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日本からアジア、そして世界へ

学校法人 北里研究所
THE KITASATO INSTITUTE

韓日,아시아 임상연구 선도위한 협력체계 구축

日本北里大学及其医学部代表团访问药物临床试验机构

신약연구·개발자를 위한

비임상시험 국제 워크숍

12Nov2012

초기임상시험 용량설정을 위한 비임상 고려사항

쿠마가이 유지

키타사트 대학교 임상시험 사업 본부 본부장

Guidance for Establishing Safety in First-in-Human Studies during Drug Development

Issued on 2 Apr 2012 by MHLW

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- Most parts are similar to EMEA's FIH Guideline.
- Emphasis on prediction of risk factors and quality control.
- Aimed on promoting FIH in Japan, not regulating.

Phase I Trial

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(Most typical kind of study: Human Pharmacology)

a) Estimation of Initial Safety and Tolerability

b) Pharmacokinetics

c) Assessment of Pharmacodynamics

d) Early Measurement of Drug Activity

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Safety of Phase I study

Monro & Metha

3 reviews of Phase I studies （n =93.399, 29.162, 27.424)
Adverse reaction 1-3 %
Transient functional dysfuntion 109 （0.073%）

Kumagai et al, 2006

JACIC's survey in 97,987 healthy volunteers
Serious adverse events 49 cases
(Side effects 23 cases)
Shock, allergic reaction, cramp, liver dysfunction etc.

Tragedy of TGN1412 case

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BBC NEWS

News Front Page

Last Updated: Wednesday, 15 March 2006, 09:52 GMT

Six taken ill after drug trials

TGN 1412 is an anti CD28 monoclonal antibody specific to human with super agonistic action.

Afr
Americas
Asia-Pacific
Europe
Middle E
South A

during a clinical drugs trial in north-west London.

In the FIH trial, all of 6 healthy volunteer suffered from cytokine storm, 2 of them were critically ill with multiple organ failure.

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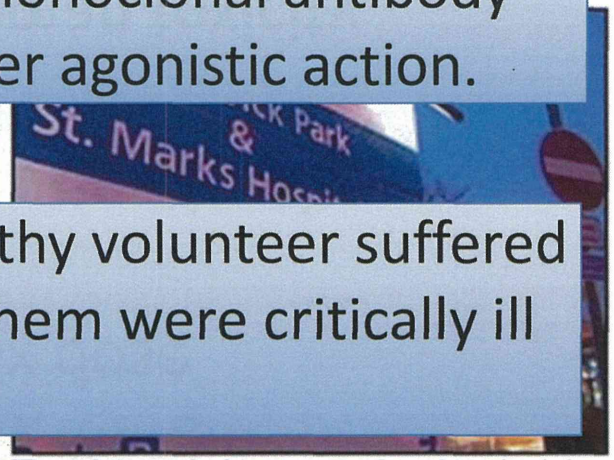
when they suffered a reaction.



The six are being treated at Northwick Park hospital

It was considered that non-clinical data did not show any toxicity to be worried.

An investigation has begun at the unit, run by Parexel, which said it followed recommended guidelines in its trial.

Was it just an illusion that phase I studies are safe?

Scien
Technology
Entertainment

trial for the drug to treat conditions such as rheumatoid arthritis and leukaemia until they were taken ill on Monday within hours of taking it.

