Handling of First-in-man trials: regulatory rethink?

BAPU Workshop: Microdosing - myths and reality; scientific, regulatory and financial perspectives

Positioning Human Pharmacology for the Future: Second Joint Annual Meeting Club Phase I and AGAH Bad Homburg, 26/27 April 2007

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Overview

1. The TeGenero Case
2. Regulatory handling of First-in-Man Trials after TGN1412
3. „Microdosing“: Considerations on a starting dose with reduced risk
4. Considerations on the Clinical Protocol

1. The „TeGenero“*) case (TGN1412)

Te genero (lat.): „I create you“

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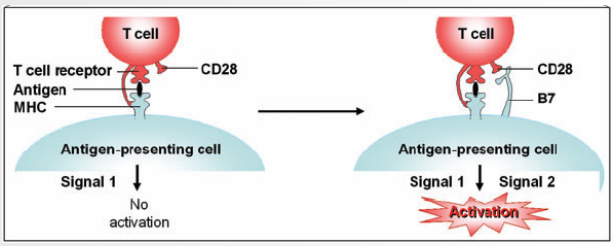
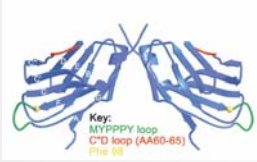
The TGN1412 case





Lühder et al. J Exp Med 2003
Evans et al. Nature Immunol 2005

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The TGN1412 case

The cynomolgus monkey as “relevant” model

- Sequence homology of CD28 (extracellular domain): 100%
- TGN1412 was well tolerated in cynomolgus monkeys at doses up to 50 mg·kg-1·week-1 for four consecutive weeks.
- No TGN1412-related signs of toxicity, hypersensitivity or systemic immune system deviation were observed.
- Moderate elevations of IL-2, IL-5 and IL-6 serum levels were observed upon TGN1412 treatment in individual animals, however, no clinical signs of a first-dose cytokine release syndrome (CRS) were observed.

=> Thus, 50 mg·kg-1 was considered to be the no-observed-adverse-effect level (NOAEL).
(N.B.: Clinical starting dose: 0.1mg/kg, corresponding to 1/160 of the human equivalent dose as calculated from NOAEL)

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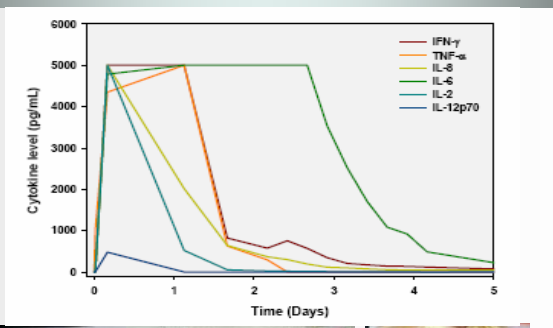
The TGN1412 case



Suntharalingam et al. NEJM 2006

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Stern no. 17, 20.04.2006

2.
Regulatory handling of First-in-Man Trials after TGN1412

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Regulatory activities after the TGN1412 incident

- **April:** **MHRA publishes interim measures for mAbs** (www.mhra.gov.uk)
- **May 2006:** **UK Expert Scientific Group on Phase One Clinical Trials (ESGPOCT) meets for the first time**
- **May 2006:** **PEI publishes potential criteria for classification of high-risk compounds** (Schneider, Kalinke, Löwer (2006): TGN1412 – A Regulator's perspective. Nature Biotechnology, 24: 493-6.)
- **July 2006:** **ESGPOCT publishes interim report** (www.dh.gov.uk)
- **July 2006:** **French AFSSAPS publishes concept paper** (www.afssaps.sante.fr)
- **November 2006:** **ESGPOCT publishes final report**
- **December 2006:** **PEI starts drafting an internal SOP**
- **December 2006:** **PEI approves first IMPD according to new requirements**
- **January 2007:** **EMEA announces** CHMP guideline on First-in-Man Clinical Trials for Potential High-Risk Medicinal Products
- **March 2007:** **EMEA publishes CHMP guideline**
- **April 2007:** **PEI implements internal SOP**

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TGN1412: Consequences

EXPERT SCIENTIFIC GROUP ON ON PHASE ONE CLINICAL TRIALS

FINAL REPORT

3O November 2006

22 Recommendations

- Pre-clinical and early clinical development (1-4)
- Regulatory review and advice (5-8)
- Determining and administering the initial doses in man (9-17)
  - Dose selection and administration (9-13)
  - Trial design and sequential inclusion of subjects (16)
  - Healthy volunteers vs. patients (17)
- Clinical environment for FIM studies (18-20)
- Developing expertise (21-22)

(www.dh.gov.uk)

TGN1412 - Consequences

EMEA consulting on draft guideline on 'first-in-man' clinical trials

Published 26/03/2007

The European Medicines Agency has today published a draft guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products. The guideline aims to provide a common approach across EU Member States to the design and conduct of such trials, and is released for public consultation until 23 May 2007.

