssaps.sante.fr)

CA / EC Core Information to provide

Core Information	CA	EC
Eudract Number and Application form	+	+
Covering Letter	+	+
Protocol	+	+
Investigator Brochure	+	+
IMP Dossier	+	GR, IT, NL
SPC for Marketed Products	+	CR, IT, NL
List of CAs submitted to	+	-
EC opinions (when available)	+	-

CA / EC Core Information to provide

MS Specific Information	CA	EC
Subject Related		
- Informed Consent form	Not BE/NL/SP/UK	+
- Subject Information	Not BE/NL/PT/SP/UK	+
- Arrangements for recruitment	-	+
IMP Related Information		
- Manufacturer's or importer's authorisation	Not in NL	IT/NL/GR
- QP Declaration	Not in NL	IT/NL
- TSE Certificate if appropriate	Not in NL	IT/NL
- Viral safety if appropriate		
Facilities, Staff, Finance Related		
- CV of Principal Investigator	AT/GE/GR/IT/IRE	+
- Provision for Insurance/Indemnity	AT/FR/GR/IRE/PT	+

Implementation of the EU CTD: Conclusion

- Main change is CA authorization
- Both reviews by EC and CA should be 30 days or less for first review for early development studies
- Further reviews by CA may be shorter
- Greater harmonization
- No major delays are expected from current situation and Europe should remain competitive and attractive for conducting early development studies

Conclusion: Opportunities

- First step towards more harmonization
- Forced harmonization through competition, which resulted in shorter timeframe of review for early development/Phase 1 studies
- EU rules for clinical trials may also evolve/improve further on
  - More standardized and rational safety reporting system
  - Training and accreditation of Ethics Committees
  - Clearer separation of EC vs. CA responsibilities
  - Mutual recognition of CTAs over MS

Implementation of the EU Clinical Trial Directive in France

Alain Patat, MD

Translational Development

Wyeth Research

Paris, France

Introduction

- Current and future situation in France
- CTA file
- Timelines for review
- Results of the Pilot phase
- Conclusion

Huriet-Seruselat Law on Biomedical Research: General Principles

1. Current situation in France

- Law in force **since 1988**
- Biomedical Research with and without therapeutic benefit
- Mandatory supervision of a **physician (MD)** with an appropriate experience. Investigator should be a medical doctor.
- **Authorization of clinical pharmacology sites** in which trials are conducted with special attention to subject's safety
- **Scientific value**: pre-clinical prerequisites, benefit-risk ratio, reference to GCP, GMP like procedures
- **Protection of the subjects** participating in the research, with special attention to patients in emergency care, children, incapacitated adults
- Mandatory **insurance** to guarantee the sponsor's liability
- **Possible inspections** by AFSSAPS

2. Future situation

- No major change, after implementation EU CTD. AFSSAPS inspection will become mandatory

Informed Consent

1. Current situation in France

- Written Informed Consent should be obtained prior to the research start
- After the participant has been informed by the investigator or his representative of:
  - Objective and design of the study
  - Expected benefits and inconveniences, including risks
  - Favorable Opinion of an Ethics Committee (CCPPRB) is required
  - Right to withdraw consent at any time
  - Register in a volunteer national file if appropriate
- Special provisions for children, patients in emergency care, prisoners, incapacitated adults etc

2. Future situation

- No major change after implementation EU CTD

Ethics Committee (Consultative Committee for the Protection of the Persons participating in Biomedical Research: CCPPRB)

1. Current situation in France

- **One or more per region, nominated by the Ministry of Health**
- **Independent from the sponsor and the investigator**
- **Constitution: 12 full and 12 ad hoc members (4 persons with at least 3 physicians, with an expertise and an appropriate experience in biomedical research, 1 general practitioner, 2 pharmacists, 1 nurse, 1 person qualified in ethics, 1 social worker, 1 lawyer, etc)**
- **Members nominated for 6 years, with half of them renewed every 3 years**
- **Quorum of at least 6 attendees required to allow meeting**
- **Submission by principal investigator**
- **Assess relevance of the research according to subject protection and information, modality to obtain ICF, subject's indemnities and qualification of the site and the investigators**
- **Review should be done within 5 weeks**

