Has MABEL kept the promise?
10 years of experience

AGAH Annual Meeting 2016

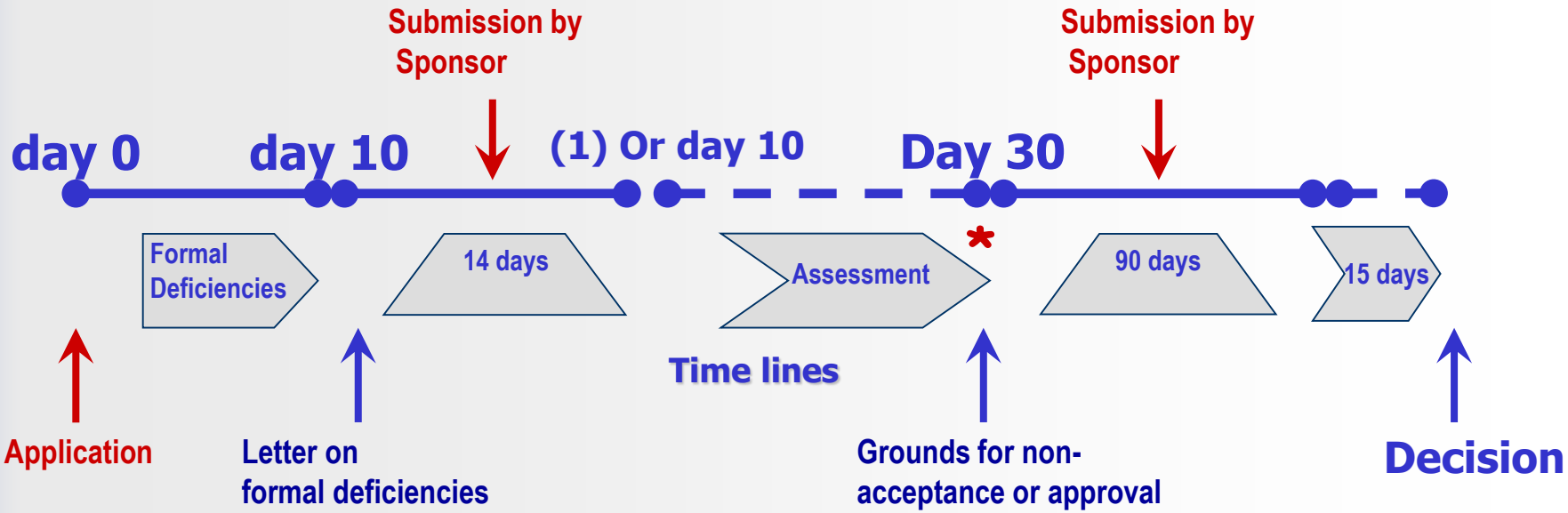
Berlin, Germany
20 – 22. April 2016

Dr. Bettina Klug, MSc
Paul-Ehrlich-Institut, Langen
Bettina.Klug@pei.de

Paul-Ehrlich-Institut
Federal Agency for Vaccines and Biomedicines

- **Clinical trial application - DE (PEI)**
- **The TeGenereo case and it‘s consequences**
- **First in men studies (FIM studies) requirements**

