Safeguarding public health

Regulatory scene setting - benefits and risks of seamless Phase II / III trials

Rob Hemmings,
Statistics Unit Manager
MHRA, London

December 2007

Definitions …

… we are concerned with inferentially seamless adaptive trials

Seamless design

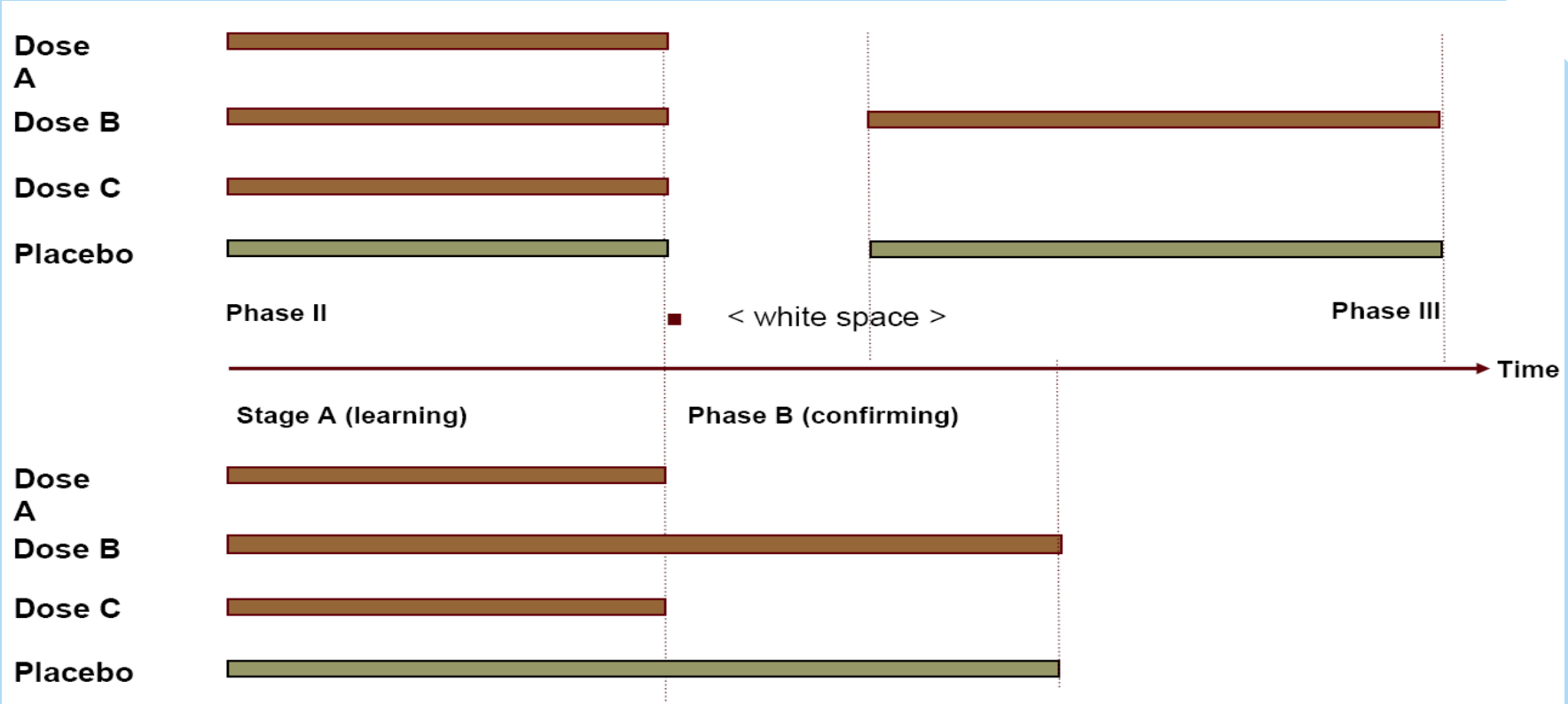
- A clinical trial design which combines into a single trial objectives which are traditionally addressed in separate trials

Adaptive Seamless design

- A seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially* seamless)

- Source: Maca, PhRMA, FDA meeting

Adaptive seamless designs



-Source: Maca, PhRMA, FDA meeting

Objectives of Phase II / III trials

- Dose selection (and) / or
- Population selection

AND

- Confirmatory evidence of efficacy

- Two issues
  - How much information is required?
  - How to collect that information?
  - At present we are predominately discussing ‘how to’ obtain sufficient evidence for licensing, not requirements for licensing per se.

Claimed Advantages

- Resource savings …
  - Time
  - Patients (i.e. efficiency)
  - Money
- Removes ‘White Space’ …
- Reduce development time …
  - Medicines to market / to patients sooner …
  - Increase value of drug to company
- May improve dose selection through encouraging larger and longer dose-finding trials.
- … without loss in information

Issues

- Can the confirmatory trial be precisely planned prior to Phase II?

- Will timelines be extended by more complex planning / logistics / regulatory interactions?

- Is adaptation logistically possible (follow-up time to endpoint relative to recruitment / duration of trial)

- Who determines the adaptations?

- Methodological challenges e.g. Type I error control

- How does the totality of evidence comparable?

- All building blocks in place – e.g. final drug formulation?

- What proportion of information to be collected in Stage I?

Regulatory questions / concerns

- Justify rationale …
  - Discuss why sufficient evidence is expected from the phase II / phase III combination trial compared to the strategy with another phase II trial that is followed by a separate phase III clinical trial.
  - Justify conduct based on benefit to regulatory decision-making, or science in general (in addition to time, cost etc. which are all acknowledged).
  - Justify that the evidence base for regulatory decision making is not diminished.

