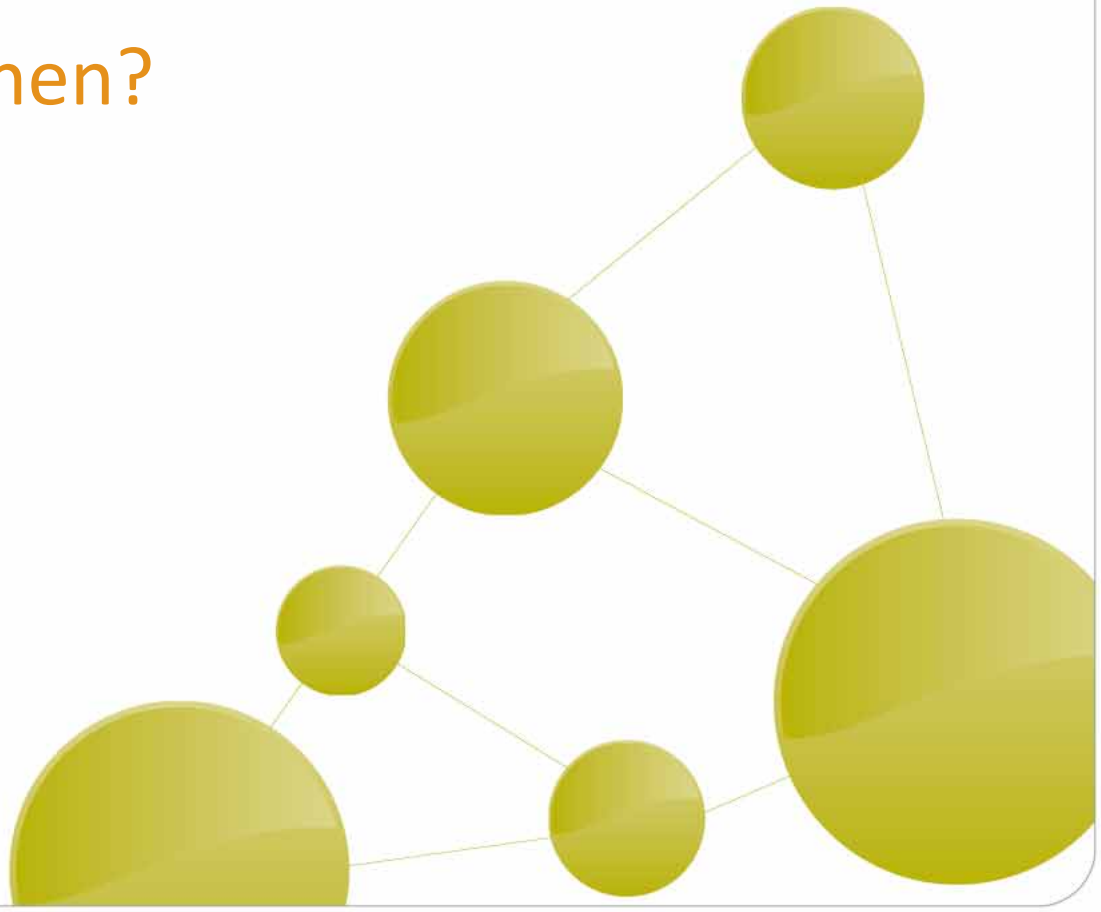
Vernalis

Clinical Trials – How, Why and When?

Candidate to Market

16th May 2012

Kirsty Kwiatkowski



Agenda

- Why are clinical trials conducted?
  - History
  - Guidelines and Regulations
- When are trials conducted?
  - Requirements before starting a trial
- How are trials conducted?
  - Processes, people and output
  - Focussed on early phase clinical trials, from ‘first-in-man’ studies through to proof of concept in patients.

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History - The first controlled trial

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1747 – James Linds studies of scurvy aboard HMS Salisbury

- 12 sailors, each with scurvy
- Divided into pairs
- Each pair given something additional to their diet
  - (cider, diluted acid, spicy paste, sea water, vinegar, oranges & lemons)
- The pair who were given oranges and lemons recovered
- Nearly 50 years before Navy made lemon juice part of sailors diets (later lime juice)

History - Belmont report

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For 40 years between 1932 and 1972 the US Public Health Service conducted an experiment on 600 poor, rural African-American men in Alabama (who thought they were receiving free health care) to study the natural progression of untreated syphilis. 399 had contracted syphilis prior to the study and 201 did not have the disease.