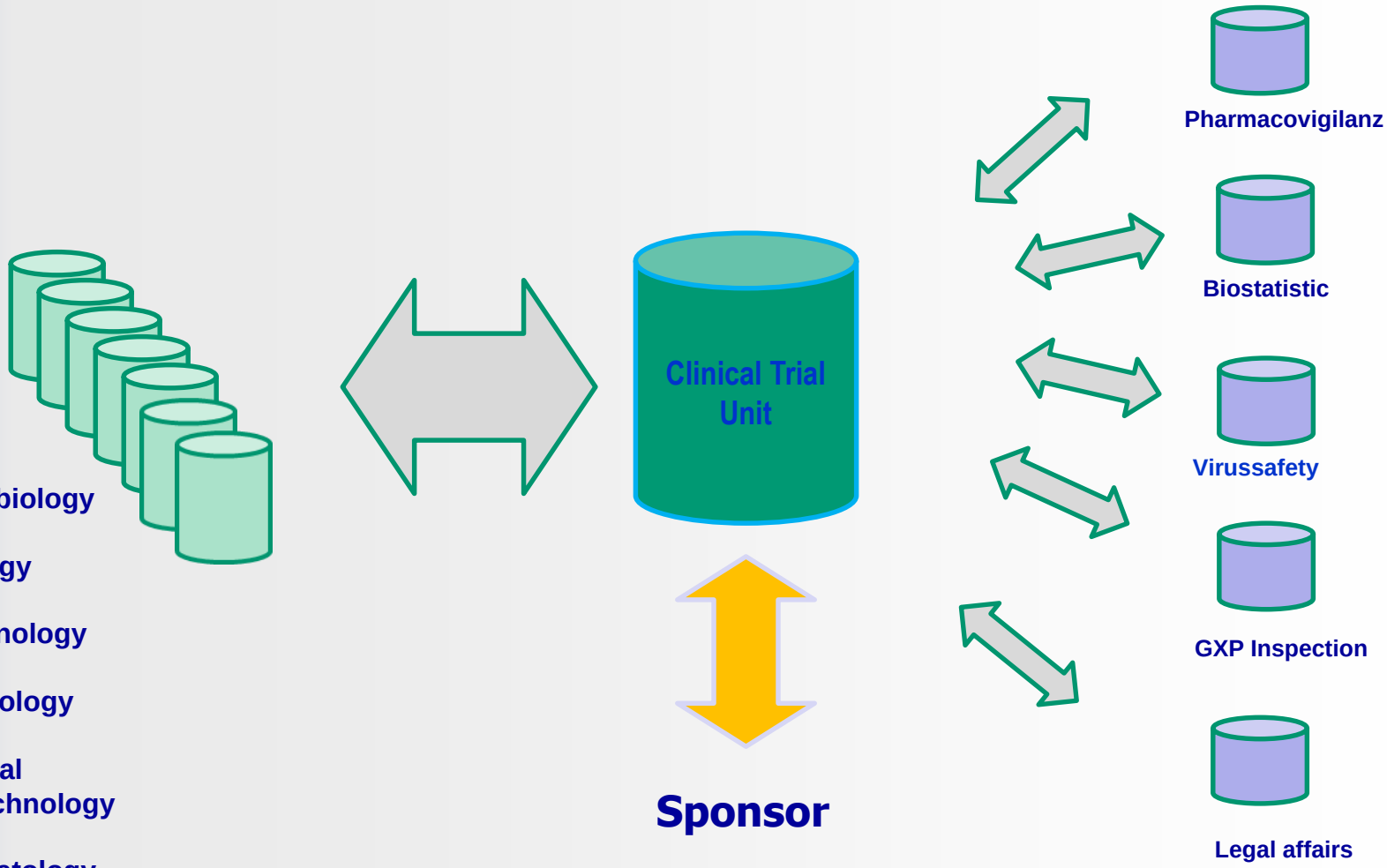
Clinical trial application (DE)



