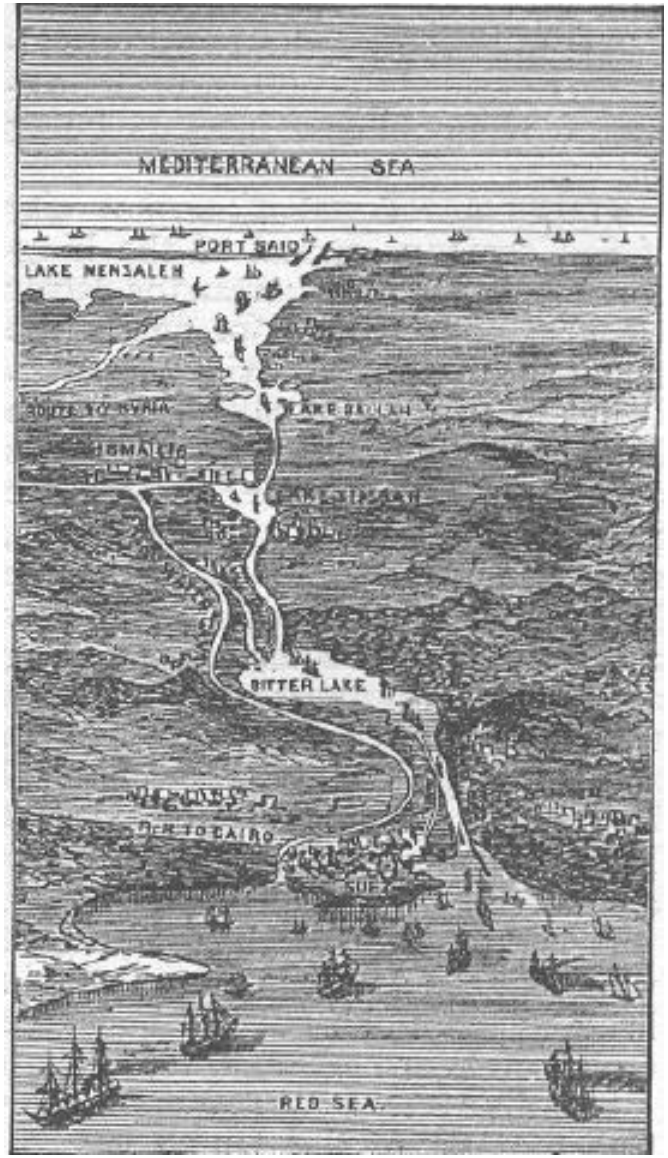
- NZ

- Dunedin


Atlantic
Ocean
Pacific
Ocean
Pacific
Ocean
Indian
Ocean
Equator
St. Paul Rock
Trindade
Cape of Good Hope
Cape Agulhas
Tristan da Cunha
Cape Leeuwin
Perth
Melbourne
Sydney
South East Cape
South
West
Cape
Roaring
Forties
Furious
Fifties
Cape Horn