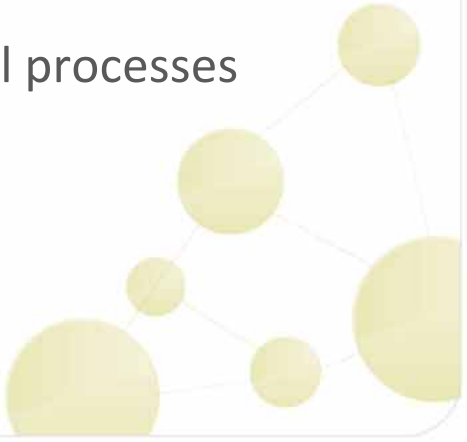
- Investigators **knowingly** withheld penicillin
- Victims included men who died of syphilis, wives who contracted the disease, and children born with congenital syphilis.

In their view, public and scientific interest outweighed the interest of the subjects.

History - Thalidomide

- Licensed as an OTC mild tranquiliser in 1956
- Also reduced morning sickness
- Animal tests did not investigate effects during pregnancy
- By 1960, concern over side effects (some patients had nerve damage following long-term use)
- Increase in births of impaired children across Europe
- Link between impairment and thalidomide made in 1961
- Over 10,000 children were born with thalidomide-related disabilities worldwide

Thalidomide tragedy led to tougher testing and drug approval processes



Why regulations?

- Rights, well being and safety of trial subjects are protected
  - Personal integrity and privacy
- Accountability for actions taken
  - During study conduct
  - Document transparently how actions have been performed
  - Arrange agreements between parties

Regulations

- 1968 Medicines Act
- **SI 1981/164:Medicines (Exemption from Licences) clinical trials**
- 1991 European Good Clinical Practice
- **SI 1995/2808 & 2809: The medicines (Exemption from Licences and certificates) relating to CTX provisions**
- 1997 Global Harmonised GCP
- April 2001 EU Clinical Trials Directive 2001/20/EC
- **May 2004 SI 2004 NO 1031**
- April 2005 Directive for GCP 2005/28/EC
- **August 2006 SI 2006 1928**

ICH GCP

- Launched in 1990
- Goal is regulatory harmonisation across Europe, USA and Japan
- Minimise duplication in clinical research
- Encourage implementation of common standards
- Mutual acceptance of clinical trial data
- Maintain dialogue between regulators and industry