Ethics Committee (Committee for the Protection of the Persons: CPP)

2. Future situation

- **One or more per region, nominated by the Representative of the Region**
- **Independent from the sponsor and the investigator**
- **Constitution: 16 (14) full and 16 (14) ad hoc members (8 persons working in the medical field with at least 3 physicians and 1 pharmacist working at an hospital, 2 social workers, 2 representatives of patients associations)**
- **Members nominated for 6 years, with half of them renewed every 3 years**
- **Quorum of at least 10 attendees with at least 4 people working in the medical area and 1 in each other categories**
- **Submission by sponsor**
- **Review protocol and amendment within 35 days**
- **Appeal possible at ministry of Health, with another review in another randomly selected CPP**
- **Opinion valid for 1 year**

Committee for the Protection of the persons

Extended responsibilities of Committee for the Protection of the Persons

- Relevance of trial and design
- Anticipated risks and benefit
- Qualification of Investigator and involved staff
- Qualification of trial site
- Adequacy and completeness of IC information and justification for persons incapable of given consent
- Indemnity or insurance
- Amounts (arrangements) compensating trial subjects
- Arrangements for recruiting subjects
- Notification of Adverse Events

AFSSAPS Involvement

1. Current situation in France

Notification to Competent Authority (AFSSAPS):

- Prior to the start of the trial, the sponsor should submit to AFSSAPS a letter of intent, with a form summarizing the protocol, provide the certificate of analysis of the drugs and the EC's favorable opinion by registered mail
- During the trial, the sponsor should also inform AFSSAPS of:
  - Serious Adverse Events and new relevant safety information
  - **Premature discontinuation of a trial and its reason**

AFSSAPS Involvement

2. Future situation in France

- CTA submission by sponsor
- AFSSAPS review and authorization
- Authorization may be written but not necessarily. Will be implicit in most of the time
- AFSSAPS review will focus on the safety of subjects
- Authorization valid for 1 year
- SUSARS
- End of study and Safety summary

Protection of the subjects
Measures to prevent overvolunteering

1. Current situation in France

- Subjects participating in biomedical research without therapeutic benefit are registered in a Volunteer National File located in the Ministry of Health.
- Subjects participating in biomedical research without therapeutic benefit may be indemnified to compensate for inconvenience. However, the total amount per year is limited to 3800 euros by the Ministry of Health.
- An exclusion period before the subject can participate in another study should be defined by the investigator in the ICF and/or the protocol. Its duration varies according to the drug and the design of the study (often 3 months is proposed).
- Before subject's enrollment, the investigator or his designee should check for subject's suitability based on exclusion period and indemnity earned in the past year in the national file.

2. Future situation in France

- No major change after implementation EU CTD

Clinical Pharmacology Facilities and Staff

1. Current situation in France

- Clinical Pharmacology Units (CPU), in which research without therapeutic benefit is conducted, should be authorized after an inspection
- 24 hours medical supervision is required when subjects are hospitalised
- CPU should have resuscitation and monitoring equipment enabling resuscitation care
- Contact with an intensive care unit close to the facility should have been established prior to the study to allow immediate transfer of the subject if necessary. This contact between the CPU and Intensive Care Unit is mandatory to get the authorization of the CPU

2. Future situation in France

- No major change after implementation EU CTD. Need for QA system, and manufacturing authorization granted for packaging and labeling provided the site has a pharmacist with at least 1 year of experience in the field

Process flow to conduct a clinical trial

1. Current situation in France

- No authorization from Competent Authority (CA) needed
- Ethics Committee (CCPPRB) favorable opinion is requested. The mean review time (between submission and written approval) is 20 days (Survey 2000-2003)
- Then, notification of the study to AFSSAPS, accompanied with the CCPPRB approval by registered mail

Process flow to conduct a clinical trial

2. Future situation – CA and CPP submission process

- Parallel submission to CPP and AFSSAPS by registered mail
- English documents accepted, except for the ICF and the notice of information for subject and drug labels
- Validation phase by AFSSAPS to check that all the requested documents have been provided. AFSSAPS will only notify the sponsor by registered mail within 5 days if there are missing documents
- IMPD content (CTD format) defined in the AFSSAPS site (www.afssaps.sante.fr)