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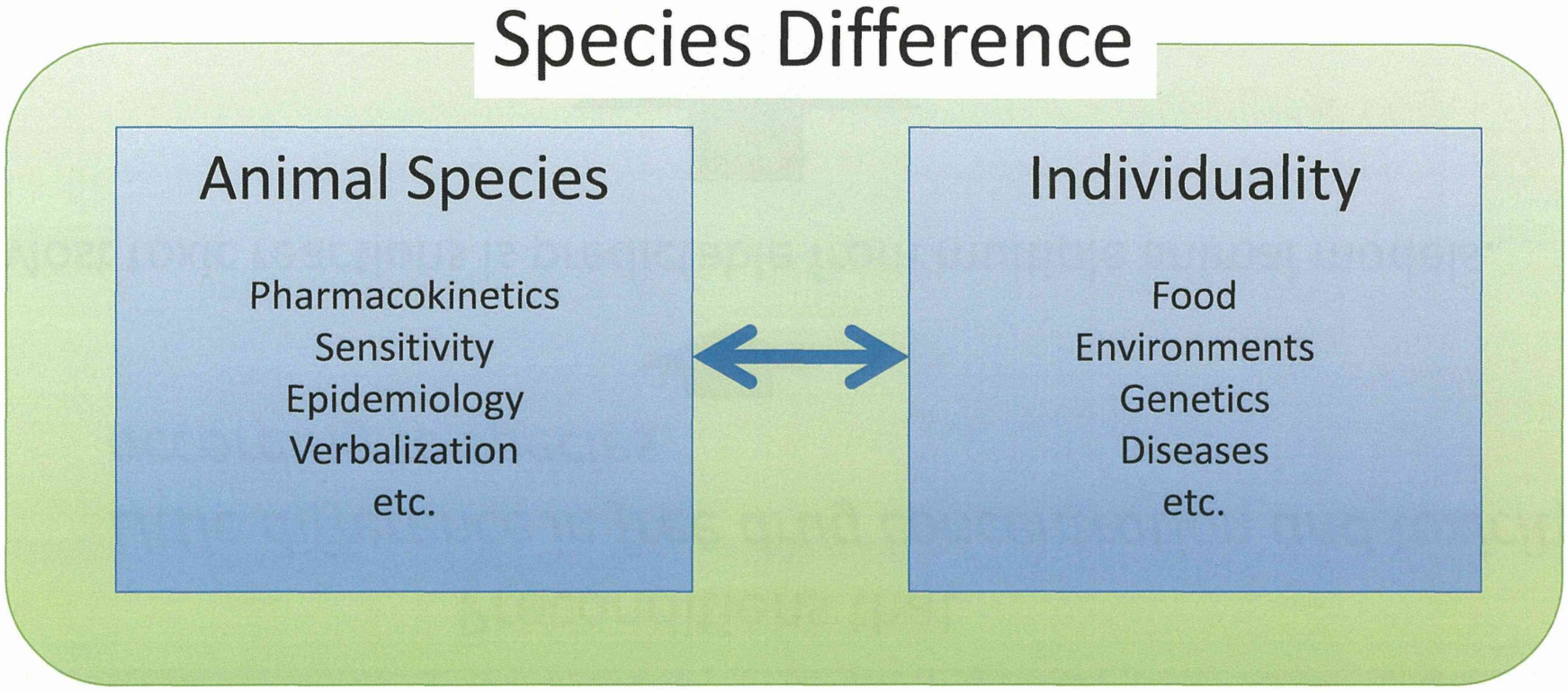
To Secure Subject's Safety

- Careful checks of non-clinical data
- Choose appropriate safety margin in setting starting and max dose
- Selection of subjects (HV or patient)
- Detect early signals of human toxicity
- Expert investigators and clinic environment

Factors in Extrapolating Animal Data To Human



Prediction will be limited in itself.

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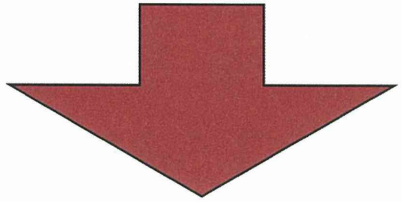
In Planning a Phase I study