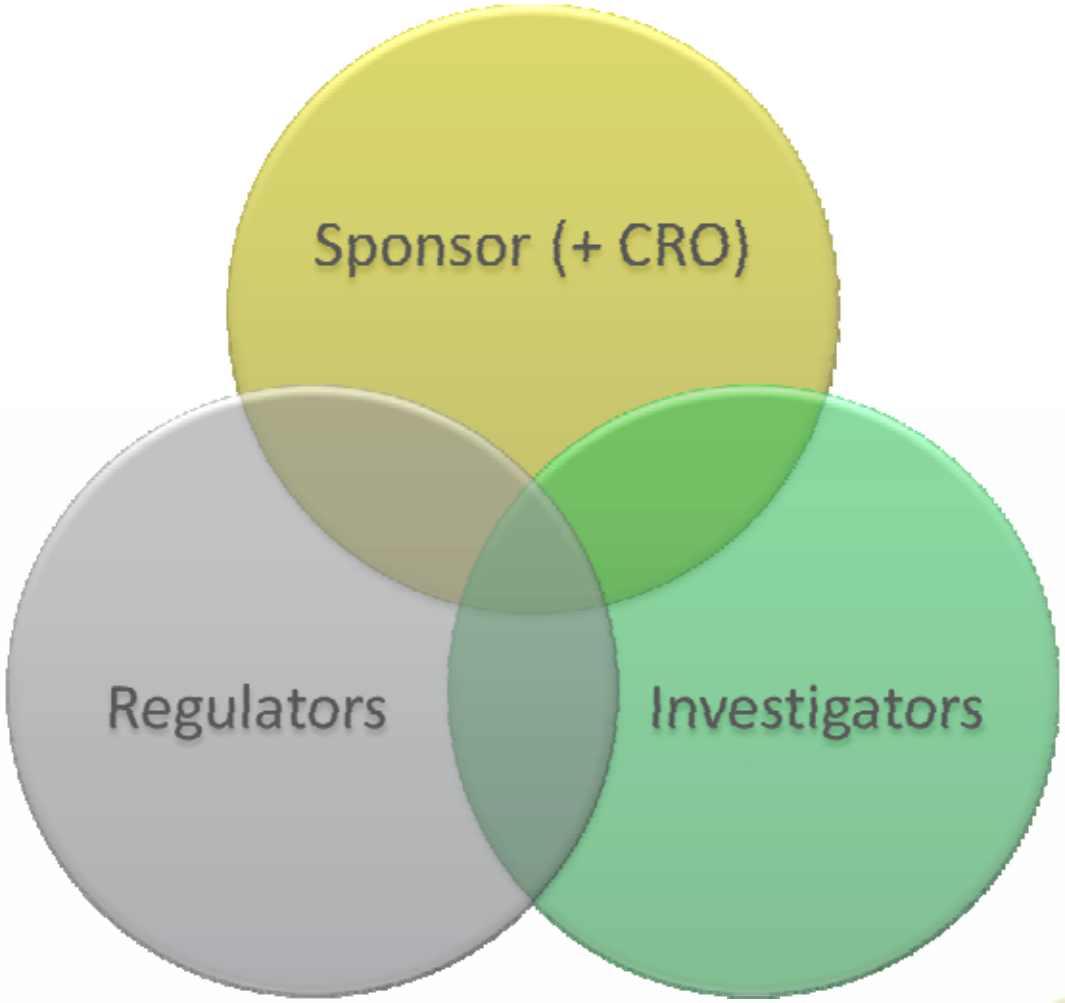
Principals of ICHGCP

- Trial to be conducted in accordance with principles of Declaration of Helsinki
- Risks should be weighed against the benefits
- Rights and safety of the subject
- Available non-clinical and clinical information adequate to support the study
- Study scientifically sound and detailed in a protocol
- Study in compliance with the protocol (Ethics approved)
- Medical care of subject responsibility of a physician (dentist)
- Each individual should be qualified by education, training and experience to do the task
- Freely given informed consent
- All clinical trial information should be recorded, handled and stored to allow accurate reporting, interpretation and verification
- Confidentiality of the subjects
- Investigational Medicinal Product (IMP) to be manufactured and handled as per Good Manufacturing Practice (GMP)
- Systems and procedures that assure the quality of every aspect of the trial should be implemented

Requirements to start clinical trials

- Develop pharmacological profile of the drug
- Acute toxicity studies in at least 2 species
- Short-term toxicity studies (2 weeks to 3 months) depending on proposed length of clinical treatment

Clinical Trials – Who is involved?



Sponsor

RESPONSIBLE FOR QUALITY AND INTEGRITY OF TRIAL DATA

- Chemistry, Manufacturing and Control (CMC) – makes and tests IMP
- Medical – design trials, medical monitoring, safety data review
- Clinical scientists – design trials, write protocol, write report
- Regulatory affairs – prepare CT application, liaise with authorities
- Clinical operations – manage investigators/CROs, prepare trial documents
- Project management – write and maintain project plans
- Monitors – review all trial data, main contact for investigator
- Data management – design database, enter and clean data
- Statisticians – analyse data
- Quality Assurance – ensures trial conducted to regulations and guidelines

Contract Research Organisation (CRO) may take on any or all of these functions

Investigator

- Principal investigator – responsible for trial conduct at that site
- Co-investigators – assist the PI, take consent
- Nurses – conduct trial procedures
- Study co-ordinators – complete case report forms, liaise with monitors
- Project managers – prepare and make submission to ethics committee

