

Current European Experience with trial approval in early development : Afssaps (France)

*Agence française
de sécurité sanitaire
des produits de santé*



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- **FIH in France**
- **Some figures / phase 1 CTs**
- **Assessment by Afssaps**
- **How to improve CTA assessment in EU/CTFG**

FIH – CT Organisation in France



1. Perform FIH in authorised/accredited research sites
2. Avoid simultaneous inclusion of volunteers in several CTs:
 - exclusion period to be specified in the protocol
 - the French registry of volunteers
3. Avoid professionalisation of volunteers :
 - total annual indemnities < 4500 euros
4. Specific modalities for conducting FIH
 - guideline on strategies to identify and mitigate risks for FIH-CT with IMP (Emea/July 2007)

Competent authority/ Ethics committee: who assesses what in France?



National Competent Authority

Quality and safety of investigational medicinal products

- quality data
- non clinical data
- clinical data
- GMP
- GLP
- GCP
- Emea, ICH recommendations

Subjects' safety, including

- inclusion / exclusion criteria
- treatment dose, duration
- safety monitoring of subjects
- choice of comparateur

Ethics Committee

Subjects' protection

- subject information / consent
- indemnities/compensation/insurance
- arrangements for recruitment

Trial design: methodology

Facilities

- quality of facilities, suitability of investigators and staff

1. Some hospital pharmacies in France may prepare

- MP:
- hospital preparations
 - including IMPs and NIMPs

• *Conditions :*

- The hospital pharmacy must be **authorised** for this activity (inspection)
- **Adapted GMP:** « Good manufacturing practice for hospital preparations » (published in 2007)
- Hospital preparations are **declared** to Afssaps
- Hospital preparations only **if no authorised MP available**

2. Some Phase 1 research sites are allowed to package, label IMPs

Exploratory trials in France



- **Working group on exploratory trials (3-5 October 2008) :**
 - Definition and scope (IMPs with factors of risk ?)
 - Concerns about the border between exploratory trials and FIH
 - M3 (5 approaches)
 - Adapted GMP could be acceptable for microdosing.
 - Perform expl. CT in autorised research sites
 - Pre submission to Afssaps for approaches 3 to 5
 - > *French recommendations pending (after step4 ICH M3 revision)*

Some Figures in France in 2008

2008 in France...



- **1 000 CTs**

- Phase 1 : 25%
- Phase 2 : 27%
- Phase 3 : 37%
- Phase 4 : 10%
- Sponsors : commercial (74%), non commercial (26%)
- Time lines (all phases) : 42 days (recevability period included)

- **2 200 subst. amendments**

- **51 380 Susars**

- 8 ● **861 ASR**

Phase 1 CTs in France (2008)



- **250 phase 1 CTs**
 - 41 FIH (17% of phase 1)
 - 26 phase 1/2 CTs (10%)
 - 181 other phase 1 CTs
- **CTA**
 - 64% authorised directly
 - 36% RFI-GNA
- **No refusal, but 7 withdrawals** (for potential refusal)
- **Time lines***
 - 32 days if direct CTA
 - 38 days (all phase 1 CTs included)
 - Longer where patients concerned

*: time lines include the recevability period

- **41 in 2008**
- **5 considered with « potential factors of risk » (FIH guidelines)**
- **25 national ; 16 international (10 F+MS ; 4 F+MS + 3rd countries ; 2 F + 3rd country)**
- **Decision :**
 - Authorisations : all
 - 35% direct CTA (no RFI nor GNA) ;37 days*
 - No refusal
 - But 7 withdrawals (3 for potential refusal)

*: time lines include the recevability period

Afssaps' assessment of phase 1 CT dossiers :

- the most frequent requests for further information RFI**
- or grounds for non acceptance (GNA)**
- in 2008**

- **Safety considerations and compliance to guidelines**
- **Internal and external expertise**
- **FIH : if potential factors of risk identified :**
 - pre-submission of the CTA dossier to Afssaps recommended
 - free of charge
 - CT experts working group
 - Procedure on www.afssaps.fr

Quality issues (26% of GNA/RFI)



1. Sterility data (RFI ; justification) :

- bioburden before sterile filtration

2. Impurities (RFI)

- quantity, control

3. Properties of the drug product :

- risk of active substance precipitation, risk of flocculation, micelles size...

