Safeguarding public health

Novel methodologies for clinical trials - do we still need to recruit patients?

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The views expressed do not necessarily reflect the views of MHRA or CHMP

Novel methodologies include…

- Pharmacometrics
- Modelling (Pop PK, PK / PD, PBPK, PBPK/PD etc.)
- Simulation
- Adaptive designs
- Bayesian statistics

- Not particularly novel…

- Bayesian Hierarchical (shrinkage) models for e.g. interpretation of subgroup findings
- ‘Indirect’ comparisons, facilitating between trial comparisons
- Data mining / Linkage analyses / Machine learning to interrogate large (safety) datasets

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Answers through examples …

- Do we still need to recruit patients?

  1. No
  2. Fewer
  3. Same
  4. More

- Science driving regulatory requirements

- The role of the regulator

No patients

- Medicine licensed in adults
- PK and PK/PD well characterised
- Dose selection required for children
- PBPK/PD modelling on justified assumptions
- ‘Relative’ PK can inform dose selection without need to study efficacy and safety in patients

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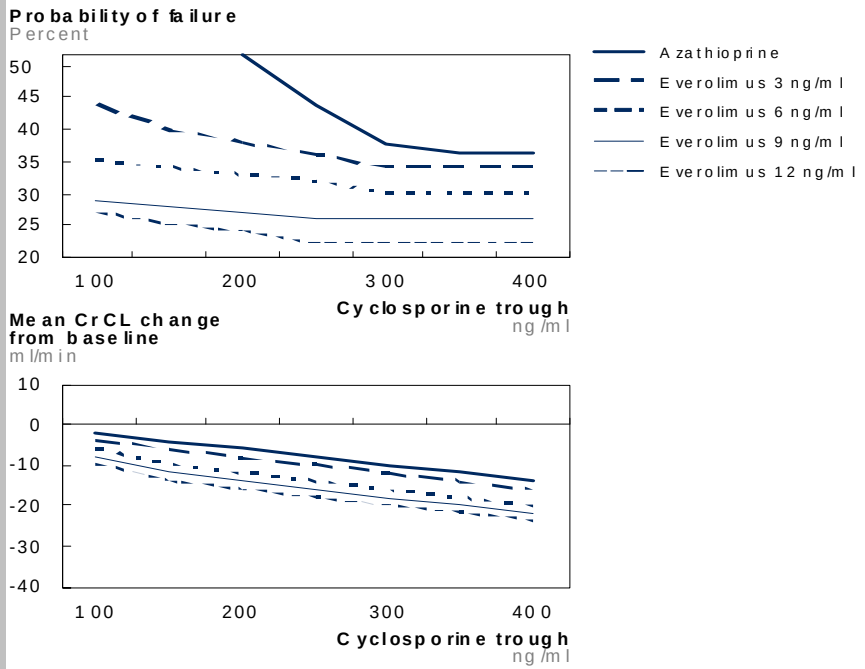
No patients

Clin Pharmacol Ther, Impact of pharmacometric reviews on new drug approval and labeling decisions--a survey of 31 new drug applications submitted between 2005 and 2006. Bhattaram VA et al copyright 2007 (year of publication)

1 PROPOSE BEST DOSES

Determining appropriate dosing for future trials



PM approach and impact

- Everolimus tablets (a prophylaxis of organ rejection following heart transplantation) needed to provide safe and effective dosing regimens that would minimize renal toxicity
- Key questions included:
  - Are the effectiveness and renal toxicity clinical outcomes related to drug exposure?
  - What is a rational dosing regimen that would maximize effectiveness (benefit) and minimize nephrotoxicity (risk)?
- Analysis conducted by 1 person for <2 months
- Simulations based on heart transplantation study to project range of outcomes of altered dosing schemes
- Determined the appropriate dosing to test in future trials

SOURCE: Reprinted by permission from Macmillan Publishers Ltd: *Clin Pharmacol Ther*, Impact of pharmacometric reviews on new drug approval and labeling decisions--a survey of 31 new drug applications submitted between 2005 and 2006. Bhattaram VA, Bonapace C, Chilukuri DM, Duan JZ, Garnett C, Gobburu JV, Jang SH, Kenna L, Lesko LJ, Madabushi R, Men Y, Powell JR, Qiu W, Ramchandani RP, Tornoe CW, Wang Y and Zheng JJ. (reference citation) 81:213-221, copyright 2007 (year of publication)