Clinical Trials

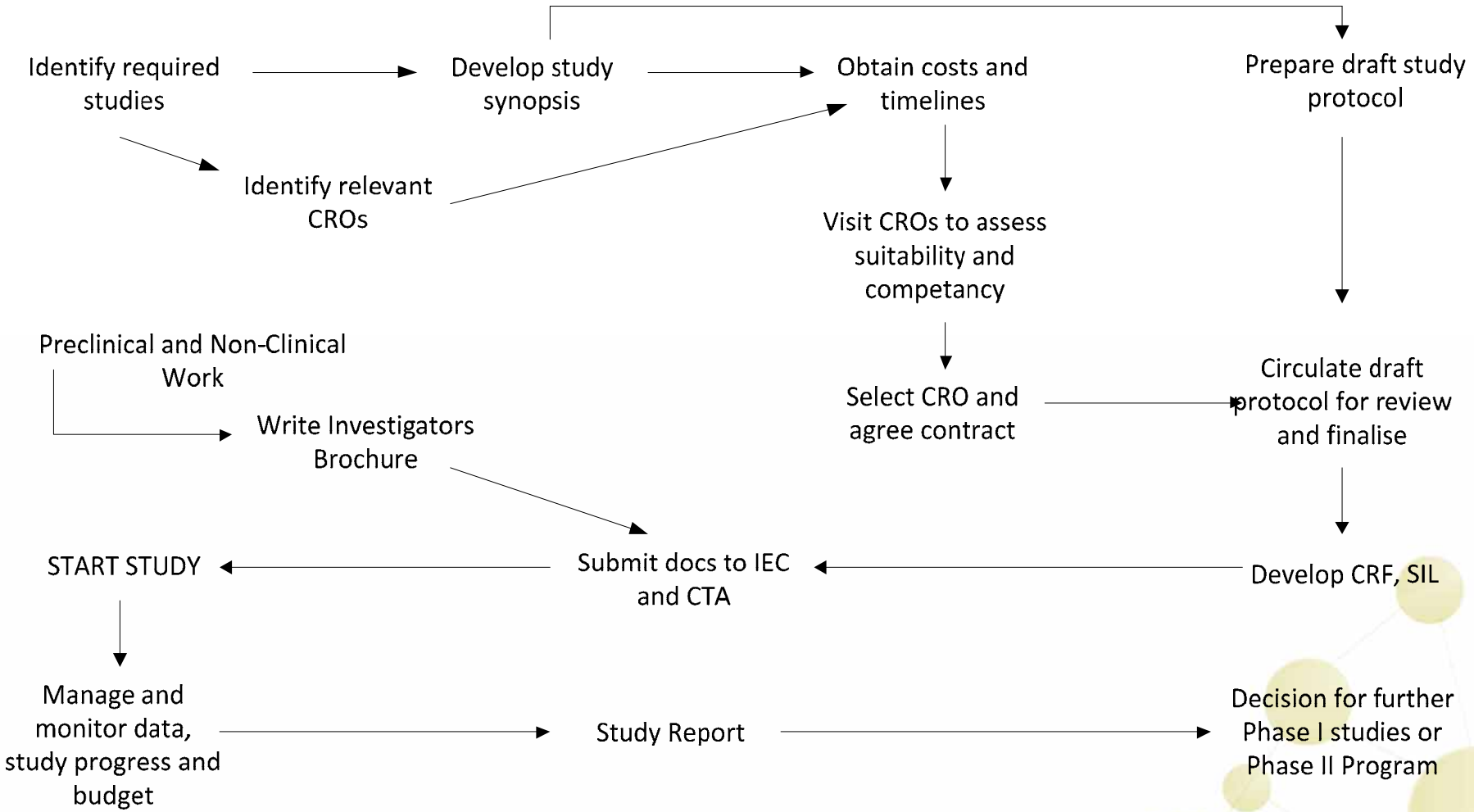
Phases of clinical research

- Phase I – trials in healthy subjects
- Phase II – trials in small number of patients
- Phase III – trials in large numbers of patients
- Phase IV – trials in the patient population once the drug is marketed

Phase I studies

- Healthy volunteers (exceptions apply), usually male
- Single doses initially
- Multiple doses
- Food effect
- Healthy equivalents of target population
- ADME
- Biomarkers
- Models of target indication (e.g. pain model studies)

Set-up of a Phase I study



Design of a FIH study

- ‘Leaping frog’:
  - Two cohorts of subjects to study several dose levels
  - Safety primary objective
  - Pharmacokinetics
  - Starting dose carefully calculated
  - Dose leaders now normal practice
  - Ascending (or descending) doses
  - Usually up to 6 dose levels