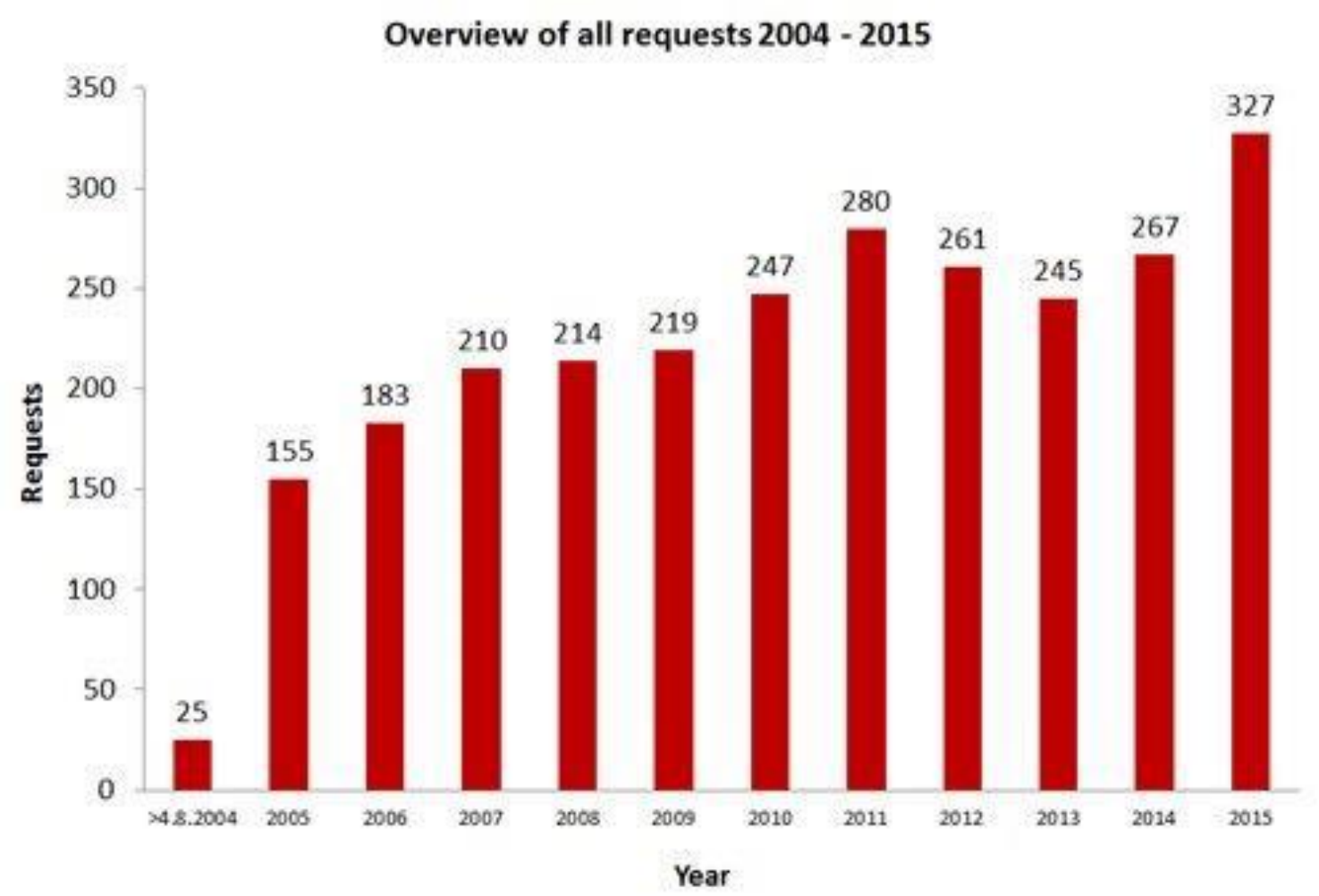
Biological Products (human or animal origin)	**60 Days**
Somatic Cell-Therapeutics; Gene Therapy Products Genetically modified Organisms (GMO)	**90 Days**
Xenogene Cell-Therapeutics	**No time-limit**

*** Products under 30 days: Vaccines; Allergens; Biotech. acc. Reg. 726/2004/EC**

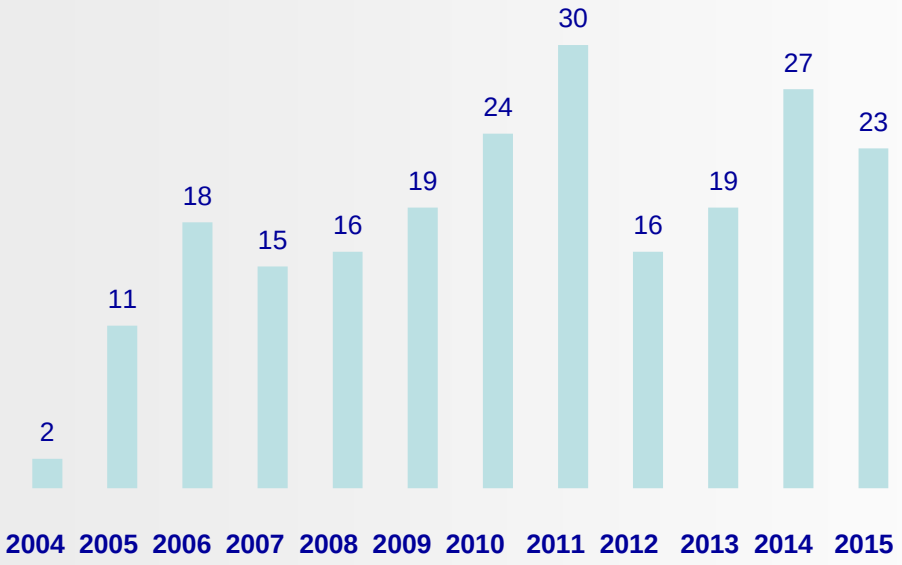
Clinical trial application



Clinical trial application (PEI)