Slide 5

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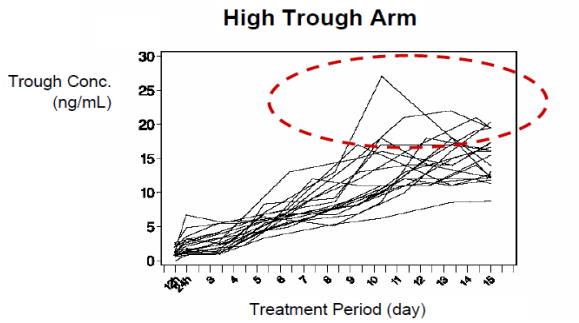
No patients

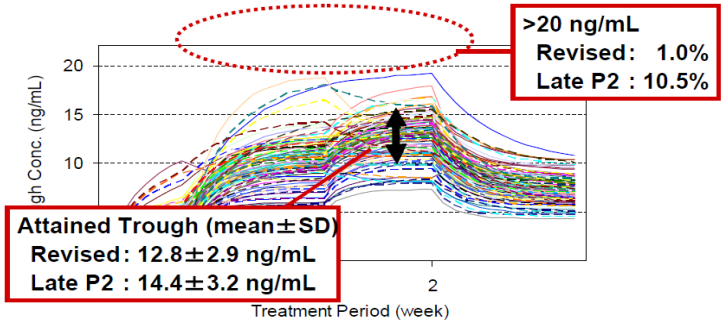
2 PROPOSE BEST DOSES

Simulating dose to justify Phase 3 design

High trough concentrations in Phase II studies



Simulated dose titration shows eliminated high trough



PM approach and impact

- Tacrolimus, a potent approved immunosuppressant, had a promising expansion as an oral therapy for ulcerative colitis (UC)
- Highly variable PK between patients and high trough concentrations in Phase II studies presented challenges to further development
- Logistic analysis of PK/response in late Phase II demonstrated trough concentration is a good predictor for response
- Simulation of dose titration based on PK/response was effective for attaining target trough concentration, demonstrating efficacy and justifying Phase III studies

SOURCE: Presented by Atsunori Kaibara (Astellas Pharma, Inc) at the "PK/PD Internal Symposium on Modeling and Simulation in Drug Development and Clinical Applications", Yonsei University Medical Center, Seoul, Korea (2006)

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No patients

9 DRUG APPROVAL

Determining dosing for drug approval

	% of subjects	
Parameter	**Model simulated**	**Observed**
Efficacy (2 consecutive serum iPTH measurements decreased by 30% from baseline)	81	87.9
Safety (2 consecutive serum calcium measurements over 11 mg/dL; hypercalcemia)	1.5	1.6

PM approach and impact

- ? Sponsor conducted 3 trials in chronic kidney disease Stage 5 patients with hyperparathyroidism for an oral paricalcitol drug
- ? Used a validated exposure-response model to define new dosing regimen that reduces the rate of hypercalcemia while maintaining acceptable therapeutic response
- ? Results of trial confirmed predicted results from exposure-response modeling and simulations, maintaining a pre-defined efficacy rate of over 80% and limiting observed rate of hypercalcemia
- ? Drug approved by FDA without need for further clinical trials in patients

SOURCE: Zemplar Capsules United States Package Information, June 2009. Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021606s004lbl.pdf, 18March 2010.