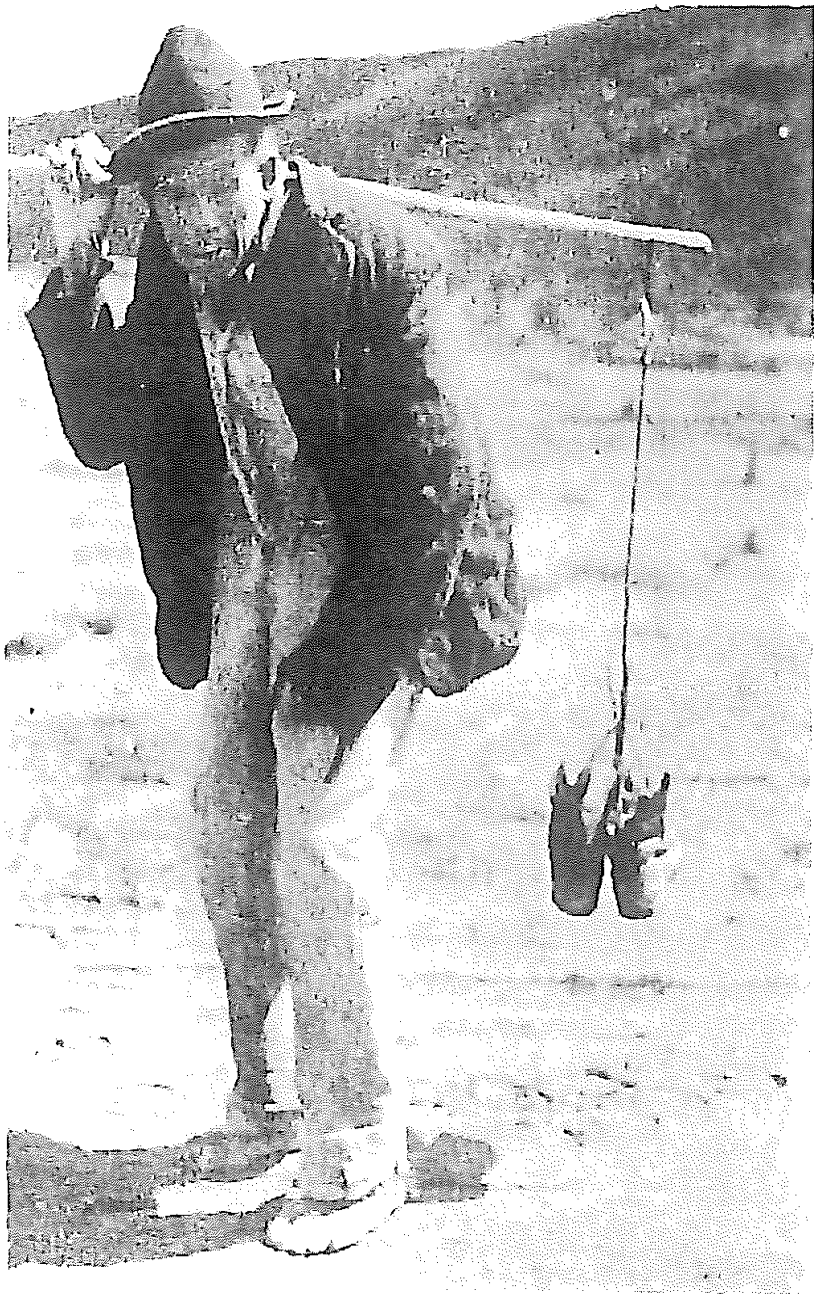
1861

# 1881

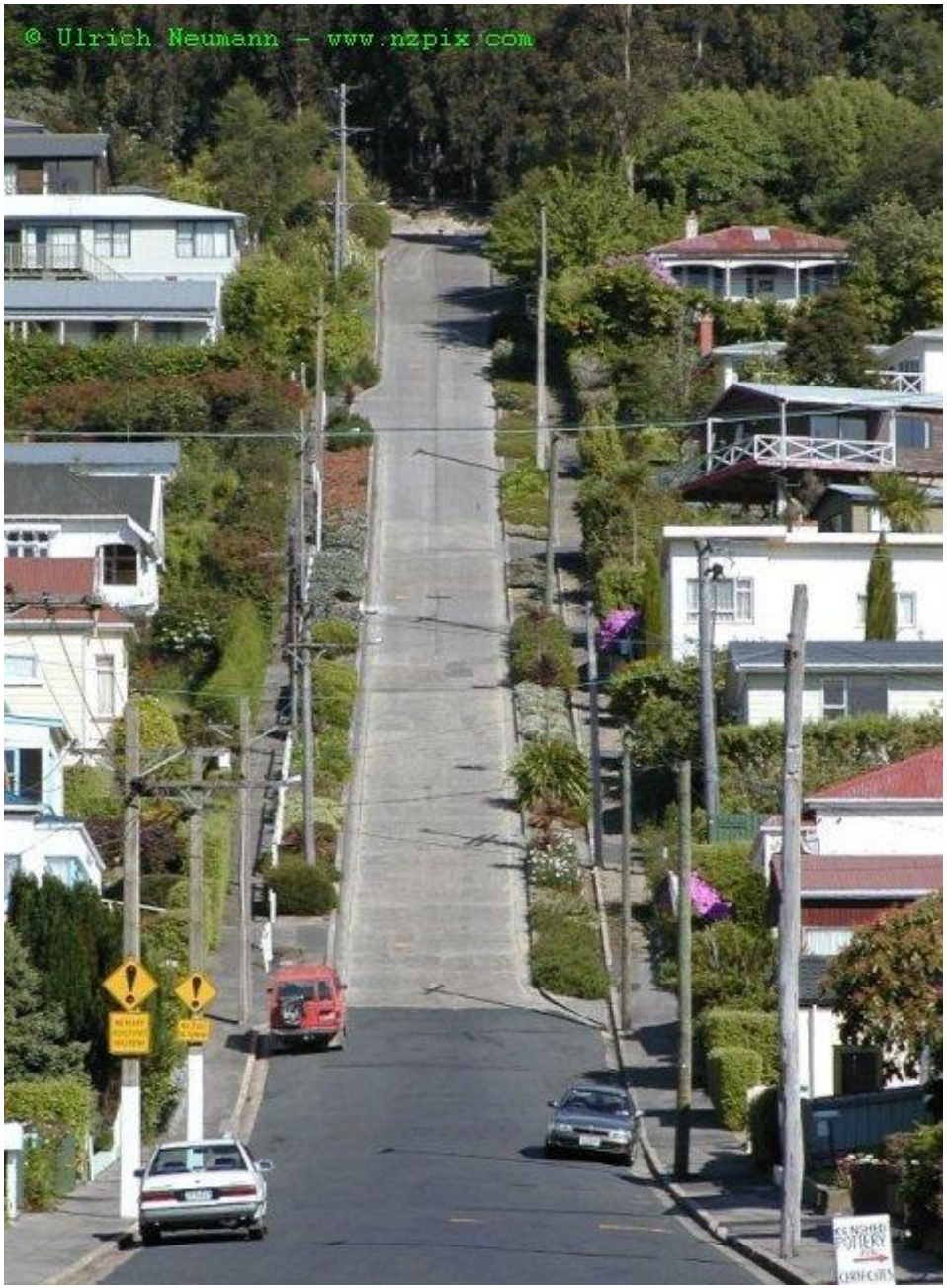

MEDITERRANEAN SEA
PORT SAID
LAKE MENSALEH
BITTER LAKE
RED SEA

# 1915

1922



- Boldwin St



# University of Otago

# Chinese Garden

# Chinese Garden

# Zentech 1987 -

- Zentech

- Phase I – BA, BE, FIH & FIP
- Phase II

# CRO

Clinical site (http://www.medsafe.govt.nz/regulatory/CSSites.htm)

# FIH & FIP

# QCT

- Quality – GCP, GLP, ISO, FDA, EU, TGA & USP  eg patient population, regulatory issues
- Cost
- Timing

