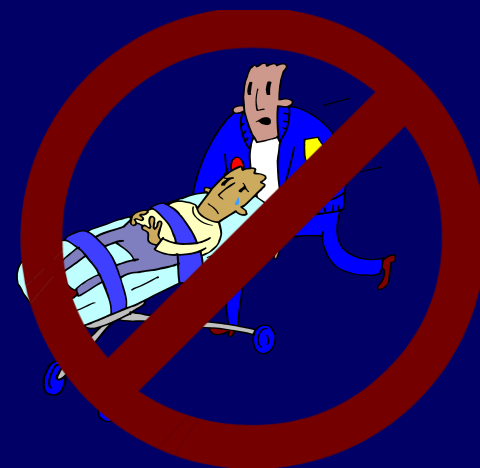


Regulatory Authority's Experience with Diverse APIs and Preclinical Safety Assessment Supporting FTIH



**Science-based preclinical safety assessment:
Decision-making to enhance regulatory success**

David Jacobson-Kram, Ph.D. DABT
ToxRox Consulting
McLean, VA

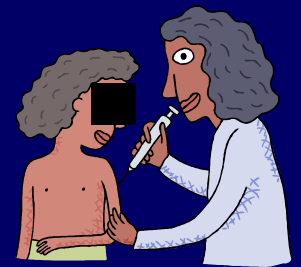


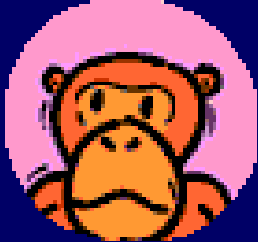
Food and Drug Administration



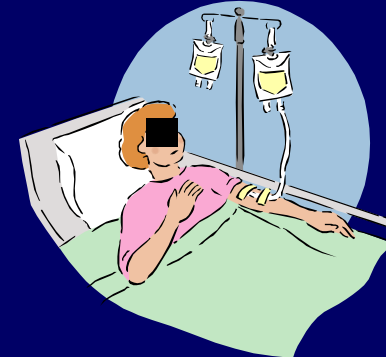
CDER guidance on “start dose”

- Selection of maximum safe starting dose for first-in-human trial (cf. Guidance for Industry: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers July 2005)
- Relevant for small molecule or biologic therapeutics
- Not intended to address dose-escalation or maximum clinical doses, or dosing in patient populations.
- Toxicity is to be avoided at the initial dose.
- Approaches other than that described may be used (e.g., PK/modeling); however, approach selected needs to be justified.





FIM Dose Calculation



- **Identification of NOAEL; often one species for biologics**
- **Conversion of NOAELs to Human Equivalent Doses (using body surface area conversion factor)**
 - ◆ BSA-CF: converts mg/kg dose in animals to mg/m² dose, then to mg/kg dose in human
- **Selection of more sensitive species (i.e., lower HED when more than one species NOAEL available)**



Safety Factor

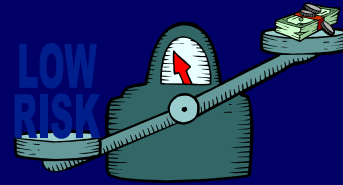
➤ Application of safety factor

- ◆ default is 10, but may not be adequate in all cases
- ◆ Increase

- Steep dose-response curve
- Severe toxicity at doses above NOAEL
- Non-monitorable toxicities
- Toxicities with no premonitory signs
- Irreversible toxicity
- Unexplained death
- Widely variable bioavailability in animals
- Non-linear PK
- Wide variability between species in doses or exposures eliciting toxicities
- Less than optimal nonclinical study design/conduct
- **Novel therapeutic targets**
- **Animal models with limited utility**



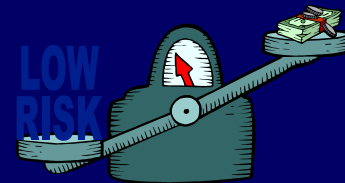
Safety Factor, continued



- ◆ Default of 10, may be decreased if:
 - Drug is a member of a well-characterized class, is being given according to an established clinical dosing regimen, and has similar PK/ADME and toxicity profiles across species, including human.
 - Toxicities are easily predicted, monitored, and are reversible.
 - Dose-response for toxicity is not steep.
 - The NOAEL upon which the HED is based was determined in longer-term nonclinical studies; this assumes that toxicities are cumulative and were not observed early in the longer-term studies.