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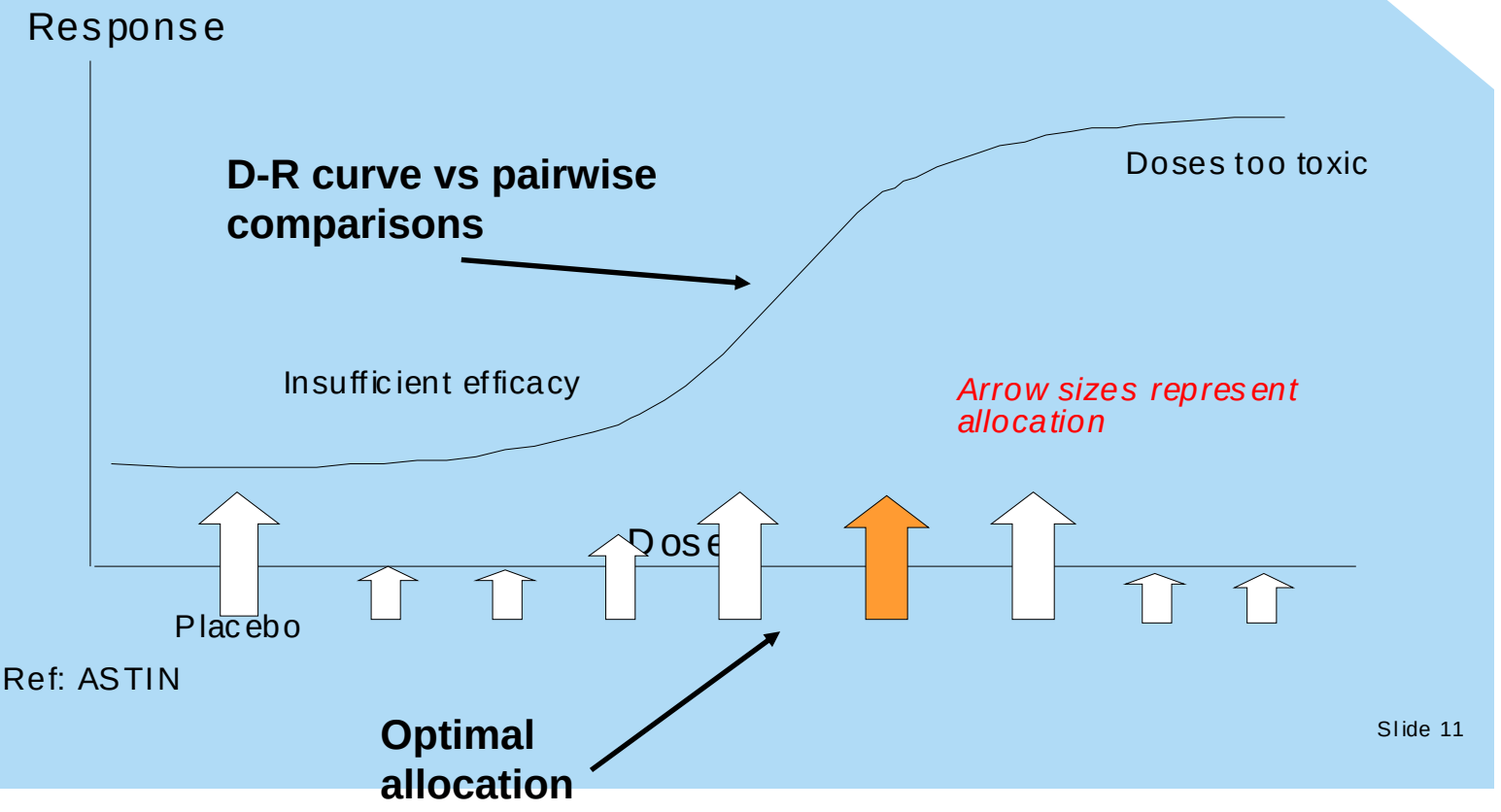
Fewer patients

