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Pharmacometrics

Regulatory Applications

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Outline

- What is pharmacometrics?
- Learning and confirming
- Rational dosing
- Why is this important for regulators?
- Pharmacometrics in Singapore

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Pharmacology

φαρμακον
pharmakon

Medicine Poison Magic Spell

Pharmacology is derived from a Greek word (pharmakon). The Greeks used this word to mean a medicine, a poison or a magic spell.

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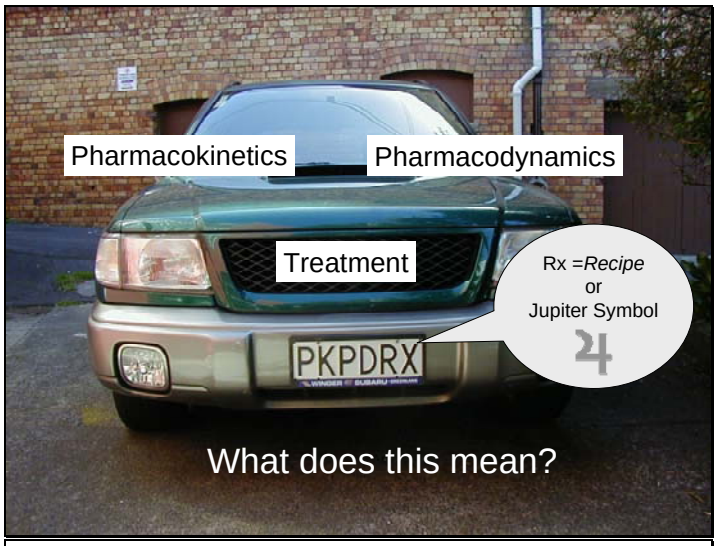

PK = Pharmacokinetics: What the body does to the drug
PD=Pharmacodynamics: What the drug does to the body
Rx=Treatment: What the prescribed and patient need to know.

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Pharmacometrics

Science	Pharmacology		
Models	Pharmacokinetics	Pharmacodynamics	
Experiment	Dose	Concentration	Effect

Quantitative Description of Pharmacology

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Regulatory Science
Asking the Right Question

Sheiner LB. Learning versus confirming in clinical drug development.
Clinical Pharmacology & Therapeutics 1997;61(3):275-91

Essential Reading for Everyone!

Sheiner brought the idea of a learn and confirm cycle to drug development. The basic idea was originally devised by George Box (a famous statistician)

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Confirming or Learning?

- Confirming tests the Yes/No Hypothesis
- If the question being asked has a **Yes/No** answer then it is a Confirming question
- If the question has a **How Much** answer then it is a Learning question

Confirming and learning require different kinds of answers.

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Confirming or Learning?

Confirming	Learning
• Making sure	• Exploration
• Outcome Expected	• Outcome Unexpected
• Analysis Assumptions Minimized E.g. Randomized Treatment Assignment	• Assumption rich analysis – E.g. PKPD model
• Questions for Drug Approval – E.g. • Does the drug work? • Can it be used safely in renal failure?	• Questions for Drug Science – E.g. • How big an effect does the drug have? • What is the clearance in renal failure?
Drug License	Drug Label

Confirming answers are Yes or No. The rejection of the null hypothesis to accept a model answers the question 'Is this model better than the other?'. It is therefore a confirming question.
Simulation can be used to define the power of a clinical trial to reject the null hypothesis.
Learning answers describe how big something is. Estimation of model parameters answers learning type questions. Simulation can be used to learn the bias and imprecision of parameter estimates.

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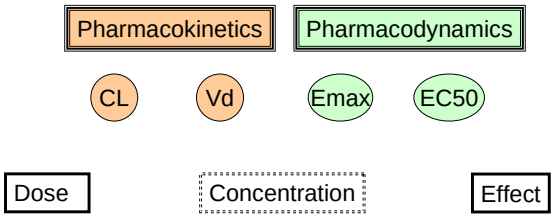
Clinical Pharmacology



Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect.
Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose.
The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (Vd).
The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (EC50).

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Volume of Distribution

Apparent Volume of Distribution describes the relationship between concentration and the amount of drug in the body

$$Amount = Vd \bullet Conc$$

The definition of apparent volume of distribution (Vd) links drug concentration to the amount of drug in the body.
Note it is an *apparent* volume. While the volume may be similar to a physical space in the body it is not necessary to assume that the apparent volume corresponds to an anatomical/physiological volume.

