

First Dose and Dose Escalation

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Introduction

- **Scope: Starting Dose (SD) and Dose Escalation Scheme (DES) in Entry-Into-Man (EIM) studies**
- **“One of the most controversial areas in Clinical Pharmacology is the choice of the initial human dose”**

Vaidya and Vaidya, J Postgrad Med, 1981

- **Safety comes first**

Outline of the Presentation

- **The different approaches used to calculate the SD**
- **Results of three surveys**
- **Dose Escalation Schemes**

Four Different Approaches

1. The dose by factor approach

- FDA method (Draft Guidance, Dec 2002)

2. Similar Drug Approach

3. Pharmacokinetically guided approach

4. The comparative approach

1. FDA Draft Guidance: Five steps

Step 1: Determine NOAELs (mg/kg) in toxicity studies



Step 2: Convert each animal NOAEL to Human Equivalent Dose (HED)



Step 3: Pick HED from most appropriate species



Step 4: Choose safety factor and divide HED (generally 10)



Maximum Recommended Starting Dose (MRSD)



Step 5: Consider lowering dose based on a variety of factors, e.g., the Pharmacologically Active Dose (PAD)

1. FDA Draft Guidance: What is behind this conversion?

- Conversion based on normalization of dose to Body Surface Area (BSA)
- NOAEL or MTD scales well between species when doses are normalized to BSA
- Basis: work of Freireich 1966 (*18 drugs*) and Schein 1970 (*25 drugs*) with antineoplastic drugs

1. FDA Draft Guidance: Example of a new retinoid

Species	NOAEL (mg/kg/d)	BSA-CF	HED (mg/kg)	MRSD (mg)
rat	50	x 0.162	8.1	49*
dog	2	x 0.541	1.08	6.5*

*Safety Factor = 10

1. FDA Draft Guidance: Critical Assessment

Pros:

- simple method, easy to implement, easy to review
- will ensure consistency across projects, companies and reviewers
- useful section about magnitude of safety factors
- useful section defining the terms e.g., NOAEL

1. FDA Draft Guidance: Critical Assessment

Cons:

- uses dose and not systemic exposure
- based on old (1966/1970) and limited observations (18+25 drugs) from only one therapeutic area (oncology)
- no retrospective “validation” despite huge database at FDA

2. The Similar Drug Approach

- When human data are available with similar drug(s)

Vaidya and Vaidya, J Postgrad Med, 1981

- Example: New retinoid (NR) and Etretrate (ET)
 NOAEL(ET) in dog = 0.1 mg/kg/day
 NOAEL(NR) in dog = 2 mg/kg/day (20X)
 Safe dose for ET in man = 10 mg
 SD(NR) = $10 \times 20 \times 1/10 = 20 \text{ mg}$

3. PK Guided Approach

- **Uses concentration (instead of dose) for the extrapolation**
- **A target systemic exposure (e.g., AUC) is defined**
- **CL in man predicted using allometric scaling or Physiologically Based PK modeling**

3. PK Guided Approach (Cont.)

Example: New retinoid (NR)

AUC at NOAEL in dog = 17.3 mg.h/L

Predicted CL in man = 16.0 L/h

SD = AUC x CL_(man) = 17.3 x 16.0 = 277 mg

SD x safety factor = 277 x 1/10 = 28 mg

4. The Comparative Approach

- **Estimate SD using all possible approaches**
- **Compare results and interpret differences**

4. The Comparative Approach

New Retinoid (NR)

<u>Method</u>	<u>HED</u>	<u>Safety F</u>	<u>SD (mg)</u>
1. FDA Guidance	65	10	6.5
2. Similar Drug	250	10	25
3. PK Guided	277	10	28

Drugs With Wide Therapeutic Window

- If SD based on NOAEL is predicted to be pharmacologically active...
- Then, lower the SD so it gives the desired pharmacologic effect...
- Using the same approaches to get the SD but with Pharmacologically Active Dose (PAD) instead of NOAEL

Outline of the Presentation

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- **Results of three surveys**
- **Dose Escalation Schemes**