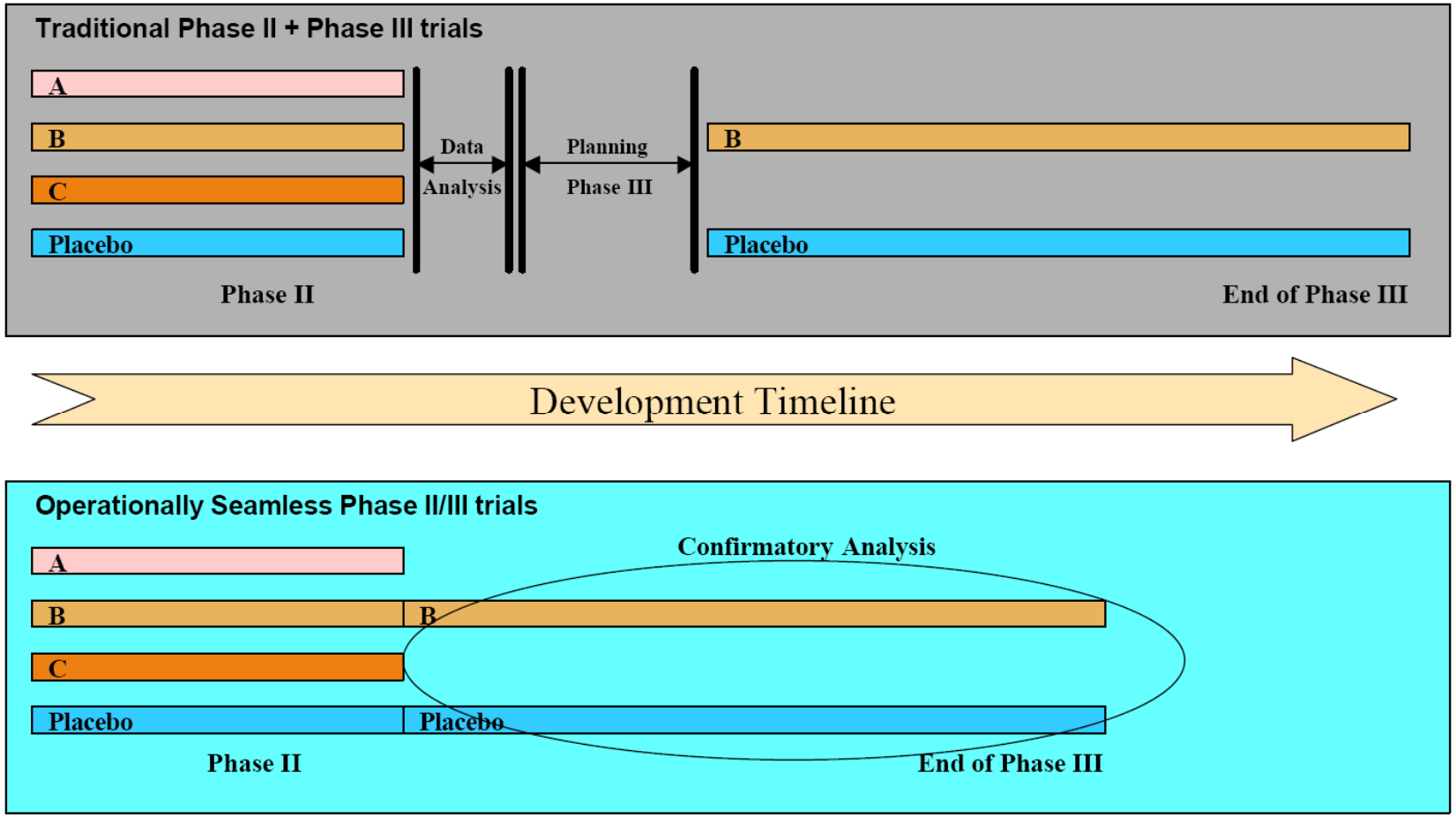
INNOVATE 'Flexible' dose-finding



Ref: ASTIN

Slide 11

Fewer patients



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