First Dose and Dose Escalation

First Joint Annual Meeting 2005 AGAH
and Club Phase 1

Bruno Reigner, Medical Science, Clinical Pharmacology
F. Hoffmann-La Roche Ltd., Basel

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**

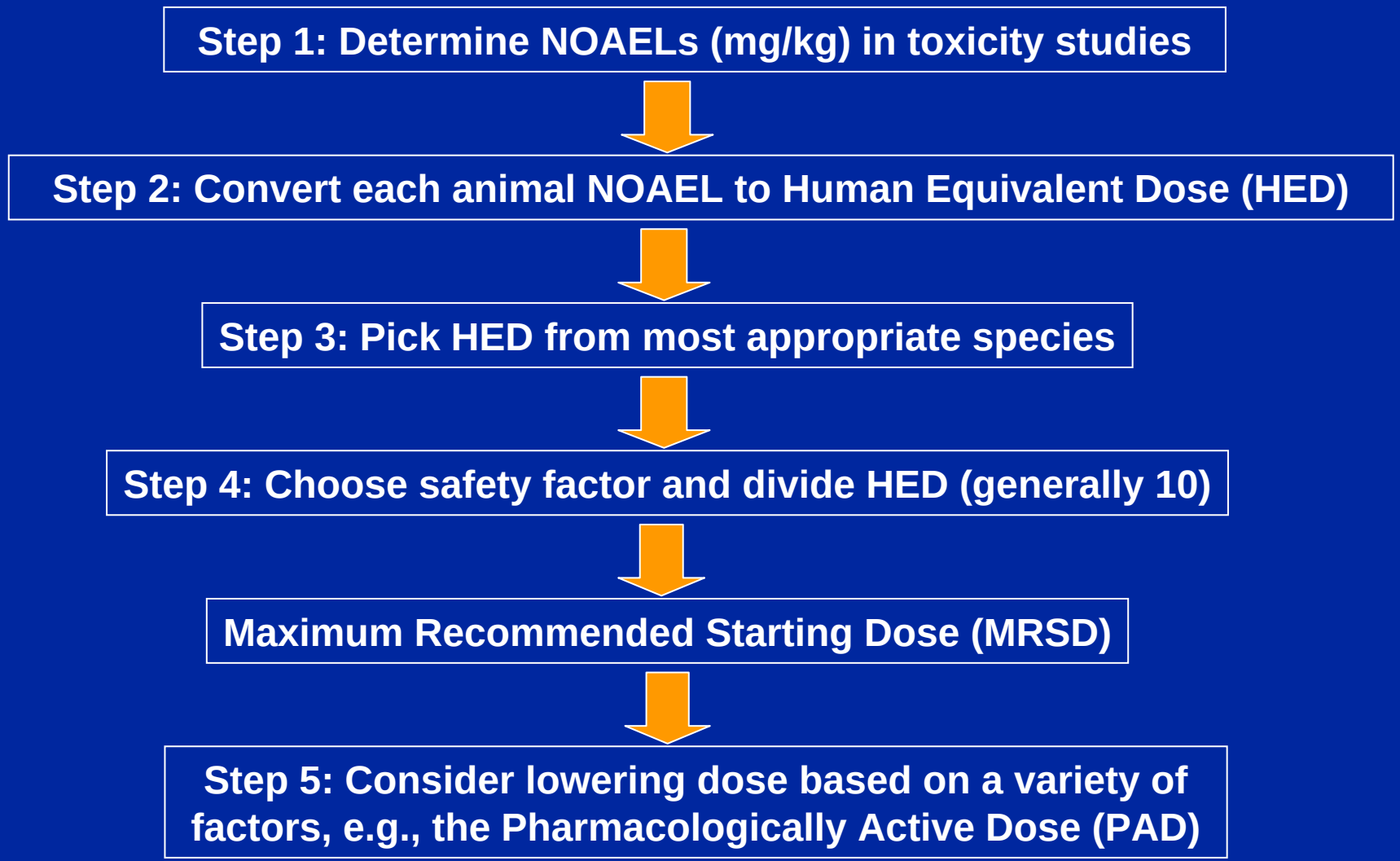
Outline of the Presentation

- 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    - FDA method (Draft Guidance, Dec 2002)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 FDA Draft Guidance: Five steps



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 FDA Draft Guidance: What is behind this conversion?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 FDA Draft Guidance: Example of a new retinoid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 FDA Draft Guidance: Critical Assessment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 FDA Draft Guidance: Critical Assessment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 Etretinate (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 x 20 x 1/10 = 20 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)