4. Methods of manufacture of the drug product :

- description, sterilisation...

5. Stability description

6. Control of the drug product or active substance

Viral safety issues



- **34/250 Phase 1 CTs concern biological IMPs**
- **15/34 : RFI or GNA**
 - Lack of any viral safety data ! (8/15)+++
 - ...

Non clinical issues



- **16%**

- **Lack of :**

1. Non clinical data according to guidances+++
2. Information on calculation and justification of the test doses (1st dose – maximal dose)++
3. Pharmacokinetic data++
4. Information on specifications

- **RFI/GNA :**

- Discussion of non clinical results
- Justification of indication, modalities of IMP administration or association with other MP
- Description and justification of impurities (Guideline on the limits of genotoxic impurities : EMEA/CHMP/QWP/251344/2006)
- 1st dose (FIH)

Clinical issues (1)



1. FIH :

1. The choice of subjects

- Healthy V or patients
- inclusion – exclusion criteria (IB – SmPC)

2. Details about decision making process and data sharing organisation (multisites FIH)+++

3. Modalities for product administration

- within cohort and between cohorts :
 - number of simultaneous administrations
 - time between subjects
 - criteria to start next cohort
 - overlap between cohorts
- stopping rules
 - the dose escalation
 - the trial

4. Safety monitoring criteria and modalities

2. Phase 1/2 :

- Lack of the results of phase 1 before starting phase 2 !

The 3 potential refusals for FIH in France (2008)



1st dossier: Need for further genotoxicity data (M3)

- clastogenicity/healthy volunteers

2nd dossier: Inclusion criteria

- limit to : severe disease where there is no therapeutic options

3rd dossier: Several issues :

- cytokines release syndrom ;
- details on monkey death ;
- justification of 1st dose (use Mabel) ;
- justification of children ;
- decision making modalities ;
- circulation of information between centres (countries)

- **Quality issues 26% of RFI**
 - **NC issues could be avoidable**
 - **Clinical issues : use the FIH Guideline from Emea!**
- **Points for improvement**

How to improve CTAs assessment in EU ?

Harmonisation of CT assessment by NCAs



- **Coordination of the scientific assessment of :**
 - Clinical trials applications (CTA)
 - CT safety : annual safety reports
- **CTA assessement :**
 - Procedure proposed by the Clinical Trial Facilitation Group (CTFG) to sponsors
 - But also an internal CTFG procedure

The clinical trials facilitation group/ CTFG



- **CTFG :**
 - An Operational working group at the EU level
 - NCAs of the 27 member states + EMEA + EU. Commission
 - In 2009 chaired by Germany, cochaired by France
 - **Terms of Reference :**
 - Improve interactions between the MS, **more coordination**
 - Promote harmonisation of decisions on CTAs, **avoid divergent decisions**
 - Get a **common interpretation** of regulatory aspects
 - Same objectives: Ensure **subjects' safety**

CTFG : how it works...



- **Monthly face to face meetings**
- **Monthly teleconferences**
- **Electronic tools to share information ; automatic alerts**
- **Links with other European working groups (Commission WG, Inspectors WG, CHMP....)**
- **CTFG assessors meetings :**
 - Quality issues :
 - Sept. 2008
 - Non clinical issues :
 - Feb. 2008
 - June 2008 (M3)
 - Exploratory trials :
 - Oct. 2008
 - Oct. 2009