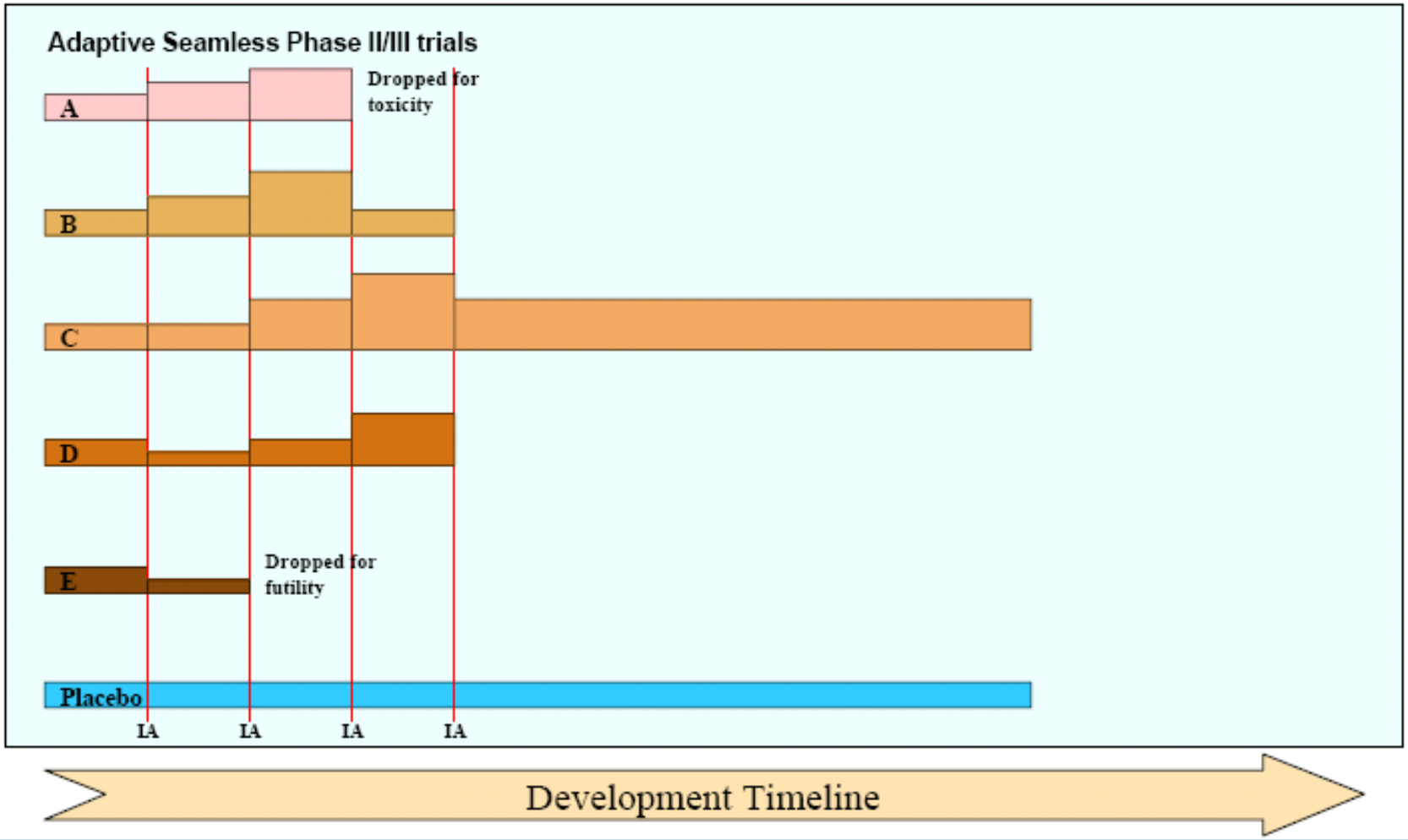
Fewer patients



Slide 10

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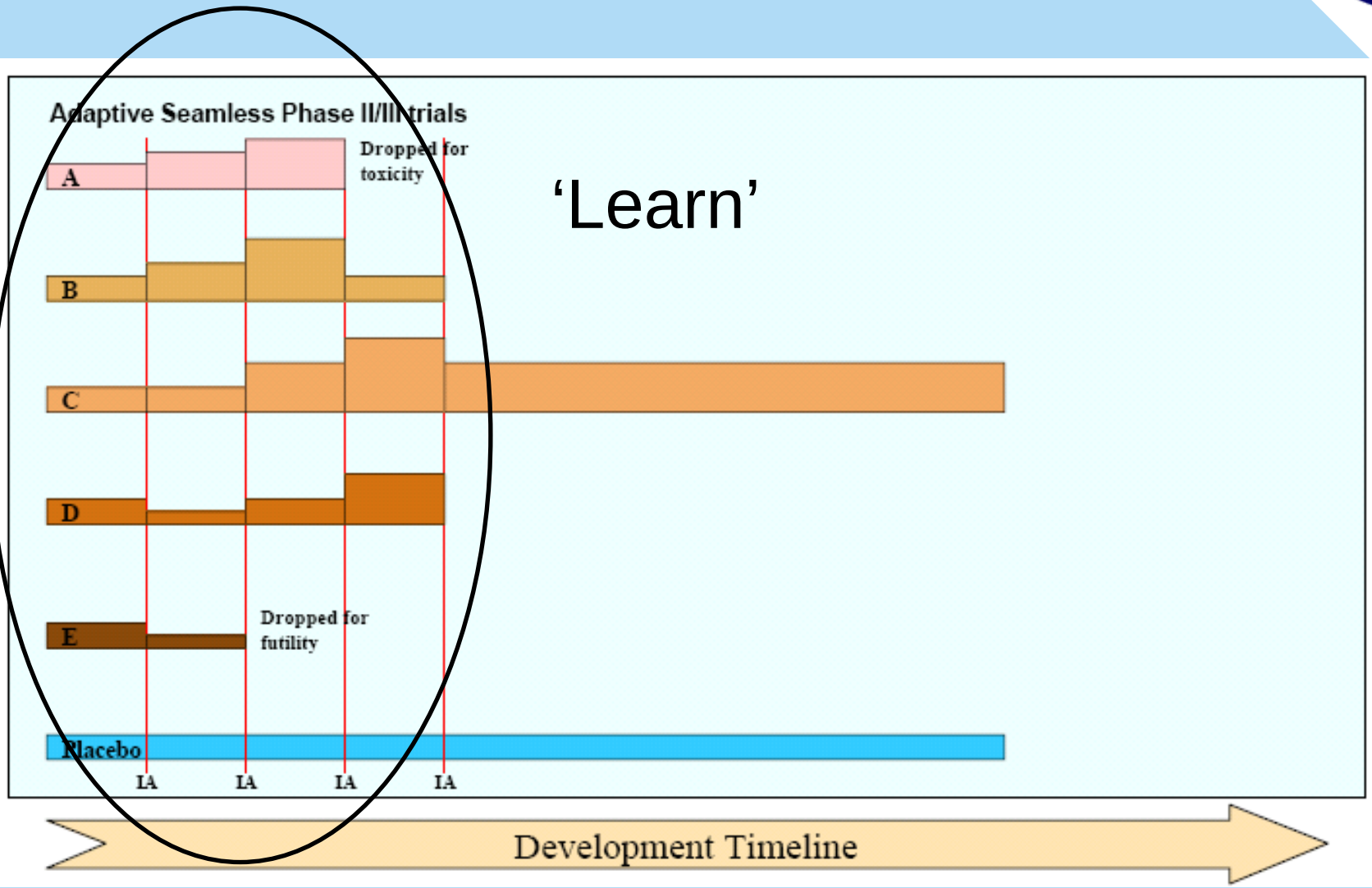
Fewer patients