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Filling Up Can be Easy

Target = 800 mg/L = 0.8 g/L

0.8 g/L x 40 L = 32 g = 4 beers *

* Bioavailability is 80%

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Clearance

Clearance describes the relationship between concentration and the rate of elimination of drug from the body

$$\text{Rate Out} = CL \bullet Conc$$

The definition of clearance (CL) links drug concentration to the rate of elimination (rate out).
Note that elimination and clearance are NOT the same thing.

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Clearance Can be Complicated

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

Mixed Order

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

$$Rout = CL \cdot C$$

First Order

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

$$Rout = V\max$$

Zero Order

The order of a chemical reaction can be defined in terms of the number of reactive species determining the rate of the reaction. Enzymatic reactions are typically saturable and can be described in terms of the maximum rate of elimination (Vmax) and the concentration producing 50% of Vmax (Km).
Most enzymatic drug metabolism appears to be driven only by the drug concentration. If concentration is small in relation to Km then the elimination rate will appear to be first-order i.e. linearly dependent only on concentration. If concentrations are large in relation to Km then the elimination rate will appear to be independent of concentration and this is called a zero-order reaction. Concentrations that are neither small nor large in relation to Km will give rise to a mixed-order reaction. The mixed-order reaction should be considered as the general case for all drugs eliminated by metabolism. The first-order approximation is very common. True zero-order elimination does not occur but is approximated at very high concentrations.

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Clinical Pharmacology
Confirming Questions

What Does Effectiveness Mean?

- Does it Work?
- Better than Placebo?
- Is the Drug Effective?

Answer: Yes or No

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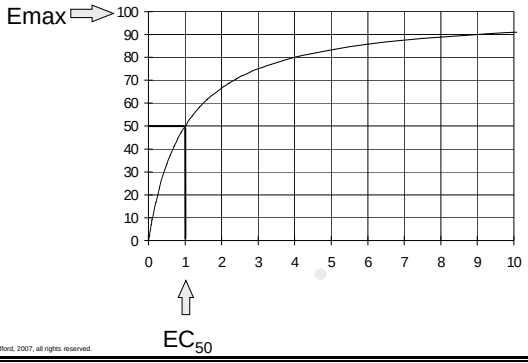
Clinical Pharmacology

Confirming Questions

What Does Efficacy Mean?



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Efficacy = Emax

$$E = \frac{E\max \bullet Conc}{EC_{50} + Conc}$$

- E is the drug effect
- Conc is the conc at the receptor
- Emax is the maximum drug effect
- EC_{50} is the conc at 50% of Emax

A Learning Question

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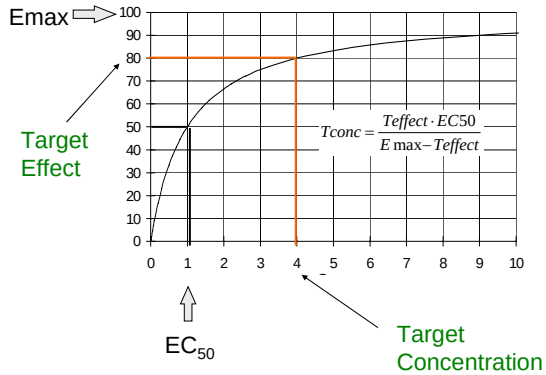
How is This Used?



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The Target Concentration Approach

Science — Clinical Pharmacology

Models — Pharmacokinetics | Pharmacodynamics

Clinical Goal — Target Dose ← Target Concentration ← Target Effect

Holford NHG. The target concentration approach to clinical drug development. Clinical Pharmacokinetics 1995;29(5):287-91

The target concentration approach starts by identifying the desired clinical benefit of treatment. The size of the drug effect required to achieve clinical benefit is the target effect. With a pharmacodynamic model to link concentrations and effects it is then possible to predict the target concentration which will produce the target effect. The final step is to apply a pharmacokinetic model to predict the dose needed to reach the target concentration.