- Lose independent replication of evidence

- Fewer patients …
  - This may be important, not least for safety
  - One argument is that safety information may actually be increased as the 'Phase II' patients are followed for longer
  - Is this simply a flaw with present Phase II designs?
  - i.e. not necessarily 'same questions answered with greater efficiency'

Regulatory questions / concerns

- Trial integrity

- Methodological considerations, including heterogeneity.

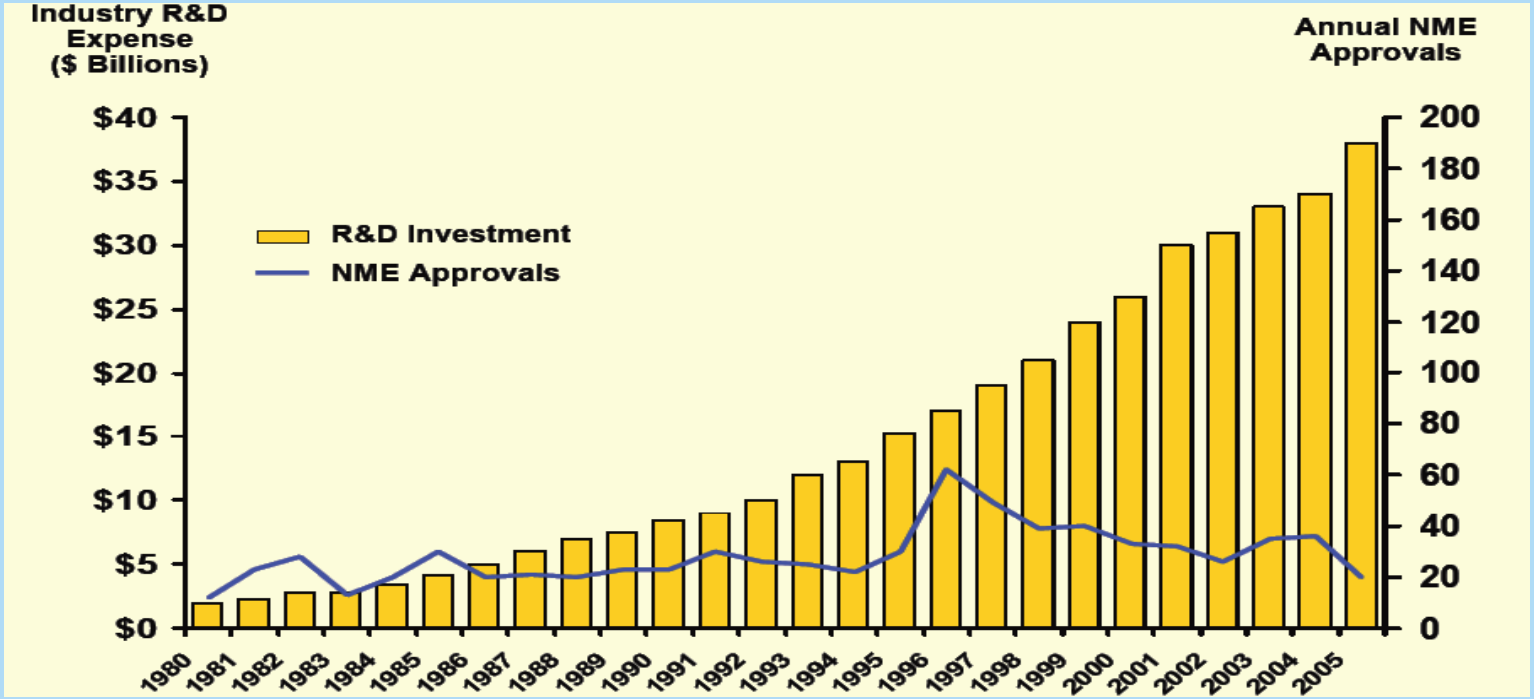
- Confirmatory evidence must relate to a particular treatment recommendation

- Can a decision on e.g. dose be taken instantly by a select few? Does all information need to be available?

- Loss of thinking / consultation time ('white space')
  - Do you really do nothing in the gap between trial phases?
  - Is this simply a flaw with present development programmes?

- More **risks**

Time to take more risks, more quickly or time for improved decision-making?



-Source: PhRMA, FDA, Lehman Brothers

- *"If we are allowed to use the trial as pivotal evidence, we'll do more extensive dose finding"*
  - Who's benefit is proper dose-finding?
  - Dose selection is predominately a company risk

On the positive side…

- Methodologically sound, Phase II / III seamless trials can be accepted.

- Given the potential risks, designs more likely to be endorsed when rationale is persuasive.

- In particular when the basis for regulatory decision-making will be improved.
  - e.g. improved use of scarce resources e.g. ‘orphan’ populations
  - e.g. improved information on dose-response

- SAWP have even suggested this strategy …

Phase II / III as a single pivotal trial

- Common proposal but discouraged

- Accepted regulatory standard is a wealth of Phase II data already available for a single pivotal study to be accepted.

- i.e. totality of evidence is changing.

- There are exceptions …
  - where information for decision making can be increased compared to conducting separate studies - e.g. orphan indications.
  - everyone thinks they are the exception!

Concluding remarks

- Common strategy and potentially acceptable
- Really want to understand benefits in terms of information, not only cost and speed
- Level of **risk** is increased
- Many proposals to date considered a sub-optimal way to conduct development
- Improving ‘standard’ development programmes without adaptive trials should be considered.

“We thought so hard about whether we could, we didn’t stop to think about whether we should”!