# Competition

- India – More CROs than contracts
- North East Asia - an extra 1,500 sites

# Collaboration

- India & China
- Other CROs
- Other Pharmas

# FIH/FIP

1) PK/PD – dose escalation for effects and side-effects

2) POC - Statistics

- **Regulatory Framework supporting clinical trial**

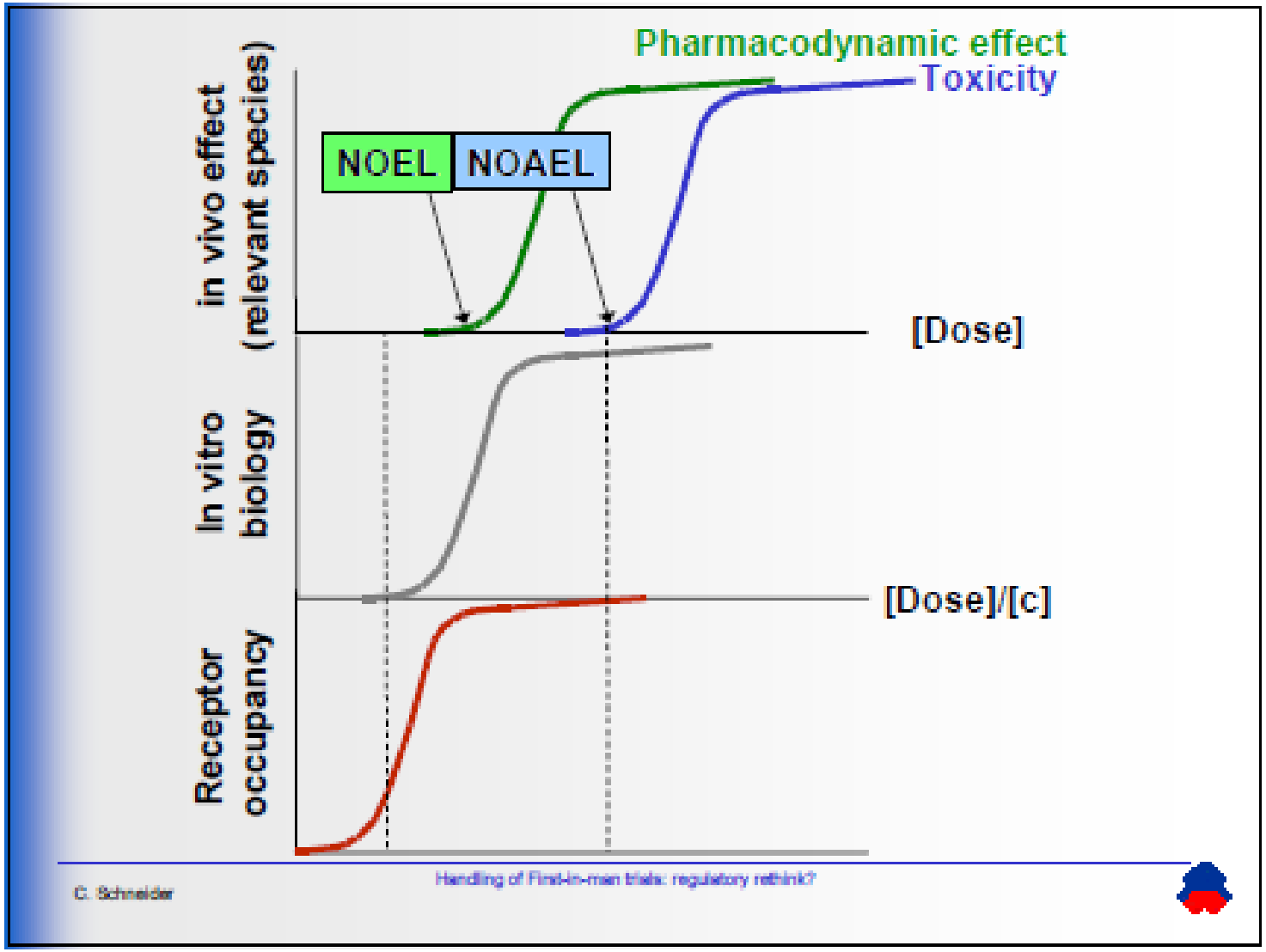
1. Ministry of health

2. Ethics committee – IB, Protocol, PI & facilities

3. SCOTT – FIH/FIP (eg 6A + 3P), NOEL(No Effect Level)/ NOAEL(No Adverse Effect Level)/MABEL (Minimal Anticipated Biological Effect Level) in a relevant species for HED (Human Equivalent Dose) and MRSD (Maximum Recommended Starting Dose)

4. DSMB - dose increase should or should not proceed

Dr. Christian Schneider
Division EU Cooperation/Microbiology



# HED

| Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area | | | |
|---|---|---|---|
| Species | To Convert Animal Dose in mg/kg to Dose in $mg/m^2$, Multiply by $k_m$ | 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 |

# Safety factors

Default safety factor is 10, i.e., divide HED by 10

Increasing safety factor (>10 or microdosing) - steep dose response curve, nonlinear PK, variable bioavailability, irreversible toxicity, limited animal data

Decreasing safety factor (<10) - known class, well characterised toxicity profile