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Rational Dosing

Target	Dose Model
Initial Peak	Loading Dose=Target Conc x Volume of distribution
Average Steady State	Maintenance Dose Rate=Target Conc x Clearance

Rational Dose prediction requires a Target Concentration

The Essential Principle for the Drug Label

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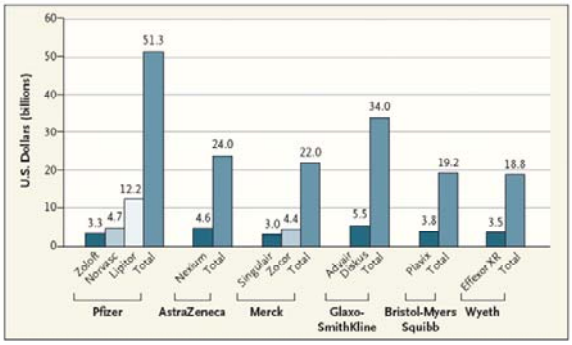
Why Is Drug Regulation Needed?



Sales of Blockbuster Drugs in 2005 as a Portion of the Total Revenues of Pharmaceutical Companies.

Cutler DM. The Demise of the Blockbuster? N Engl J Med. 2007 March 29, 2007;356(13):1292-3.

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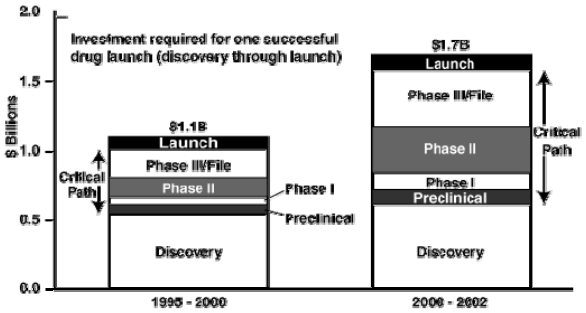
US FDA Critical Path Initiative



SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf March 2004

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Regulatory Science Learning Questions

- What is the shape of the dose-response curve?
- What is the maximum response?
- What is the time course of the response?
- Is disease progress modified?
- Which patients respond to the drug?

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Impact of Pharmacometrics at US FDA

Bhattaram VA, Booth BP, Ramchandani RP, Beasley BN, Wang Y, Tandon V, et al. Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. AAPS J. 2005;7(3):E503-12.

Bhattaram VA, Bonapace C, Chilukuri DM, Duan JZ, Garnett C, Gobburu JV, et al. Impact of pharmacometric reviews on new drug approval and labeling decisions--a survey of 31 new drug applications submitted between 2005 and 2006. Clin Pharmacol Ther. 2007 Feb;81(2):213-21.

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Critical Path Opportunities

Table 1 Critical path opportunities for clinical pharmacologists

Taking responsibility for optimal dosing
Developing disease state models
Designing and simulating phase 3 clinical trials
Estimating probabilities of benefit and risk decisions
Identifying biomarkers as potential diagnostic tests
Using therapeutic drug monitoring to individualize dosing

Lesko LJ. Paving the critical path: how can clinical pharmacology help achieve the vision? Clin Pharmacol Ther. 2007 Feb;81(2):170-7.

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Taking Responsibility for Optimal Dosing

The zoledronic acid (Zometa) story…

Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 ml/min.

Creatinine clearance is calculated by the Cockcroft-Gault formula (Creatinine clearance (CLcr, mL/min)= (140- age)*weight (kg)/X*(plasma creatinine concentration, where X= 72 for males, and X=85 for females). Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=6.5(CLcr/90)$^{0.4}$.

These formulae can be used to predict the Zometa AUC in patients. CL = Dose/AUC. The average AUC in patientswith normal renal function was 0.42 mg*h/L (%CV 33) following a 4 mg dose of Zometa.

However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS)

http://www.fda.gov/cder/foi/label/2002/21386lbl.pdf

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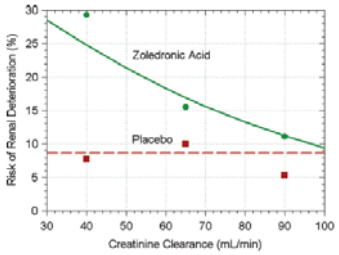
Why did it take so long?

- Zometa approved by FDA in 2001
- Novartis issued "Dear Doctor" letter 20 Dec 2004 with warning to reduce dose in renal disease
- FDA publishes graph for risk of renal deterioration in 2005
- 3 fold risk increase at 30 ml/min!