Results from three surveys at Roche

1995 Survey

- 15 projects
- EIM between 1982 and 1995

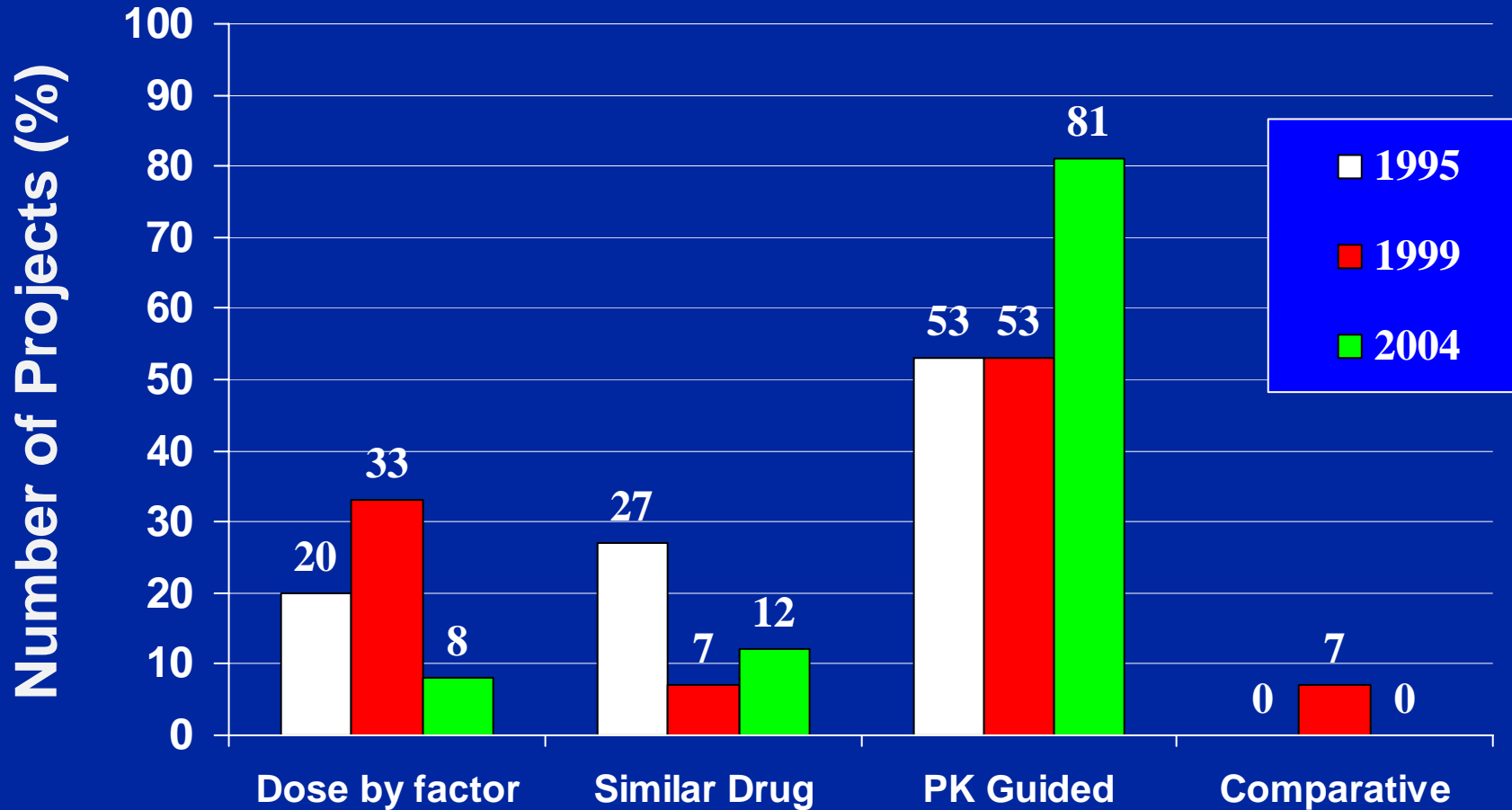
1999 Survey

- 15 projects
- EIM between 1996 and 1999

2004 Survey

- 26 projects
- EIM between 1998 and 2004

Three Surveys: PK guided is first choice



What will be the impact of the FDA guidance?