Read more in the press release **here**
Access the draft guideline **here**

European Medicines Agency

London, 22 March 2007
Doc. Ref.EMEA/CHMP/SWP/28367/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007

(www.emea.europa.eu)

TGN1412: Consequences

- **CHMP guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products:**

1. Introduction

"Attention should be given to the calculation of the initial dose to be used in humans and to the subsequent dose escalations, intervals between doses to different individuals and the management of risk."

3.
„Microdosing":
Considerations on a starting dose with reduced risk

„Microdosing“

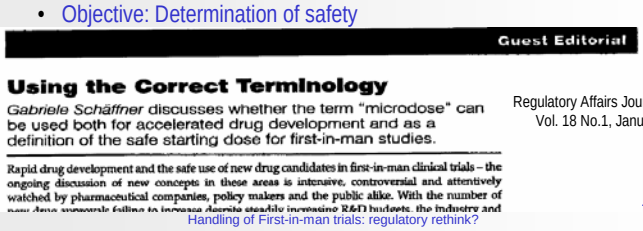
Pieter Bruegel der Ältere (1525-1530-1569)
The Tower of Babel, 1563

Starting dose for a first-in-man trial

- **Microdose**
  CPMP Position paper on non-clinical safety studies to support clinical trials with a single microdose. CPMP/SWP/2599/02
  - Definition: *„less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained in vitro and in vivo (…)“*
- **Maximum Recommended Starting Dose**
  FDA Draft Guidance for Industry and Reviewers: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers
  - Definition: *„The MRSD should be obtained by dividing the HED by a safety factor“*
- **Minimum Anticipated Biological Effect Level**
  CHMP guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products. EMEA/CHMP/SWP/28367/2007
  - Definition: *“The MABEL is the anticipated dose level leading to a minimal biological effect level in humans.”*

„Microdose“: Terminology that matters

- **Terminology:**
  - **„Microdose“:**
    - Used for accelerated drug development for new drug candidates
    - Based on reduced non-clinical development
    - Objective: Determination of pharmacokinetics, not safety
  - **„MABEL“:**
    - Used for development of potential high-risk medicinal product
    - Used for determination a starting dose with reduced risk
    - Based on extended/suitable non-clinical development
    - Objective: Determination of safety



Guest Editorial

Using the Correct Terminology

Gabriele Schäffner discusses whether the term "microdose" can be used both for accelerated drug development and as a definition of the safe starting dose for first-in-man studies.

Rapid drug development and the safe use of new drug candidates in first-in-man clinical trials – the ongoing discussion of new concepts in these areas is intensive, controversial and attentively watched by pharmaceutical companies, policy makers and the public alike. With the number of

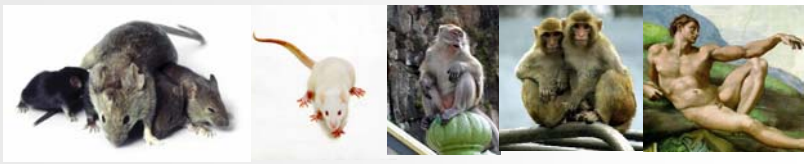
Regulatory Affairs Journal Pharma, Vol. 18 No.1, January 2007

First-in-man trials with potential high-risk medicinal products:

Basis for dose calculation:
The relevant animal model

Demonstration of relevance

Central aspect: biotechnological products are species-specific.



A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

*NfG on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6)

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„A question of relevance.“

Demonstration of relevance of an animal model:

- **Sequence homology of epitope / receptor**
  z. B. CD28 human – cynomolgus monkey (Macaca fascicularis)
- **Binding (ELISA, BioCoRE: Affinity constant, cell culture, immunohistochemistry)**
  affinity higher / equal / lower?
- **Agonistic / antagonistic downstream effects: Binding alone is not sufficient!**
  e.g., cytokine release and T cell activation by anti-CD28 antibodies
- **Data on functionality of corresponding functional systems, e.g. the FcR system**
  see TGN1412!