Changes in start dose



- It is always acceptable (from a safety perspective) to use a clinical start dose lower than the MRSD.
- Use of pharmacologically active dose (PAD)
 - ◆ May use if lower than MRSD
 - ◆ May be used to justify lowering the MRSD, e.g., in cases in which toxicity is due to exaggerated pharmacologic effects.



Start Dose for Oncology Drugs

- A common approach for many small molecules to set a start dose at
- $1/10$ the severely toxic dose in 10% of the animals (STD 10) in rodents.
- If the nonrodent is the most appropriate species, then $1/6$ the highest non-severely toxic dose (HNSTD) is considered an appropriate starting dose.
- The HNSTD is defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings.



History of Safety

- Phase 1 clinical trials, especially in healthy subjects have a long history of safety.
- With the exception of a few instances, the paradigms we currently use for selecting safe starting and stopping doses have served us well.
- One glaring failure: TGN1412.





Balancing your Immune System

TeGenero is a biopharmaceutical company dedicated to the identification and development of innovative, highly effective and broadly applicable immunotherapeutics.

We strive to provide patients the means to regain a functional and balanced immune system.

Drug trial creates 'Elephant Man'

Thursday, March 18, 2006 Posted: 09:51 GMT (17:51 HKT)

LONDON, England -- Two men are in critical condition in a London hospital and four others are in serious condition after taking part in a clinical trial for a new drug.

One victim, whose head and neck were reported to have increased to three times normal size, was described by a friend as resembling "the Elephant Man."

The men were admitted late Monday to the intensive care unit from an independent medical research unit at Northwick Park Hospital after reacting badly to the drug, which is intended to treat chronic inflammatory conditions and leukemia.

The volunteers suffered extreme reactions while participating in a drug trial run by clinical research company Parexel International, based in Boston, Massachusetts.



Mylanwy Marshall, the girlfriend of a man who took part in a drug trial, outside Northwick Park hospital.



Events in clinical trial

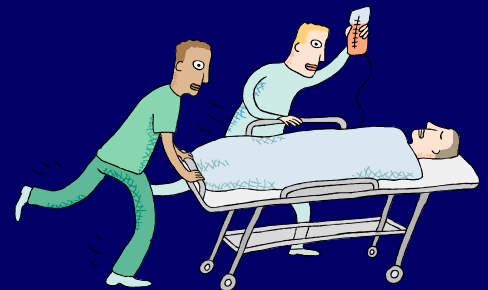


- **TeGenero contracts with Parexcel for a first entry into man study of monoclonal antibody, TGN1412.**
- **Application received by MHRA on December 23, 2005, trial authorized on January 27th, IRB approved February 14th, trial begun on March 13th.**
- **Four single doses of 0.1, 0.5, 2.0 and 5.0 mg/kg were planned to be administered to 4 groups of 8 subjects.**
- **Six subjects given 0.1 mg/kg IV in the course of one hour. Two subjects given placebo.**



Events in clinical trial

- Headache and nausea onset within one hour of dosing and subjects (now patients) admitted to intensive care 10 hours after dosing.
- Subjects suffered multisystem failure and required pulmonary and renal support.
- All subjects recovered but may experience sequelae.



CD28 Monoclonal Trial in UK

- No evidence of contamination of the product.
- Conduct of the trial appeared to have followed the protocol, e.g., no dosing errors.
- Nothing in the preclinical data predicted the overwhelming systemic reaction to the antibody. Findings of lymph node enlargement in the monkeys, but the monkeys did not demonstrate the toxicological response seen in humans.
- Dose in humans was 1/160 of the NOAEL in monkeys, so it was well within accepted safety margins.
- Adverse reaction considered to be a "cytokine" storm that was triggered by the antibody and not predicted by the animal testing.



Preclinical toxicology studies

- **Pivotal study was 28 day repeated dose study in cynomolgus monkeys (n=26). Four weekly doses given by infusion. Two male and two females sacrificed on day 28 and remaining animals used in recovery/observation period of 6 weeks.**

No mortality

No clinical signs

No effect on body weight or food consumption

No ECG changes

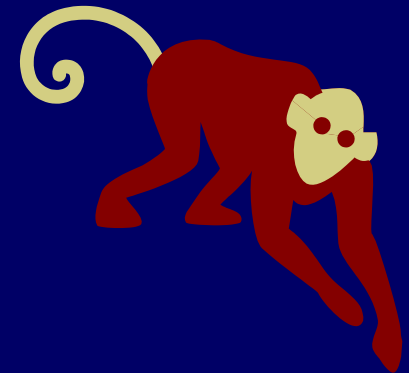
Clinical chemistries and hematology normal

No findings at necropsy

No significant histological findings

4 out of 16 animals had titres of anti-TGN1412

Mean half-life of approximately 8 days was calculated



Could this toxicity have been predicted?