Future situation after implementation: CA & CPP submission

- EC (CPP) Review within 35 days
- AFSSAPS Review:

	Review	Answers	Authorization
Phase 1	D14	D24	D30
Phase 2-4	D30	D45	D60

- AFSSAPS agrees that maximum duration for the review is 30 days for early development clinical pharmacology studies
- Substantial amendments: CPP and AFSSAPS review within 35 days or less (Objective is 14 days)
- In summary, EC (CPP) positive opinion and AFSSAPS authorization should be provided within 30 days

Status of the implementation of EU CTD in France

- Public Heath Code : Chapter 2 Biomedical Research Articles 42 to 50
- Discussed at Parliament and Senate from October 2003 to July 2004
- Approval of the law by August 2004
- Application decrees: first draft sent for review on January 2005, final version should be issued in May 2005. The decrees will be applicable 4 months after their publication in order to allow constitution of CPP.

Transitional arrangements in France (www.afssaps.sante.fr)

- Studies started after implementation will required submission of a CTA to CA, authorization from AFSSAPS and positive opinion from CPP
- On-going studies starting prior to implementation will not need a CTA submission, and can be completed, according to the law in force at time of EC approval. Amendments may follow this regulation for 1 year after implementation

EC / AFSSAPS : Information to be submitted

Information	EC	AFSSAPS
Eudract No. + Application form	+	+
Covering Letter	+	+
Protocol	+	+
Investigator Brochure	+	+
IMP Dossier	-	+
or SPC for Marketed Products	-	+
Informed Consent form	+	+
Subject Information	+	+
Arrangements for recruitment	+	-

EC / AFSSAPS : Information to be submitted

Information	EC	AFSSAPS
IMP Related Information		
- QP Declaration	-	+
- Manufacturer's Licence	-	+
- TSE Certificate	-	+
- Viral safety Studies	-	+
- Import licence for non-EU countries	-	+
- Certificate of analysis	-	+
Facilities & Staff Related		
- CV of Principal Investigator	+	-
- CPU's authorization	+	-
Insurance Certificate	+	+

Results of AFSSAPS Pilot Phase

- Run from November 17th 2003 to April 30th 2004 for early Phase 1 protocols only
- Objective: check IMPD content and train both sponsor and AFSSAPS
- Expanded to Phase 1 to 4 trials from May 2004
- Did not delay the conduct of the study, as study may start as soon as EC (CCPPRB) favorable opinion is notified to AFSSAPS
- AFSSAPS provides **written comments to sponsor**
- 10 dossiers between Nov 2003 and May 2004 reviewed with a maximum time of **30 days**
- 45 dossiers reviewed from 1June to 30 Sept 2004 with a mean initial time of **22 days** (range 18-25) for 5 Phase 1 trials and a mean initial review time of 28 days for phase 2 –3 trials.
- All trials approved : about 50 % after the initial review and 50 % after appropriate answers

EU CLINICAL TRIALDIRECTIVE : Implementation in France

- What will not change or minimally change:
  - Reference to GCP
  - EC (CPP) composition and process
  - Notification of CPP positive opinion to AFSSAPS
  - Phase 1 Units' inspection and authorization
  - Volunteer National File
  - Sponsor Insurance
  - SAE / New safety information notification

EU CLINICAL TRIAL DIRECTIVE : Implementation in France

- What will change :
  - Notification becomes Clinical Trial Authorization
  - Extended responsabilities o CPP
  - Legal requirement for GMP material
  - CTA submission to AFSSAPS
  - Extended pharmaceutical information in IMPD
  - End of study notification to AFSSAPS and EC
  - Study safety summary and annual safety report to AFSSAPS and EC

Implementation of the Clinical European Directive in France : Conclusion

- Main change is AFSSAPS authorization
- Both reviews by EC and AFSSAPS should be completed within 30 days
- Previous experience with regulations from 1988
- No major issues are expected from current situation and France should remain competitive for conducting early development as well as late development clinical pharmacology studies