COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS

FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS

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Actions triggered by TGN412 incident in EU

- Expert Group in the UK (Duff) report November 2006
- European Commission and Heads of Agencies (national authorities) request for a EU guideline addressing FIM clinical trials on High Risk Medicinal products
- CHMP strategy written in November 2006

Expert Drafting Group designated by CHMP in December 2006

Representatives from

- CHMP Safety Working party
- EMEA Management
- HMA Clinical Trial Facilitation Group
- EC's Ad hoc Group for the update of implementing Guidelines for Directive 2001/20/EC

Main issues to be covered in the guideline

- Definition of high risk
- Nonclinical requirements
- Estimation of the starting dose
- Study design of the FIM trial
- Aspects of the site location and risk management

SCHEME OF ACTIVITIES

- MEETINGS IN 2007
  - January brainstorming and first draft
  - February 2nd draft, internal consultation
  - March final draft for consultation outside
  - June Workshop
  - July Finalization of the guidance(?)

Intention of the guideline

- Assists sponsors in the transition from non-clinical to early clinical development.
- Provides criteria to classify new IMP's as potential high risk products
- Gives guidance on
  - Quality
  - Nonclinical testing
  - Design for first-in-man clinical trials for HR products

FIRST MESSAGE

- Accidents are rare
- Avoid single case regulations
- For most of the new medicinal products, the conventional non-clinical programme provides an acceptable safety estimate for a first administration in humans.

However,

- **for high-risk medicinal products this programme might not be sufficiently predictive of serious adverse reactions in man and their development programme might require special considerations.**
- **Transition from non-clinical to clinical testing therefore requires special considerations.**
- **Clinical testing might require special precautions**

SCOPE

The guideline covers:

- **high-risk medicinal products, including**
  - **both chemical “conventional”, “small”**
  - **and biological products**
- **regarding**
  - **the first administration of a single dose of a high-risk medicinal product**
  - **and the initial escalating dose phase of clinical development.**
- **exclusiding**
  - **Cell and Gene therapy is excluded**

Definition of high-risk products

when there are concerns about the possible occurrence of serious adverse reactions in first-in-man clinical trials

- **In fact the guideline defines its scope as a circle:**
  - **The guideline is on high risk products**
  - **What are high risk products?**
  - **See the guideline for definition.**

Evaluation applicable to all First-in-human trials

Definition of high-risk products

Particular knowledge

Or

Lack of knowledge and uncertainties

Definition of high-risk products

Particular knowledge or uncertainties on

1. **the mode of action, and/or**
2. **the nature of the target, and/or**
3. **the relevance of animal models.**

Duplication of Guidelines ?

Available guidelines in this area

- FDA Estimation of Safe Starting Dose
- ICH M3 Nonclinical requirements in relation to timing of clinical studies
- CHMP Microdose approach
  - All above not applicable to biotechnology-derived products
- ICH S6 Preclinical safety evaluation of Biotechnology-derived Medicinal Products

Comparison

- These guidelines does not cover the whole spectrum of the HR Guidance

E.g.

- ICH M3 specifies the need for safety studies at the transition stage, **but does not specify the risks to be dealth with.**
- ICH S6 hardly touches on requirements for First-in-human trials

Need for examples ?

- Some examples are present (see Mode of action)
- Examples might be interpreted too rigidly and may just stimulate checklist approach
- EU guidance documents does not contain too much examples

Key elements in the guideline

- Non-clinically emphasis on:
  - The relevance of the animal model
  - Calculation of the dose
    - Not on toxicity endpoints
    - Based on a pharmacological effects, e.g. receptor occupancy or substrate binding (enzymes)

Key elements in the guideline

- Clinically emphasis on:
  - Choice of study population
  - Protocol design
  - Dose escalation and monitoring
  - Organisation and decision making

General comments

- Definition of high-risk approach
  - Too vague
  - Tendency to choose the most safe approach
  - And a higher level of requirements
  - Less innovative research climate in Europe
  - Leading to disharmony in Europe
  - Resulting in an unacceptable “stamp” of the compound (and the trial)

General comments

- Proposal:
  - A Points-to-consider document should be given on
  - Risk mitigation strategies through integrated analysis of nonclinical data and appropriate design of clinical studies
  - While adressing the risk management strategies

Application of Risk Mitigation Approach

- Advantages
  - Flexibility in definition of high-risk, i.e. just identifying risk factors
  - No direct labeling of individual products
- Disadvantage
  - Still disharmony between member states (a need for more centralized decisions?)
  - Uncertainty about appropriate measures

Further discussion during the plenary discussion

THANK YOU