# TGN 1412 MRSD dose calculation

**Toxicology**

NOAEL : 50 mg/kg

HED : 16 mg/kg

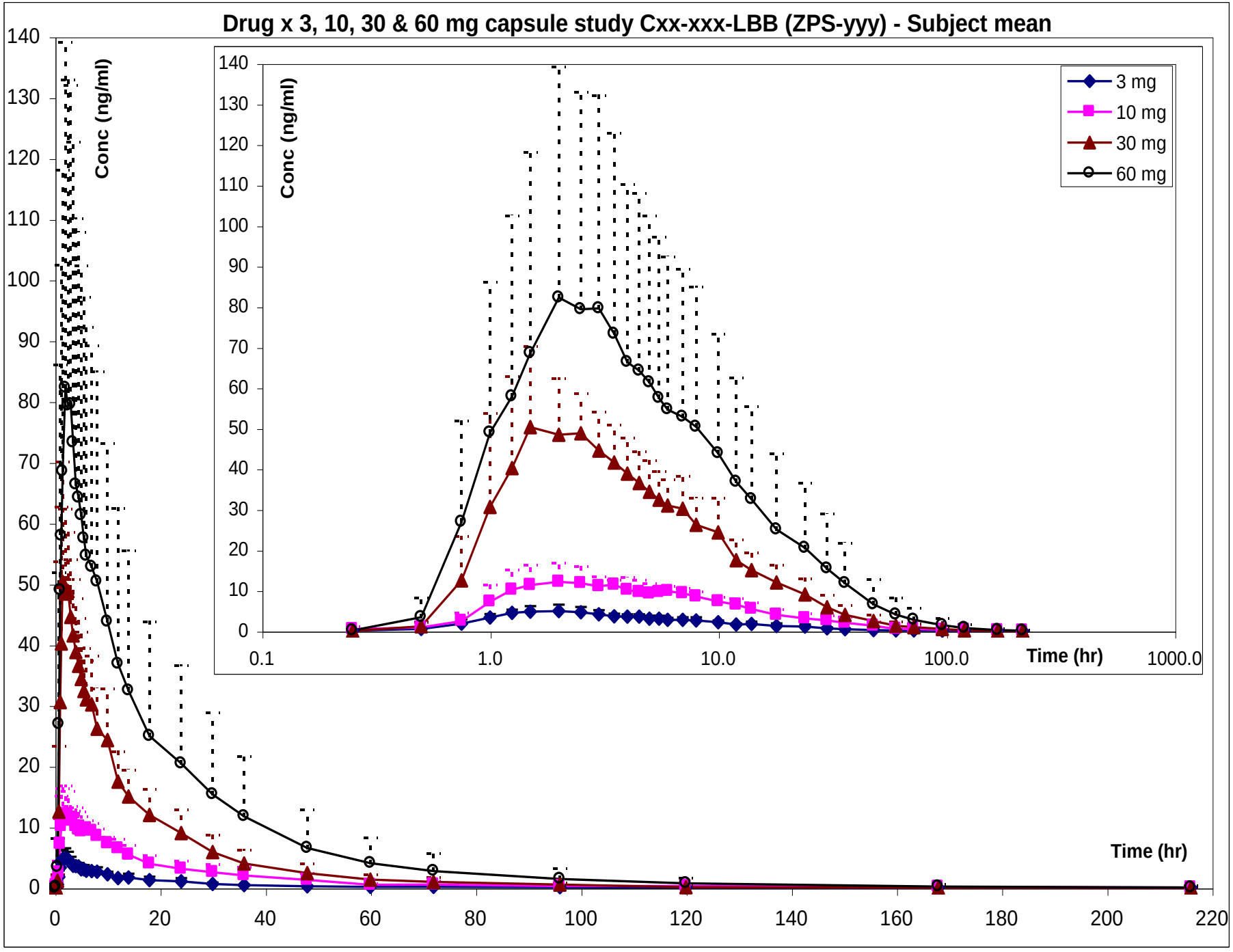
Default safety factor 10: 1.6 mg/kg

Increased to 160 fold: 0.1 mg/kg (100 ug/kg)

**Pharmacology (MABEL)**

10% receptor occupancy at 0.05 ug/kg

MRSD = in-vitro conc x plasma vol = 0.005 ug.kg x 50 ml/kg = 0.25 ug/kg


Drug x 3, 10, 30 & 60 mg capsule study Cxx-xxx-LBB (ZPS-yyy) - Subject mean
Conc (ng/ml)
Time (hr)
3 mg
10 mg
30 mg
60 mg
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
0
20
40
60
80
100
120
140
160
180
200
220
0.1
1.0
10.0
100.0
1000.0

# M & C

- $ - Government or OPM
- Decision Makers
- Pot Black