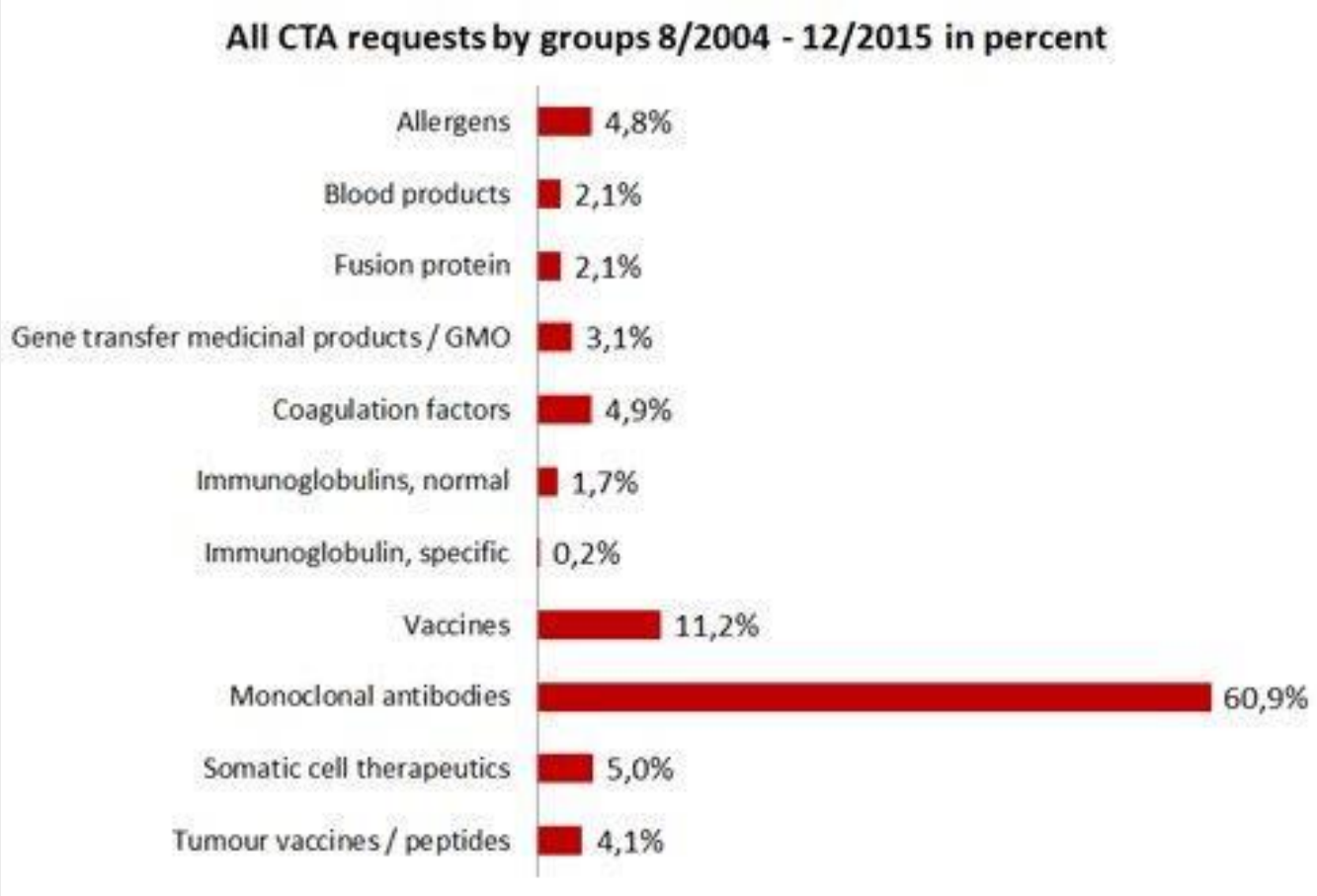


FIM Studies – PEI



8/2004 - 12/2015

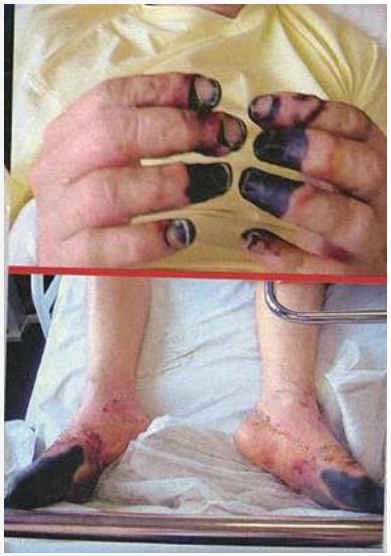
Clinical trial application (PEI)