Preconditions that

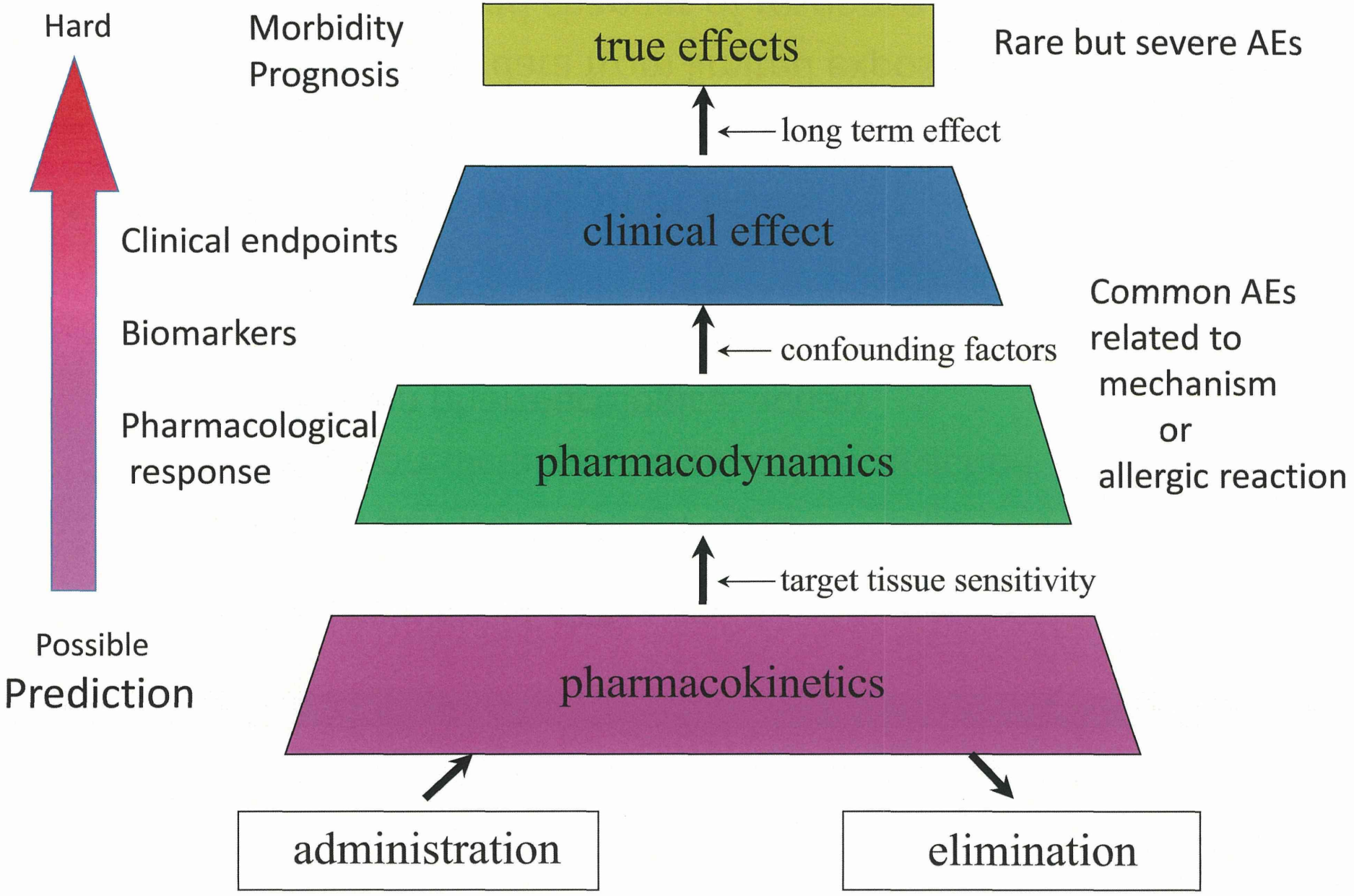
Little difference in free drug concentration and toxicity according to species

Most toxic reactions is predictable from multiple animal models.



Prepare as many observations and means as possible to minimize possible risks.