Method	HED	Safety F	SD (mg)
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

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

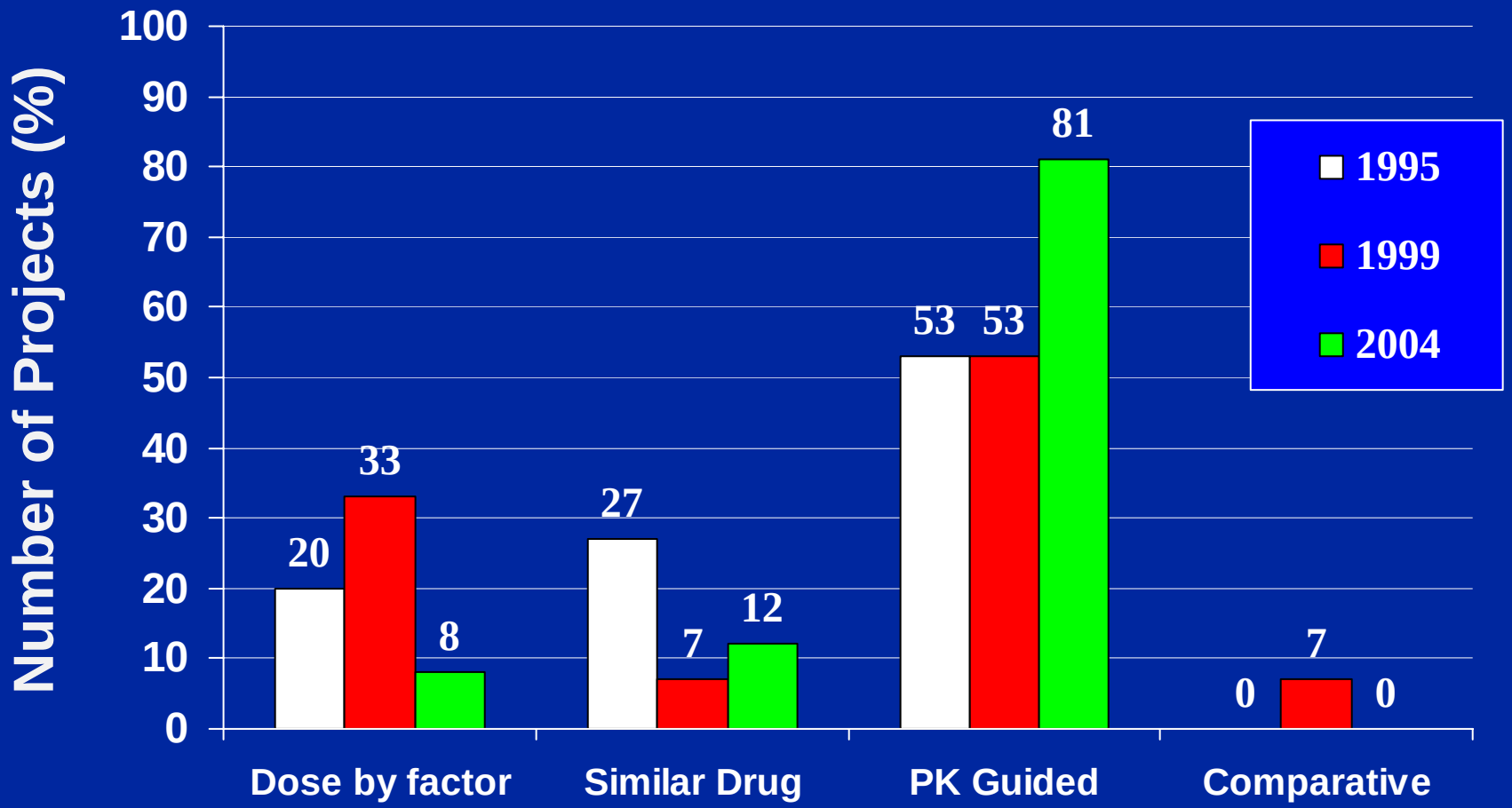
Results from three surveys at Roche

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

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

Dose Escalation Schemes

- **Arithmetic escalation: x, 2x, 3x, 4x, 5x...**
- **Geometric escalation: x, 2x, 4x, 8x, 16x…**
- **Modified Fibonacci: x, 2x, 3.3x, 5x, 7x, 9x, 12x, 16x…**

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 ≠ 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 dose[2]. 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 Cmax) 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".

[2]Footnote 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 LD_{10} 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