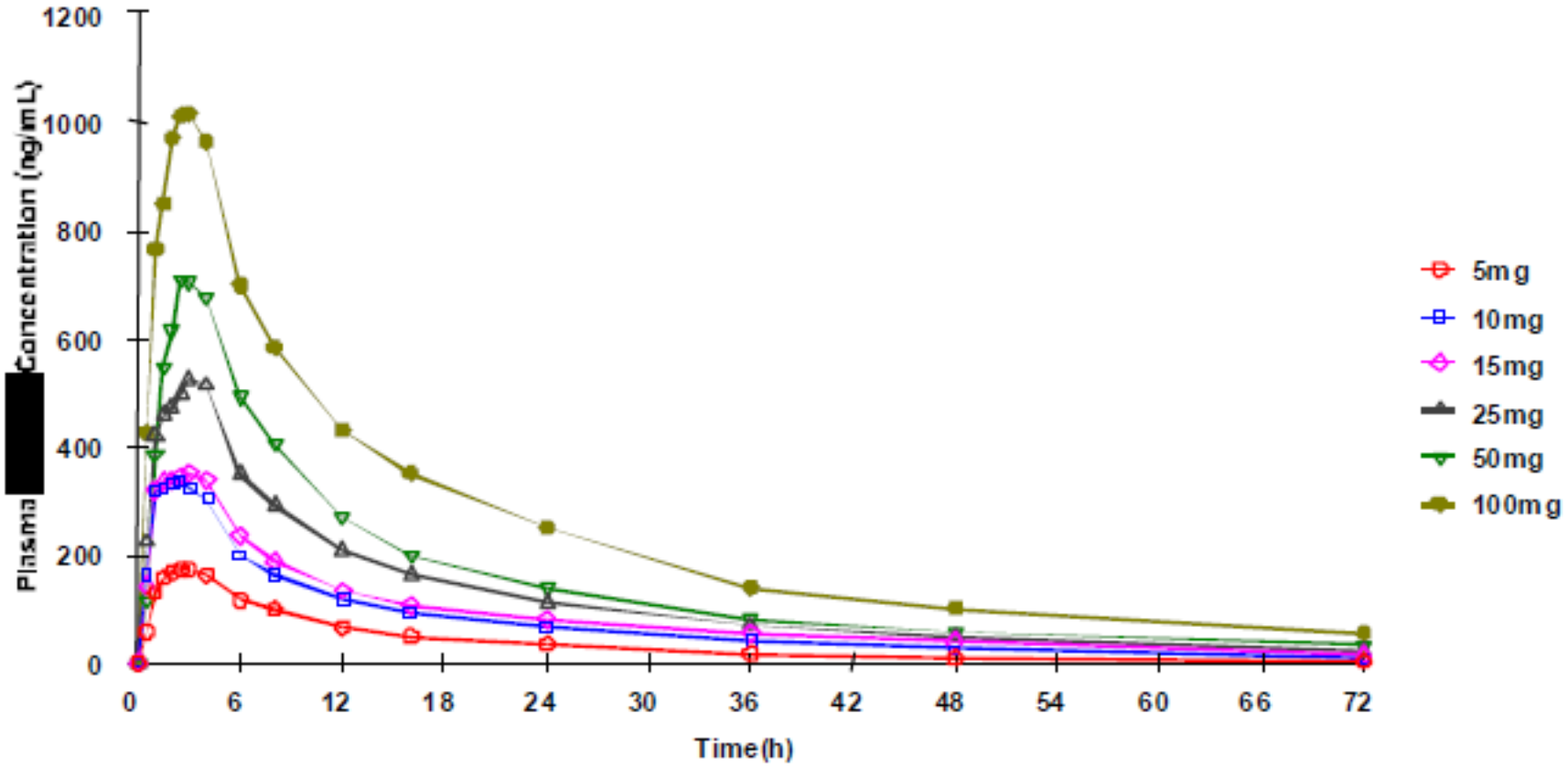
Recent FIH study

	Screen visit	Each Treatment Period																						Post-study
		Day -1	Day 1																	Day 2		Day 3	Day 4	
Assessment			Pre-dose	0 h	30 m	1 h	1.5 h	2 h	2.5 h	3 h	4 h	4.5 h	6 h	6.5 h	8 h	9.5 h	12 h	13 h	18 h	24 h	36 h	48 h	72 h	
Med History	X																							
Physical exam	X																							X
Weight	X																							X
Height	X																							
Drugs of abuse	X	X																						
Dose				X																				
Meal/snack		X										X		X		X		X						
AE monitoring			X			X		X							X					X		X		X	X
Vital signs[1]	X	X	X		X	X		X		X	X				X		X			X	X	X		X	X
12-lead ECG	X		X[2]			X		X			X				X		X			X				X	X
Continuous Telemetry				X----------X																						
Safety labs	X		X																	X				X	X
PK blood			X		X	X	X	X	X	X	X		X		X		X		X	X	X	X	X	X		
PK urine			X	X----------X													X	X----------X		X--------X		X--------X		X--------X		
PD blood			X		X	X	X	X	X	X	X		X		X		X		X	X	X	X	X	X		
PD blood			X			X		X			X				X		X		X	X						