- Hindsight is always 20/20.
- Limited amount of time in which to make safety decisions.
- There were some clues.



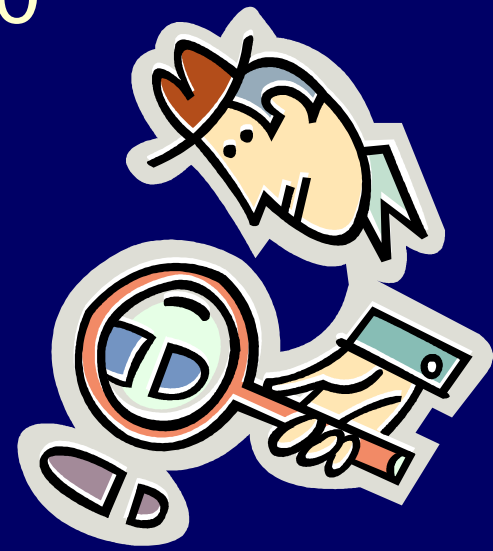


- Initial dose 0.1 mg/kg would achieve plasma level of ~16nM compared with binding affinity of 2nM. 8X the binding affinity of “super agonist” might result in 90% CD28 receptor binding on first dose.
- This occupancy ok for antagonist but too high for FIH with agonist. If starting dose was established using pharmacological principles, might have started 100X lower.



Other clues

- OKT3, murine monoclonal antibody used to suppress rejection of organ transplants.
- Adverse reactions include “cytokine release syndrome.”
- Clinical dose is approximately 70 micrograms/kg.



Cytokine Changes

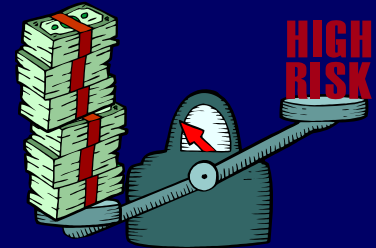
Table 68: Mean peak serum concentrations in each dosing group after administration of TGN1412 in cynomolgus monkeys

Cytokine	Mean peak cytokine level (range) pg/ml		
	Control group (0 mg/kg)	Low dose group (5 mg/kg)	High dose group (50 mg/kg)
IL-2	37 (20-60)	25 (0-84)	100 (25-211)
IL-4	12 (0-18)	13 (8-18)	17 (0-40)
IL-5	6 (3-7)	49 (6-139)	107 (11-458)
IL-6	7 (0-22)	68 (32-101)	128 (24-390)
TFN-alpha	20 (11-26)	20 (15-27)	22 (19-26)
IFN-gamma	18 (0-35)	23 (19-32)	33 (17-93)



Reaction to Tegenero Incident

- EMEA Draft Guideline, March 2007:
Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products.
- High Risk: concerns of serious adverse reactions in first-in-man trial
 - ◆ Mode of action
 - ◆ Nature of target
 - ◆ Relevance of animal models



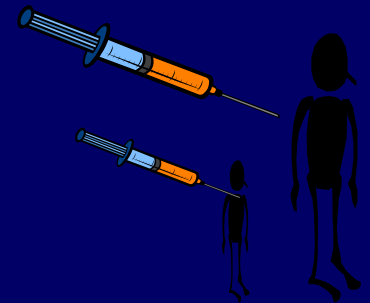
Mode of Action

- Nature and intensity (extent, amplification, duration, reversibility) of the effect of the drug on the target
- Shape of dose-response curve
- e.g. mechanism that bypasses physiological control mechanisms, CD3 or CD28 (supra-) agonists.



MABEL Approach

- “Minimal Anticipated Biological Effect (MABEL).
- The anticipated dose level leading to a minimal biological effect in *humans*.
 - ◆ Receptor binding and receptor occupancy studies in vitro in target cells from human and the relevant animal(s) species and in vivo in the relevant animal species.
 - ◆ Concentration-response curves in vitro in target cells from human and the relevant animal(s) species and dose response in vivo in the relevant animal species.
 - ◆ Exposure at pharmacological doses in the relevant species.



EMA Draft Guidance

- On its face, this guidance does not appear to significantly change our current practices.
- Even without this guidance, any sponsor proposing to test an immune system agonist and any regulatory reviewer is going to exercise extreme caution.