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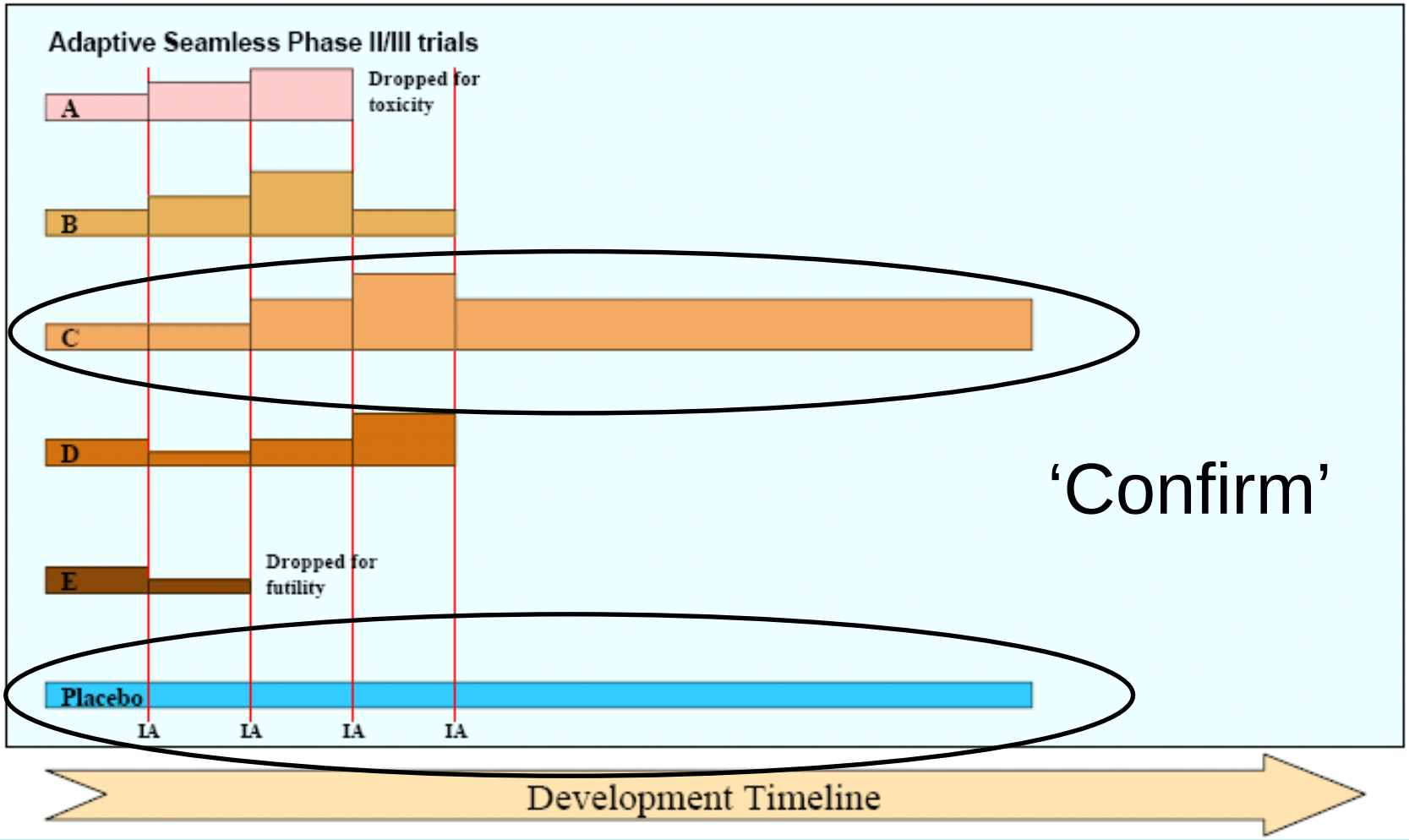
Fewer patients