TGN1412

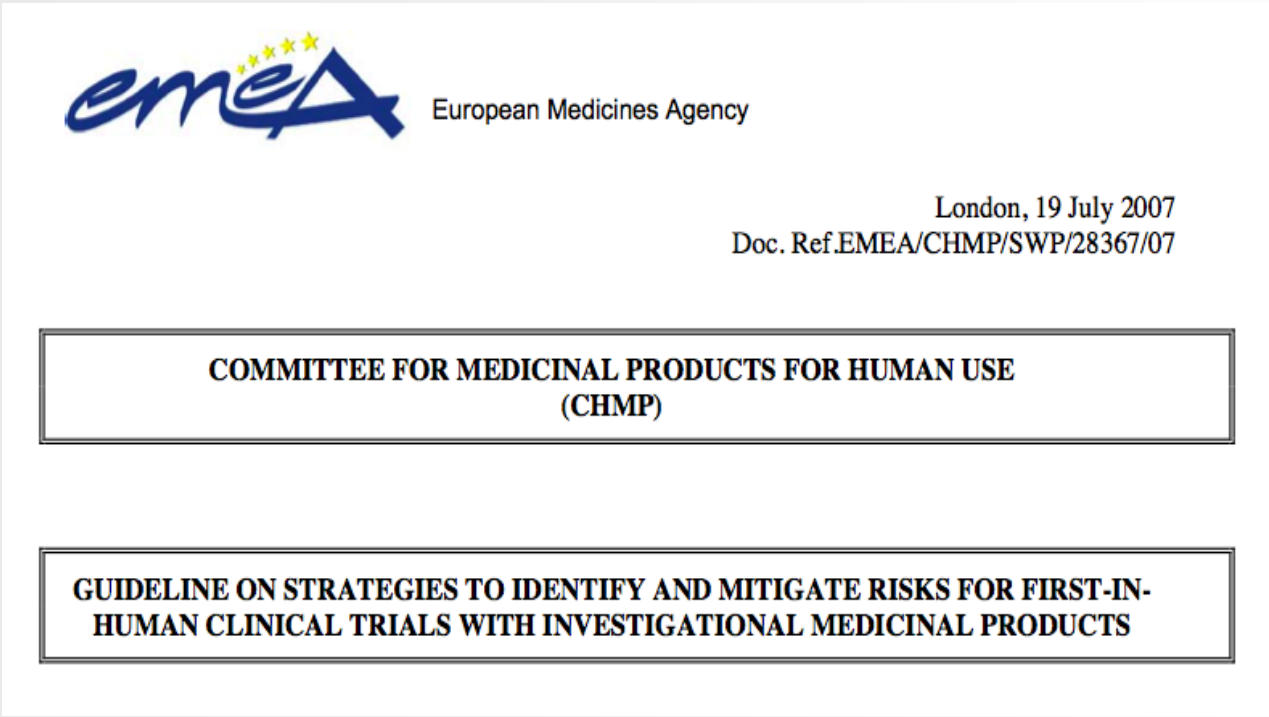
FIM trial

- Target CD28 (CD28 agonist; hypothesis: activation of Treg; expression of anti-inflammatory cytokines)
- 8 subjects (2 placebo; 6 TGN1412)
- "Sub-clinical" dose; 500 fold lower than safe dose in animals
- dosing 10 min apart
- SIRS (6 subjects); MOF (4 subjects)



"Risk mitigation guideline" - CHMP/SWP/28367/07

Scope: All new chemical and biological IMPs



European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

FIM studies
Key issues

- Identification of risk factors
- Risk communication
- Risk mitigation

Identification of risk factors

- **Mode of action**
  - **Extent of knowledge of the supposed mode of action**
  - **Nature and intensity (extent, amplification, duration, reversibility) of the effect**
  - **Dose response**
- **Nature of the target**
- **Relevance of animal model**

