First Dose and Dose Escalation

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and Club Phase 1

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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”


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   - FDA method (Draft Guidance, Dec 2002)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 FDA Draft Guidance: Five steps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

- **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 FDA Draft Guidance: What is behind this conversion?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 FDA Draft Guidance: Example of a new retinoid

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL (mg/kg/d)</th>
<th>BSA-CF</th>
<th>HED (mg/kg)</th>
<th>MRSD (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat</td>
<td>50</td>
<td>x 0.162</td>
<td>8.1</td>
<td>49*</td>
</tr>
<tr>
<td>dog</td>
<td>2</td>
<td>x 0.541</td>
<td>1.08</td>
<td>6.5*</td>
</tr>
</tbody>
</table>

*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 FDA Draft Guidance: Critical Assessment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 FDA Draft Guidance: Critical Assessment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)


• 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\textsubscript{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)**

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

- 1995: Dose by factor (20), Similar Drug (8), PK Guided (53), Comparative (0)
- 1999: Dose by factor (27), Similar Drug (7), PK Guided (53), Comparative (0)
- 2004: Dose by factor (20), Similar Drug (8), PK Guided (81), Comparative (0)
What will be the impact of the FDA guidance?

- Pfizer survey: retrospective analysis of 35 drugs
  Actual SD < MRSD in all cases

- Roche survey: retrospective analysis of 26 drugs
  Actual SD << MRSD (10 fold on average)

⇒ Use the comparative approach

Chan et al., CPT, P8, 2004
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...
- Factor 3 for first 2 or 3 steps, then factor 2 for subsequent 2 steps and factor 1.5 at the end

Spilker, 1991
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/m² 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
“…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\textsuperscript{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”.

\textsuperscript{2}Footnote of 19 lines highlighting the limitations of the PK-guided approach
1. FDA Draft Guidance: Summary

- Uses dose in mg/m² 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