Pyramid of Efficacy and Adverse Effects



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Prediction of Adverse Reactions in CT

- In early stages of CTs
  - Mainly from nonclinical data
    - Known predictable pharmacological action
    - Unknown pharmacological action
    - Human specific responses
- In later stages and practices
  - Nonclinical and limited clinical data
    - Utilization of data from limited exposure
    - Disease-related changes of response

Recommended non-clinical studies before first-in-human trial

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1） **Safety pharmacology**
2） **Toxicokinetics and pharmacokinetics**
3） Single dose toxicology (2 species)*
4） **Repeated dose toxicology** (>2 weeks)
5） **Genotoxixity**
6） Carcinogenisity*
7） Reproducive toxicology*

* not needed in initiating human studies.

NOAEL is obtained by a repeated toxicity test most frequently in NCEs, and it is not a case for biologics.

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Findings obtained in nonclinical studies

Safety Pharmacology

- Screening for events in clinical settings

Toxicology studies

- Screening for toxic events in high exposures
- Toxicokinetic data are generally more precise than PK studies.

Duration of action, dose-response relationship, recovery

Species difference in clioquinol induced myelo-optico-neuropathy

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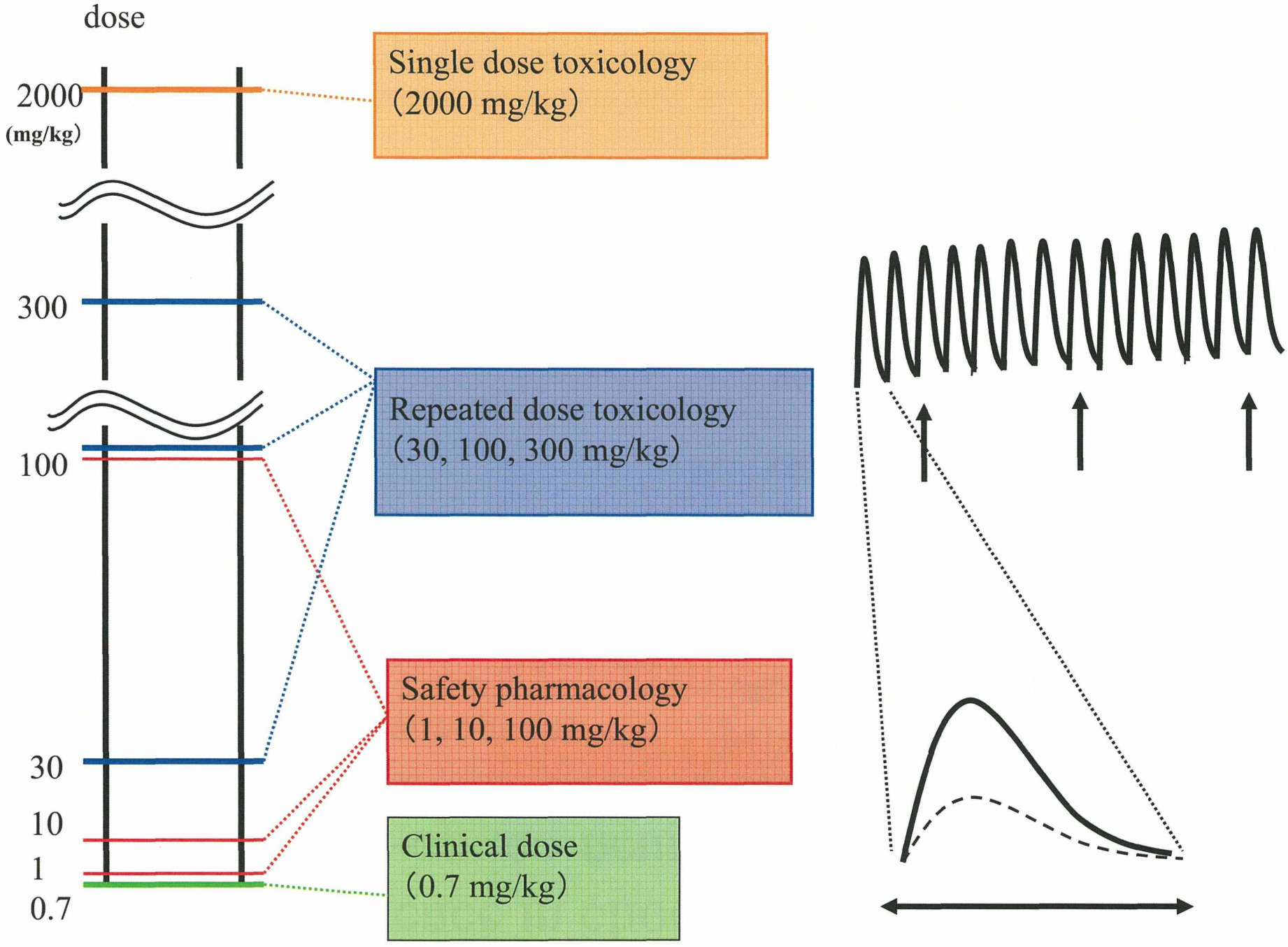
	Neuropathy		Daily dose (mg/kg/day)	Total dosage (g/kg) (mean)
	Ataxia	Visual dysf.		
Monkey	+		200 – 700	
Dog	+	+	60 - 144	1.7 – 16.6 (4.1)
Beagle	+	+	350 – 450	7.4 – 17.9 (17.0)
Cat	+	+	90 – 250	1.5 – 10.5 (5.7)
Rabbit	+		125 – 150	1.5 – 4.5
Rat			1000 *	
Mouse			150 *	
Guinea pig			240 *	
Hamster			500 *	
Chicken	+		500	10 – 20
Cotumix	+		600 - 3000	9 - 24