Alternatives in case of lack of animal model (e.g., EpCAM, CD3, bispecific mAbs):

- **Human cell lines, ex-vivo data**
- **transgenic animals**
  (e.g., hEpCAM transgenic mouse)
- **surrogate antibody**
  (e.g., murine anti-murine CD3 mAb)

Data from a non-relevant species are not required!

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The „classical“ approach

„Classical“ approach for determination of the „Maximum Recommended Starting Dose (MRSD)“:*)

- Determine **NOEL** (No Effect Level) / **NOAEL** (No Adverse Effect Level) in a relevant (!) species
- Conversion to Human Equivalent Dose (**HED**)
  (Correct with Body Surface Area Conversion Factor = **BSA-CF**)
- Apply **Safety Factor** (Usually 10)

Guidance for Industry and Reviewers

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

DRAFT GUIDANCE

www.fda.gov/CbER/gdlns/dose.pdf

Dose calculation of the starting dose

Table 1: Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area

Species	To convert animal dose in mg/kg to dose in mg/m², multiply by km below:	To convert animal dose in mg/kg to HED[a] in mg/kg, either:	
		Divide animal dose by:	Multiply Animal dose by:
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the formula:
HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This km is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, stumptail.

Dose calculation of the starting dose

=> This approach might not be sufficient for („high-risk“) biotechnological products!

Novel approach (as suggested by ESGPOCT and taken up in the CHMP guideline): Broader approach

- Consider novelty / mechanism of action / species specificity
- Consider dose-response curve of biological effects (both in animal and human cells)
- Consider calculation of receptor occupancy vs. concentration
- Consider calculated exposure of target / target cells in vivo

=> **„MABEL approach“, based on any biological effect („Minimal Anticipated Biological Effect Level“)**

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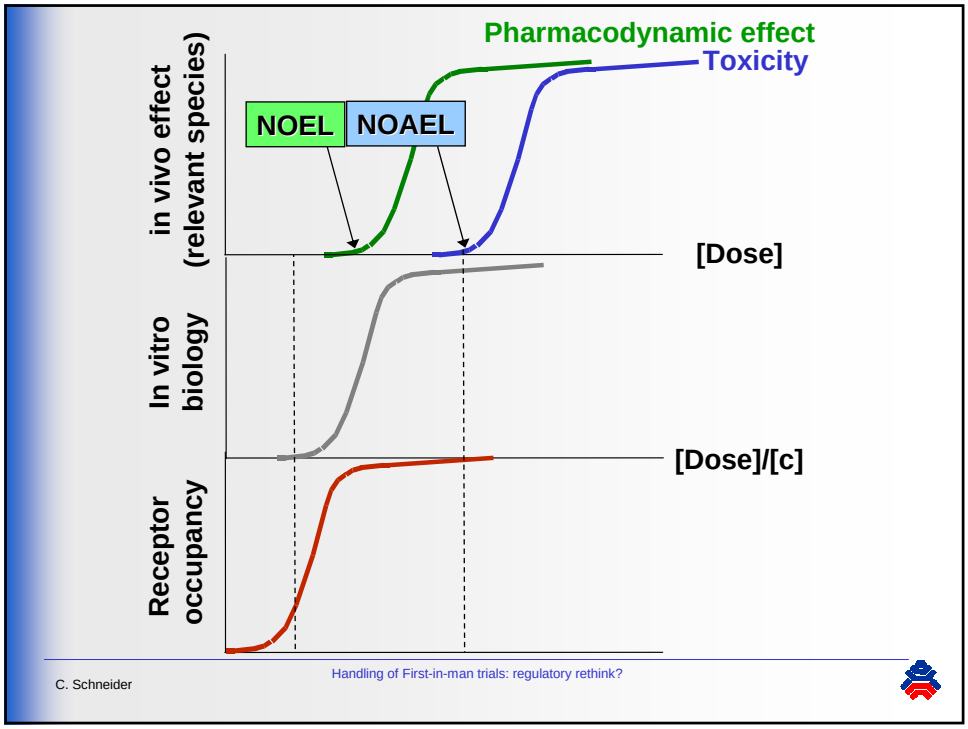