- **Risk communication**
  - **IB / reference safety information, protocol**
    - ✓ **Potential risks**
    - ✓ **Known risks**
  - **Patient information**

Risk mitigation

- **Study design**
  - **Study population**
  - **Trial sites (e.g. facility for resuscitation)**
  - **Dosing (starting dose, dose escalation increments)**
  - **Stopping rules and communication**
  - **Decision making process**
  - **AE management**

FIM studies
Design issues

Study population

- **Healthy subjects vs patients**
  - **Presence of the target**
  - **Higher variability in patients**
  - **Better tolerability of potential AEs in healthy subjects**
  - **Potential pharmacogenomic difference between target population and healths subjects**
  - **Predictive value of data derived from healthy subjects**

FIM studies
Design issues

Starting dose

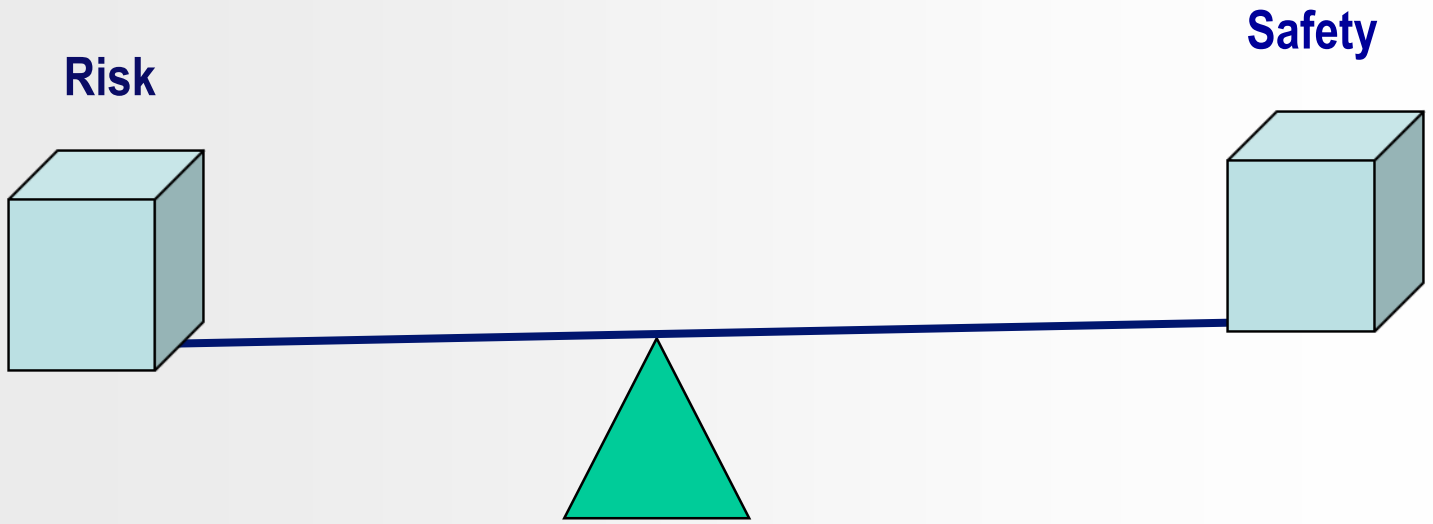
- **IMP**
  - **Strength and potency**
  - **Reliability of very small**
- **First in human dose (MABLE)**
  - **In vitro and in vivo information from PK/PD data**
- **Route of administration**
- **Staggered approach**
  - **Adequate length of observation**

FIM studies
Design issues

Adverse events

- **Guidance on early detection and management**
  - **Adeverse events of special interest**
  - **Treatment guidance (insitutional guidelines)**
- **Reporting lines**

Risk mitigation - 10 years of experience



Risk mitigation - 10 years of experience

- **Implementations of various measures to enhance the safety of the patient in clinical trials, including FIM trials came in force**
- **Administering a safe stating dose may not prevent the occurrences of unexpected adverse events.**
- **Robust measures to detect these and manage these events must be in place**

Thank you for your attention

This presentation represents my personal view and not the view of the Paul-Ehrlich-Institut or any other regulatory body