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

Agence française
de sécurité sanitaire
des produits de santé

afssaps

Dr Chantal Bélorgey
Head, Clinical Trials and special status MP Department

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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
- safety monitoring of subjects
- treatment dose, duration
- 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

IMP/NIMP

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, labell 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**
- **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**

FIH CTs

- **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 withrawals (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

Assessment of CTA by Afssaps

- **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 floculation, 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 impureties : 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

Clinical issues (2)

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)

Conclusions

- 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**
- **Eletronic 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

Coordination of assessment of Multinational CTA by Members states

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

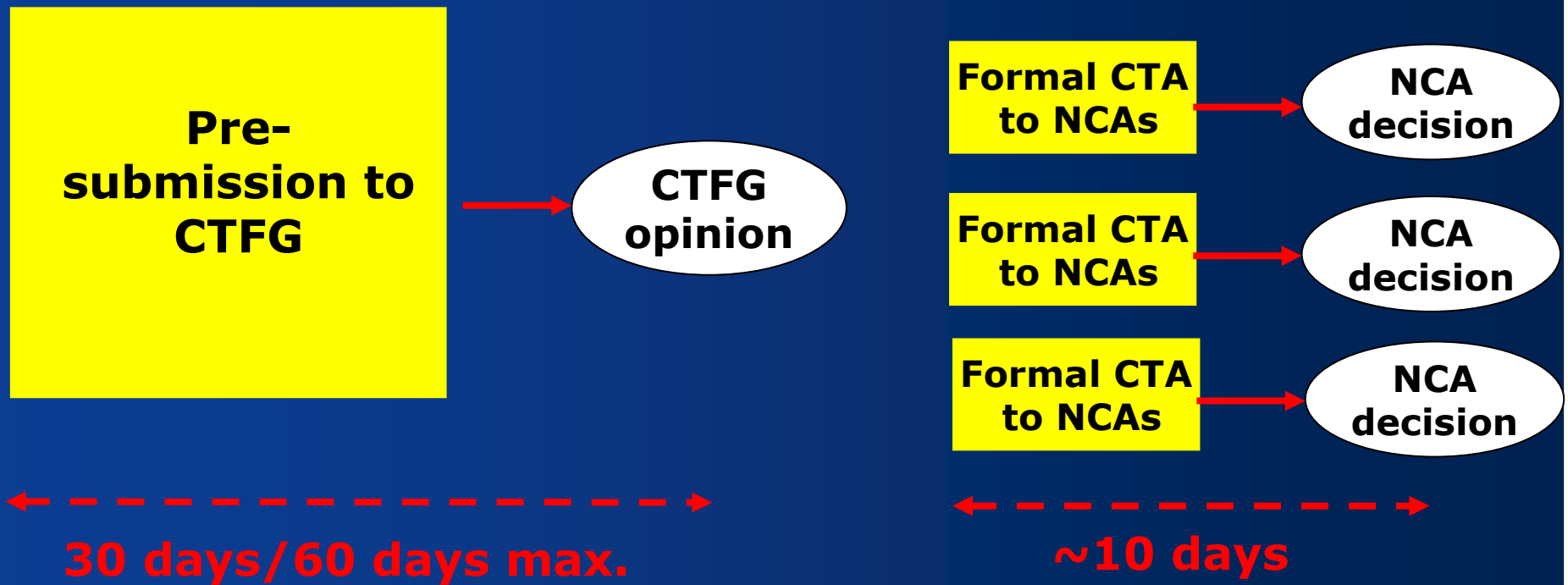
1. Pre-submission of CTA to CTFG

- 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 : flowshart



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***

Furthermore

- **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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