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Fewer patients - caution

- Clinical trial ‘toolkit’

- Hurdles:
  - Scientific
  - Logistical
  - Corporate

- Endorsed, indeed proposed by SAWP, accepted by CHMP

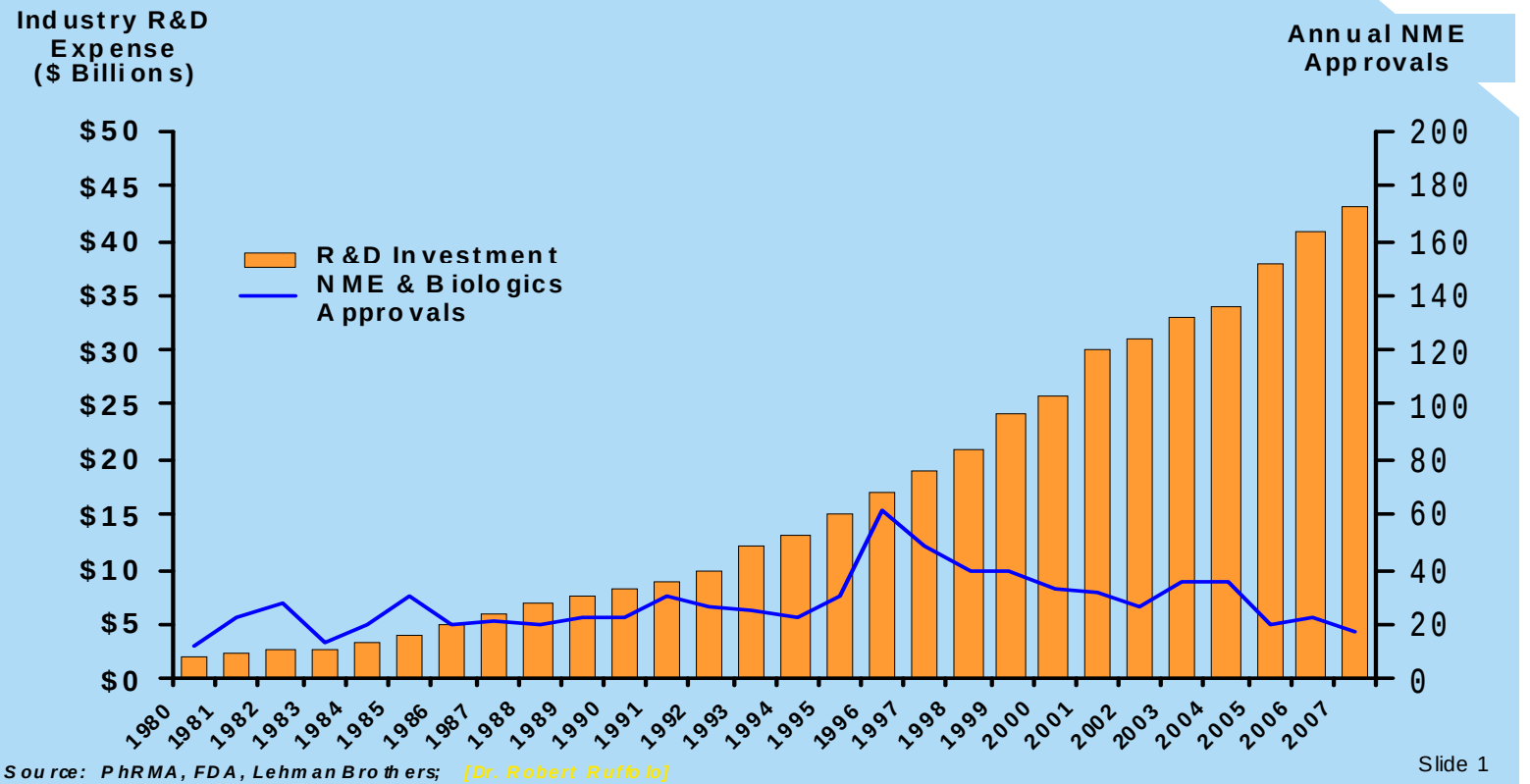
Same – role of clinical trial simulations