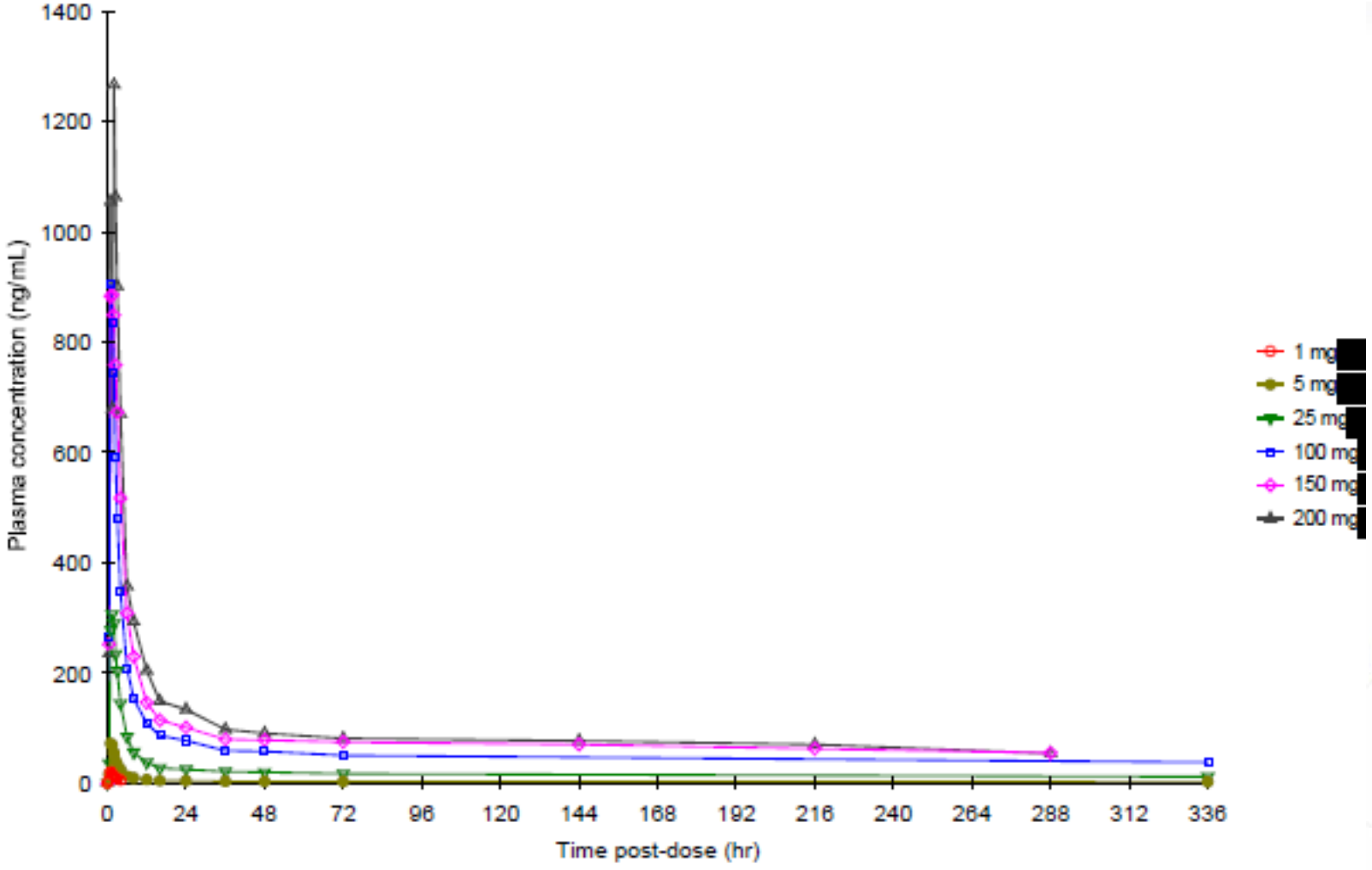
Phase I Unit

Source: http://www.hmrlondon.com/brochures/

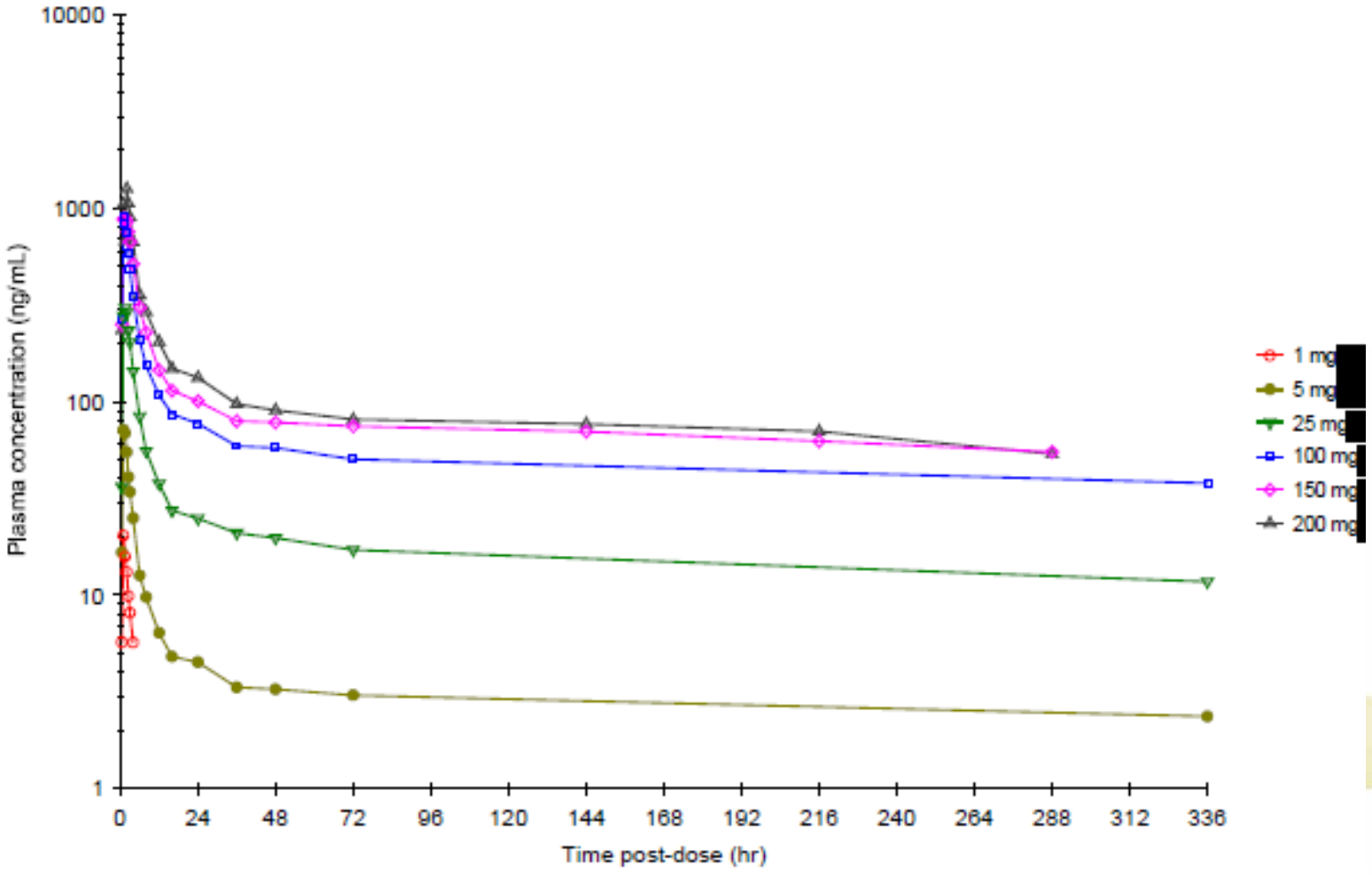
Single ascending dose PK data (example 1)



Single ascending dose PK data (example 2)



Single ascending dose PK (example 2)



Phase II - Proof of concept studies in patients

- Phase II trials study patients for the first time
- May include a dose-range finding study
- Placebo-controlled to give an indication of efficacy
- Modest numbers of patients
- Often split into Phase IIa and Phase IIb

Summary

Why?

- To test potential new medicines
- To protect the right of trial subjects

When?

- Once safety in animals is demonstrated

How?

- Established processes
- According to guidelines and regulations
- Many different disciplines involved in clinical trials, including plenty of chemists!

‘If we knew what it was we were doing,
it would not be called research, would it?’

Albert Einstein