**The CTFG Guidance document
for a
Voluntary Harmonisation Procedure
(VHP)**

<http://www.hma.eu/77.html>

A pilot Phase starting Feb. 2009

The VHP : a 2-step process



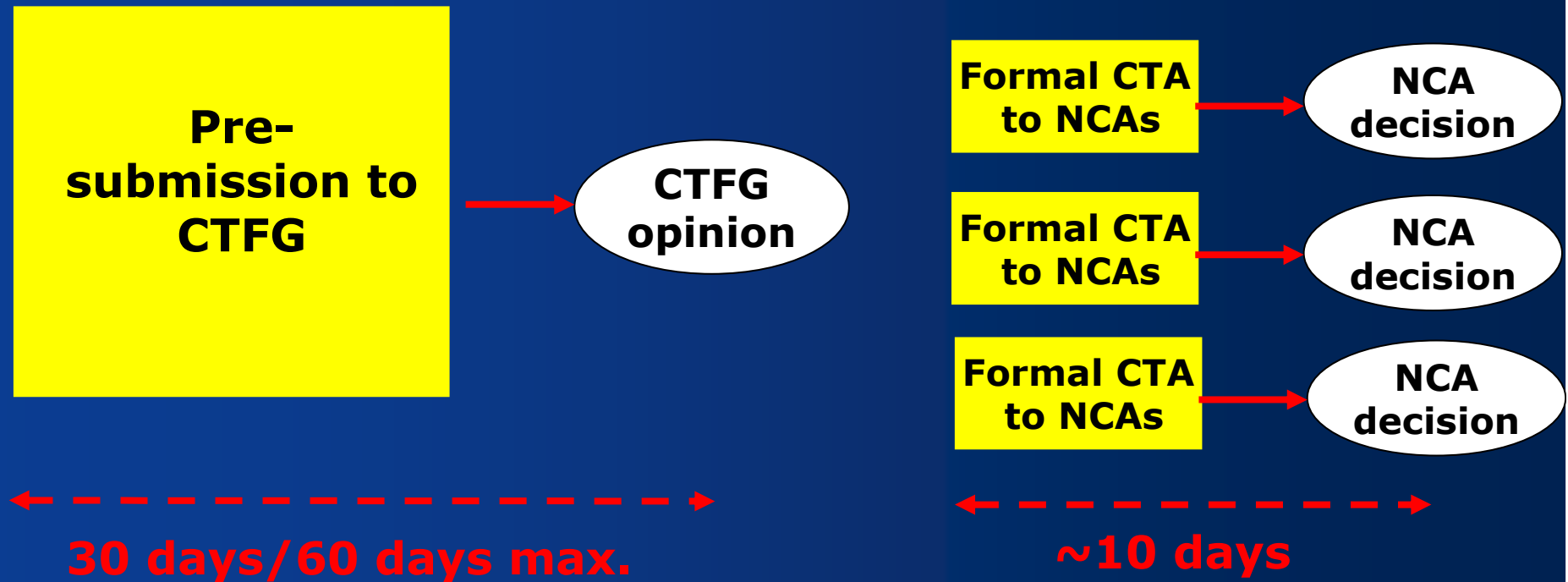
1. Pre-submission of CTA to CTFG

- Single repository, electronic submission, same CTA dossier, at the same time for NCAs
- Common and simultaneous scientific review by all the participating NCAs
- Timelines :
 - 1st common position around D30 (OK or RFI/GNA),
 - total period : maximum 60 days (if RFI or GNA)
- scope of assessment : quality and safety of IMP ; safety of subjects++

2. Then, the National step

- Formal CTA application to NCAs
- Formal decision by NCAs within short timelines (~10 days)

The VHP : flowchart



Scope of the pilot phase



- MultiNational CTs and
- IMP with no MA in EU and
- Where there are “critical” medicinal products/trials e.g.:
 - FIH and particularly with IMP with “potential factors of risk”
 - Or specific IMP
 - Or specific trial populations (rare population, unmet medical needs, paediatrics)
 - Or very large population (e.g. phase 3, several 5-10 MS concerned)

➤ ***VHP : a common and simultaneous assessment of CTs by several NCAs***

- **An internal procedure for assessment sharing if Multinational FIH**
- **The NIMP dossier, a common approach (pending)**
- **Information on the CTFG website**
 - <http://www.hma.eu/77.html>
 - mandate
 - action plan
 - contact points in NCAs
 - who assesses what in MS
 - other documents: VHP,

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