- Simulation-based evaluations to guide modern protocol design
  - essential to understand operating characteristics and for scenario planning
  - compare different design options
  - fine-tune the design parameters

- Limitations:
  - lack of advanced clinical trial simulators
  - need for case-by-case implementations leading to problems of resources, validation / reproducibility, ...
  - skills / experience in how to communicate outputs

More patients

Drug development needs to be made more efficient



Source: PhRMA, FDA, Lehman Brothers; [Dr. Robert Ruffolo]

Slide 1

More patients

- High PIII failure rate because of:
  - Inadequate efficacy - doesn't beat placebo, not competitive in marketplace
  - Emerging toxicity
  - Inadequate B-R

• Lots of PII questions – demonstrate activity, quantify dose-response, what dose, will we beat placebo, what effect size, what toxicity profile, how do efficacy and safety change in broader patient population, …? Ultimately go / no-go decision.

• PII trials are too frequently not designed to address these questions with adequate precision. Thus initiating PIII is at best an informed gamble. Can sponsors be better informed?

More patients

- Hypothesis 1: Exploratory development programmes are shrinking and are not fit for purpose. Increasing exploratory development ('learn') will reduce failure rate in confirmatory trials.

- Hypothesis 2: Information needs to be collected efficiently. Novel clinical trial designs add to the 'toolkit' and will bring benefits in some indications / development programmes. There is the possibility for adverse effects of novel approaches in other experimental situations. There are many improvements that could be made to the current paradigm without being 'novel'.

1. With what certainty (how much data) do we wish to address each question of interest?
2. How can we collect the data efficiently?

Focus of current discussion seems to be only on Q2

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More patients … fewer ‘wasted’ patients

• Simulation work has shown that ‘optimal’ dose is rarely identified by a standard phase II trial.

- *Innovative Approaches for Designing and Analyzing Adaptive Dose-Ranging Trials Bjorn Bornkamp et al, Journal of Biopharmaceutical Statistics, Volume 17, Issue 6 November 2007 , pages 965 – 995*

- *Pinheiro et al. (2010) Stat Biopharm Res (Special Issue; to appear)*

• Does Phase II need to be even more extensive than accepted standards to reduce PIII failure rate?

Science driving regulatory requirements

- Assessing CV risk in Type II diabetes mellitus

- CPMP/EWP/1080/00 Rev. 1 Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus

- Advice on patient population, endpoints, analysis but recognition that decisions must depend on the particular situation

Science driving regulatory requirements

“At the time of the MAA, the overall results of this safety program should be submitted and discussed in terms of internal and external validity and clinical justification of the safety outcome. Acceptability of the data presented will be decided based on its overall quality, the point and interval estimates obtained for the calculation of specific risks, including cardiovascular risk compared to controls, and the reliability of these estimations. A summary of what is known about CV risk should be proposed for the SPC.”

“Indications of increased risk of certain adverse events or unacceptable lack of precision are an important concern and may trigger the request for additional specific CV outcome trials to exclude an unacceptable increase in CV risk associated with the new agent before granting of MA.”

The role of the regulator

- Driven by science and open to change
- Share experiences, aim to help optimise (not minimise) through ‘Scientific’ Advice
- Hurdles for licensing and post-licensing should be those that are necessary to demonstrate Q, S, E and favourable benefit-risk
- ‘Front-load’ development: pharmacology, pharmacometrics, CT simulation, comprehensive but efficient ‘learning’ phase
- Main challenge is availability of expertise and software

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