Bhattaram VA, Booth BP, Ramchandani RP, Beasley BN, Wang Y, Tandon V, et al. Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. Aaps J. 2005;7(3):E503-12.

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Ernest Rutherford

"*Science is either stamp collecting or physics*"

Stamp Collecting → Models → Physics

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Paving the Critical Path
Model Based Drug Development

MBDD is a unifying concept that has drawn its inspiration from a quote by the late Dr Lewis B Sheiner:

''*My thesis is the current drug development is largely empirical and does not adequately exploit current scientific knowledge. Science is our understanding of our natural world and mathematical scientific models are the precise and quantitative language in which we express that understanding*.''

Lesko LJ. Paving the critical path: how can clinical pharmacology help achieve the vision? Clin Pharmacol Ther. 2007 Feb;81(2):170-7.

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Development of a Pharmacometrics Resource for Singapore

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Why is Pharmacometrics Needed in Singapore?

- Large, active clinical research programs
- Multi-million dollar investments in clinical trials and research methodology
- Naïve clinical trial designs based on dose
- Empirical ‘stamp collecting’ approach to interpretation

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How Can Pharmacometrics Help?

- Explicit models for interpretation of complex biological systems
- Quantitation of between patient variability and identification of predictable components
- Better experimental/clinical trial designs leading to more informative outcome (and maybe cheaper and shorter)

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Pharmacometrics Resource

- Training
  - » Clinician scientists (medicine, pharmacy)
  - » Pharmaceutical scientists (biotech)
  - » Regulatory scientists
- Consulting
  - » Oversight of clinical trials of medicines in SGP
  - » Core facility in research grants
  - » Ad hoc projects
  - » Drop in advice

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Who Needs Pharmacometrics?

- National University of Singapore
  - » Issues degrees/certificates
  - » Graduate training programs in medicine, pharmacology, pharmacy
- National University Hospital
  - » Major non-University client
- Lilly NUS Clinical Pharmacology
  - » Potential client/sponsor
  - » Local Pharmacometric expertise
- HSA
  - » Current initiatives to introduce PKPD into regulatory processes

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Organization

- Director
  - » Manages personnel and programs
- Pharmacometric Specialist
  - » Provides consulting/training
- IT Specialist
  - » Supports IT hardware/software
- Database Manager
  - » Manages data collection and gives datasets to the pharmacometrician

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Training Programs

- Undergraduate
  - » Medicine, Pharmacy
  - » Basic PK, PD, trial design principles
- Graduate
  - » Intermediate PK, PD, design principles
  - » Training in use of pharmacometric tools
- Postgraduate
  - » Advanced Principles
  - » Specialist pharmacometric tools

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Further Resources

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Pharmacometrics – ICH Guidelines

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- Three regions
  - » USA FDA
  - » Japan MHLW
  - » EU EMEA

http://www.ich.org/cache/html/250-272-1.html

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Pharmacometrics – FDA Guidances

- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application* 1987
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro 1997
- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products 1998
- Pharmacokinetics in Patients with Impaired Renal Function 1998
- In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling 1999
- Population Pharmacokinetics 1999
- Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications 2003
- Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling 2003
- Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling 2004
- Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling 2005
- Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling 2006

http://www.fda.gov/cder/guidance
http://www.fda.gov/cber/guidelines.htm

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Pharmacometrics – EMEA Guidelines

- CHMP Final Guideline on pharmacokinetic studies in patients with renal impairment, 2004.
- CHMP Final Guideline on evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function, 2005.
- CHMP Final Guideline on the clinical development of medicinal products for the treatment of HIV infection, 2006.
- CHMP Final Guideline on the evaluation of anticancer medicinal products in man, 2006.
- CHMP Final Guideline on the evaluation of medicinal products for the treatment of Hepatitis B, 2006.
- CHMP Draft Guideline on reporting the results of population pharmacokinetic analyses, 2006
- CHMP Final Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population, 2006
- CHMP Final Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins, 2007.
- CHMP Requirements for First-in-Man Clinical Trials for potential high-risk medicinal products. 2007

http://www.emea.eu.int/htms/human/humanguidelines/efficacy.htm

Adopted from talk by Dr Janet Wade, Exprimo, at Noordwijkerhout, April 2006