- Pfizer survey: retrospective analysis of 35 drugs

Actual SD < MRSD in all cases

Chan et al., CPT, P8, 2004

- Roche survey: retrospective analysis of 26 drugs

Actual SD << MRSD (10 fold on average)

⇒ Use the comparative approach

Outline of the Presentation

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Dose Escalation Schemes

- Arithmetic escalation: $x, 2x, 3x, 4x, 5x\dots$
- Geometric escalation: $x, 2x, 4x, 8x, 16x\dots$
- Modified Fibonacci: $x, 2x, 3.3x, 5x, 7x, 9x, 12x, 16x\dots$

Spilker, 1991

- Factor 3 for first 2 or 3 steps, then factor 2 for subsequent 2 steps and factor 1.5 at the end

Current trend: PK or PD Guided DES

- On line PK to assess systemic exposure and compare to NOAEL AUC
 - On line pharmacodynamic results to make decision about next steps
 - E.g., increase in reticulocyte count
- ⇒ First rapid DE (x2 or x3) until target (PK, PD or safety) and then, more cautious (e.g., x 1.5)

DES: Points to Consider

- **Steepness of dose/concentration-response curve**
- **Seriousness and reversibility of toxicities**
- **Monitorability of potential AE in humans**
- **Nonlinear (>proportional) PK with dose**
- **Systemic exposure compared to NOAEL AUC**

SD and DES is Team Work

- SD and DES \neq use of magic formula
- Discuss with toxicologist, pre-clinical pharmacologist, pharmacokineticist and investigator
- Experienced Clinical Pharmacologist, able to evaluate pre-clinical results (toxicology, pharmacokinetics, chemistry, formulations...)
- Sufficient knowledge of specialized methodologies (e.g., allometric scaling)

Summary

Starting Dose:

- Four different approaches: Dose by factor, similar drug, PK guided and comparative approaches
- FDA Guidance: Uses dose in mg/m^2 to extrapolate
- At Roche: most common is PK guided approach

Dose Escalation Scheme:

- Case by case, trend towards PK, or PD guided DES
- Not an algorithm - Team work is needed
- **Safety comes first!**

High technology,
Well trained professionals,
Nevertheless...



Back-ups

1. Dose by Factor: Goals of FDA Draft Guidance

- **SD in healthy volunteers - oncology not included**
- **Goals of the document:**
 - (1) Establish consistent terminology**
 - (2) Provide consistent conversion factors (BSA-CF)**
 - (3) Delineate a strategy for selection of SD, regardless of the projected clinical use**

FDA Draft Guidance: Section about PK and modeling

“...an alternative approach could be proposed that places primary emphasis on animal PK and modeling rather than dose. In a limited number of cases, animal PK data may be useful in determining initial clinical dose². However, in the majority of new INDs, animal data are not available in sufficient detail to construct a scientifically valid, PK model whose aim is to accurately project an MRSD”.

“Measurements of systemic levels or exposure (i.e., AUC or C_{max}) cannot be employed for setting a safe SD in humans and it is critical to rely on dose and observed toxic response data from adequate and well-conducted toxicology studies”.

²Footnote of 19 lines highlighting the limitations of the PK-guided approach

1. FDA Draft Guidance: Summary

- Uses dose in mg/m^2 to extrapolate
- Based on old and limited data in oncology
- Dose by factor approach (ignores PK)
- Old fashion and conservative approach
- PK approach still possible but acceptance questionable

The Present and Future

- **Over the years: Evolution from empirical to more physiologic/mechanistic approaches**
- **Has started at Roche: Prediction of human PK based on PBPK modelling instead of allometric scaling**
- **The Future: PBPK + Mechanism-Based Pharmacodynamic Modelling - simulations including stochastic simulations**

Gomeni et al., Eur J Pharn Sc, 2001

Methods Used in Cancer Chemotherapy

- 1/3 of TDL (Toxic Dose Low) in large animal species

Penta et al., Cancer Chemother Pharmacol, 1979

- 1/10 of LD₁₀ in mice

Rozencweig et al., Cancer Clin Trials, 1981

- Pro: - usually provide safe SD
- Cons: - high number of doses needed to reach MTD
- large number of cancer patients treated at ineffective doses