dose
2000
(mg/kg)
300
100
30
10
1
0.7
Single dose toxicology
(2000 mg/kg)
Repeated dose toxicology
(30, 100, 300 mg/kg)
Safety pharmacology
(1, 10, 100 mg/kg)
Clinical dose
(0.7 mg/kg)

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Change Paradigms

- Our experience and prediction has been based on the findings in toxicity studies, and it seemed successful.

- Toxicities are "off target action" of the expected drug action.

- TGN case was owing to excessive pharmacological action, and we should turn to another side.

- ON TARGET approach to select a starting dose is being interested.

MHRA ESG recommendation

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MABEL (Minimum anticipated biological effect level)

A broader approach to dose calculation, beyond reliance on 'No Observable Effect Level' or 'No Observable Adverse Effect Level' in animal studies, should be taken. The calculation of starting dose should utilise all relevant information. Factors to be taken into account include the **novelty** of the agent, its **biological potency** and its **mechanism of action**, the degree of **species-specificity** of the agent, the **dose-response curves** of biological effects in human and animal cells, dose-response data from *in vivo* animal studies, pharmacokinetic and pharmacodynamic modelling, the calculation of the **target occupancy** versus concentration and the calculated exposure of targets or target cells in humans *in vivo*.

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Calculating MABEL

By PK/PD data obtained from in vitro or in vivo studies.

- Target binding and receptor occupancy studies in vitro in cells from human and relevant animal species
- Concentration – response data in vitro in target cells from human and relevant animal species
- Dose/exposure – response in vivo in relevant animal species
- Exposures at pharmacological doses in relevant animal species

The lowest level should be selected considering reliability of models and species.

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Check points in designing a human study

- consideration from tox findings-

Are there any non-invasive measures to detect the toxicological events in human?

Can the measure decrease risk of subjects?
That is if we can get rid of toxicity before it turns to irreversible.

We should make every effort to avoid subjects' permanent dysfunction.

Use of safety biomarkers is encouraged.

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Detection of Adverse Reaction in CT

Choose available markers from profiles such as pharmacological action, toxicological findings, drug distribution to organs and so on.

Checking symptoms

Vital signs

Laboratory and physiology

- CBC, chemistry, urinalysis
- ECG, EEG,....
- Imaging....