

A decorative border surrounds the slide content. It consists of four thick, L-shaped arrows pointing inward towards the center. The top-left arrow is red, the top-right is orange, the bottom-right is grey, and the bottom-left is cyan. The background of the slide is a solid blue color.

# 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 1<sup>st</sup> Symposium

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# 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

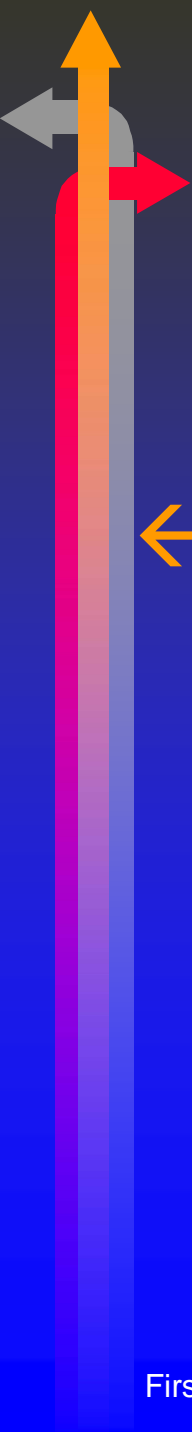
- ← To provide **harmonization** in the requirements for clinical trial authorizations and transparency in the authorization of clinical trials in Europe
- ← To establish legal basis for implementation of **GCP** and application of **GMP** to investigational products
- ← To establish legal basis for 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**

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# 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 1<sup>st</sup> 2004 (25 states) and EEA (2)

# Scope of European CT Directive

- 
- A decorative vertical bar on the left side of the slide. It features a gradient from blue at the bottom to orange at the top. At the top, there is a grey arrow pointing left, a red arrow pointing right, and a grey arrow pointing up.
- ← 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 responsibilities
- ← 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

## SUSARs (and other safety issues)

Fatal and life-threatening SUSARs  
Type title here

All other SUSARs

Other safety issues (e.g.  
unexpected outcome of SAE,  
increased frequency of SAE)

Initial report within 7 calendar days

Report within 15 calendar days

Report within 15 calendar days

Complete report within 15 calendar days

### *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](http://www.mca.gov.uk)) and France ([www.afssaps.sante.fr](http://www.afssaps.sante.fr))

# CA / EC Core Information to provide

<i>Core Information</i>	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

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

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# 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](http://www.afssaps.sante.fr))

# Future situation after implementation: CA & CPP submission

← EC (CPP) Review within 35 days

← AFSSAPS Review:

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

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← 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 Health 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](http://www.afssaps.sante.fr))

- ← Studies started after implementation will require 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	+	+
<b>IMP Dossier</b>	-	+
<b>or SPC for Marketed Products</b>	-	+
<b>Informed Consent form</b>	+	+
<b>Subject Information</b>	+	+
<b>Arrangements for recruitment</b>	+	-

# EC / AFSSAPS : Information to be submitted

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

# Results of AFSSAPS Pilot Phase

- ← Run from November 17th 2003 to April 30<sup>th</sup> 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 1 June 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 TRIAL DIRECTIVE :

## 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 responsibilities of 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