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Starting dose: EXAMPLE

- **Example: Monoclonal antibody**
  - **Testing of the following doses in cynomolgus monkey as the relevant species:**

0.1 mg/kg
0.3 mg/kg — **NOEL**
0.5 mg/kg First pharmacological effect
1.0 mg/kg
2.5 mg/kg
4.0 mg/kg
5.0 mg/kg — **NOAEL**
7.0 mg/kg ~~Toxicity observed~~ — **LOAEL**
10.0 mg/kg Toxicity observed

  - **In vitro: maximal binding to target ~40% at 0.2µg/ml**
  - **20% saturation at 0.01µg/ml**

Starting dose: EXAMPLE

- **Calculation based on NOAEL (Human Equivalent Dose):**

$$\text{Starting Dose} = \frac{\text{HED}}{\text{Safety factor}} =$$

$$= \frac{\text{NOAEL}}{\text{Safety factor} \bullet \text{Body surface area conv. factor}}$$

$$= \frac{5.0\ \text{mg/kg}}{10 \bullet 3.1} = 0.16\ \text{mg/kg} = 160\ \mu\text{g/kg}$$

Starting dose: EXAMPLE

- **Calculation as „Microdose“**
  (although terminology is not applicable!)

  Definition: 1/100 of the dose that elicits a pharmacodynamic effect

  $$\text{Starting Dose} = \frac{0.5\ \text{mg/kg}}{100} = 5\ \mu\text{g/kg}$$

Starting dose: EXAMPLE

- **Calculation by MABEL approach**

  based on any effect and/or receptor occupancy and other considerations, if applicable.

  20% receptor saturation at 0.01ug/kg (in plasma)

  Starting Dose = (in-vitro concentration) • (Plasma volume) =
  = 0.01ug/kg • 50ml/kg = 0.5µg/kg

- **RESULTS:**
  - HED based on NOAEL: 160 µg/kg
  - Microdose: 5 µg/kg
  - MABEL: 0.5 µg/kg
- **Choose lowest dose of all approaches**
  [MABEL not necessarily the lowest, e.g. prodrugs]

4.
Considerations on the Clinical Protocol

Clinical study protocol requirements

- **Careful selection of the target population**
  (healthy volunteers vs. volunteer patients)
  - Studies in healthy volunteers are still possible
  - Justification
  - Consider relevance of data
  - Consider potential long-term consequences
- **Justify calculation of starting dose**
- **Sequential inclusion of subjects…**
  - Safety interval to be selected on PK and PD (<= non-clinical!)
  - Appropriate clinical environment
  - Long-term final observation visit (after completion of core study)
    (not necessarily a pre-requisite to proceed to next phase!)
  - Placebo non-blinded / single-blinded
  - Patient alert card

Regulatory challenge: Scientific Progress vs. Patient Safety and Regulatory Control

Murphy's laws

„If anything can go wrong, it will."

„If you perceive that there are four possible ways in which something can go wrong, and circumvent these, then a fifth way, unprepared for, will promptly develop."

„Left to themselves, things tend to go from bad to worse."

- **Clinical trials with mAbs require enhanced safety measures:**
  - => **Sequential inclusion** of subjects
    - „24 hour" approach not commonly possible
    - Interval between subjects needs to take into account:
      - **Pharmacokinetic properties** (bioavailability, half-life)
      - **Pharmacodynamic properties** (half-life of the biologic effect; sequential downstream effects)

Regulatory challenge: Scientific Progress vs. Patient Safety and Regulatory Control

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- **Clinical trials with mAbs require enhanced safety measures:**
  - Theoretical considerations based on the mechanism of action: Safety measures need to be implemented proactively *(„you will only see what you are especially searching for")*
  - Consider unknown mechanisms *(consider every safety signal as a potential drug-related effect)*
  - Consider other factors
    - Impurities, quality defects, stability defects, inappropriate handling
    - cross-reactivity

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Current regulatory thinking: THE NEXT STEPS

- **European harmonisation**
- **Enhanced interaction between:**
  Regulators – industry – academia
- **Challenge: Regulatory control versus innovation**
  - Higher requirements for high-risk products (?)
  - Sequential inclusion prolongs trial
- **Thorough evaluation of risk**
  - **not every product is a high-risk product!**
  - **not every product requires the MABEL approach!**

Murphy's Law of Thermodynamics:
Things get worse under pressure.