Current regulatory developments relevant to human pharmacology in the EU:

The CHMP Guideline on the Requirements for First-in-Man Trials for Potential High-Risk Medicinal Products

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

Dr. Christian Schneider
Division EU Cooperation/Microbiology
Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Germany
http://www.pei.de

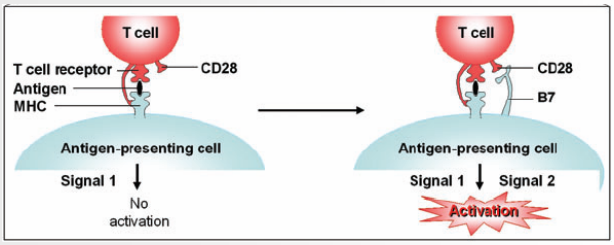
Overview

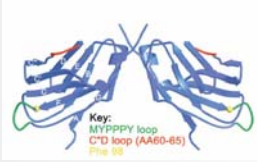
1. The TeGenero Case
2. TGN1412: Regulatory history
3. European activities: The new CHMP guideline

1. The „TeGenero“*) case (TGN1412)

Te genero (lat.): „I create you“

The TGN1412 case





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

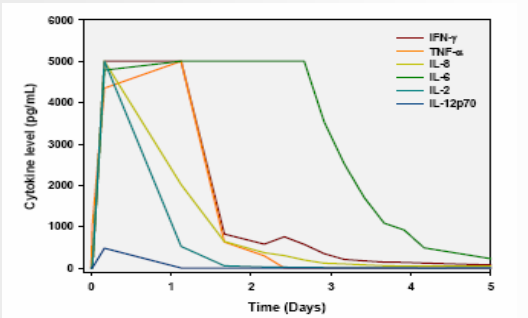
The TGN1412 case

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)

The TGN1412 case



Suntharalingam et al. NEJM 2006

Lessions from the TGN1412 case

What are the lessions to be learnt?

- **Predictivity of animal data not 100% (estimates: 70-80%)**
- **Nevertheless non-clinical data of highest importance**
- **Not all MAbs are that dangerous, still major „drugs of hope“**

=> Definition of „high-risk“ mAbs for which enhanced precautions need to be employed:

- **extended pre-clinical development before human testing**
- **sequential inclusion of subjects into phase I first-in-man trial**

„High-risk“ monoclonal antibodies

Criterion 1:

The mAb employs a new mechanism of action

1. mAbs interfering with „master switches“ of the immune system
2. Inducers / modulators of pleiotropic cytokines (IFNγ, IFNα, IL-10)

Criterion 2:

The mAb addresses a target that lacks appropriate animal models

1. (sub-)epitopes that are only present in humans
2. No surrogate model exists
3. Interference with signaling pathways with human-specific properties

Criterion 3:

The mAb comprises a new type of engineered structural format

1. Engineered Fc parts
2. Divalent (bispecific) antibodies etc.

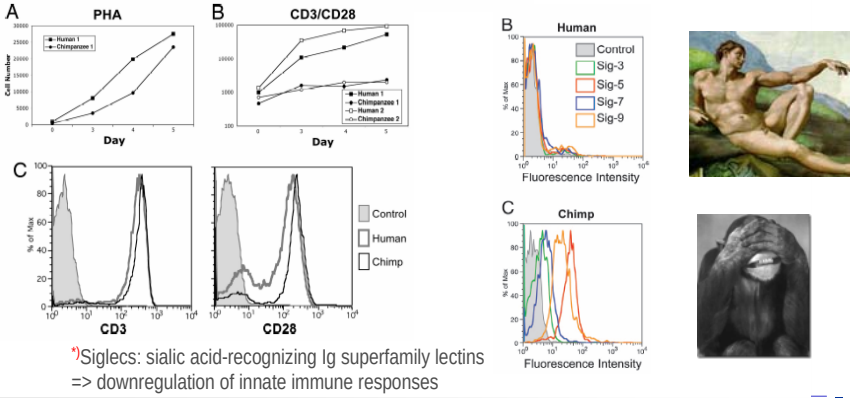
Schneider CK, Kalinke U, Löwer J, Nature Biotechnology 2006 May;24(5):493-6

The evolution of the immune system

Loss of Siglec*) expression on T lymphocytes during human evolution

Dzung H. Nguyen*†, Nancy Hurtado-Ziola*†‡, Pascal Gagneux*, and Ajit Varki*§

PNAS | May 16, 2006 | vol. 103 | no. 20 | 7765–7770



*)Siglecs: sialic acid-recognizing Ig superfamily lectins
=> downregulation of innate immune responses

2.
TGN1412: Regulatory history

TGN1412 – „Regulatory timetable“

Date	Action	Dead Lines
13.06.05	1. Scientific advice meeting at the PEI	
08.07.05	2. Scientific advice meeting at the PEI	
24.08.05	Approval by the Berlin Ethics Committee	
20.09.05	Arrival of the CTA at the PEI	
28.09.05	Letter of receipt of the CTA sent to Applicant	10 days
20.09.05 -17.11.05	Assessment of the CTA	60 days
17.11.05	Letter to applicant with grounds for non-acceptance (9 issues in the preclinical dossier and 5 issues in the clinical dossier)	
17.11. 05-18.01.06	Time for the applicant to react on issues raised by PEI	90 days
18.01.06	Receipt of answers to the letter on grounds for non-acceptance	
18.1.06 – 17.2.06	Assessment of the response by PEI	30 days
in between	Discussion by phone on remaining open issues	
03.02.06	Commitment by the sponsor to amend the study protocol and the Patients Informed Consent Information on safety issues not resolved yet, that were to be solved before the start of the CT	
10.02.06	Submission of amended Protocol and Patients Informed Consent Information	
17.02.06	Approval of CTA	

TGN1412: „Regulatory timetable“

Germany, PEI		United Kingdom, MHRA	
		27.01.2006	Approval of CTA
17.02.2006	Approval of CTA	14.02.2006	Approval by the Brent Medical Ethics Comm.
		13.03.2006	Start of clinical trial
16.03.2006	Clinical trial put on halt	14.03.2006	Clinical trial put on halt

PEI: Paul-Ehrlich-Institut

MHRA: Medicines and Healthcare Regulatory Agency

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:** **PEI implements internal SOP**

3. European activities: The new CHMP guideline

European activities on high-risk products

- **EMEA website (www.emea.europa.eu), 26.3.2007:**

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

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