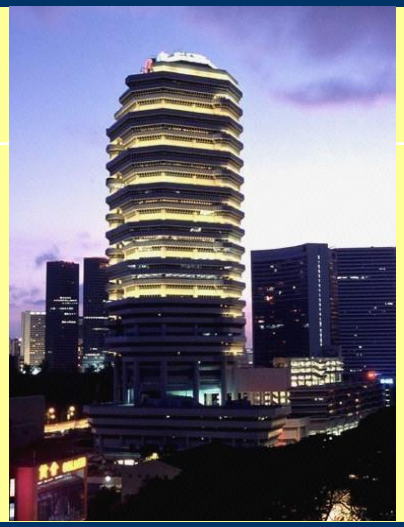
Boehringer Ingelheim



Boehringer Ingelheim Singapore Pte Ltd

Global Strategies of Early Clinical Development

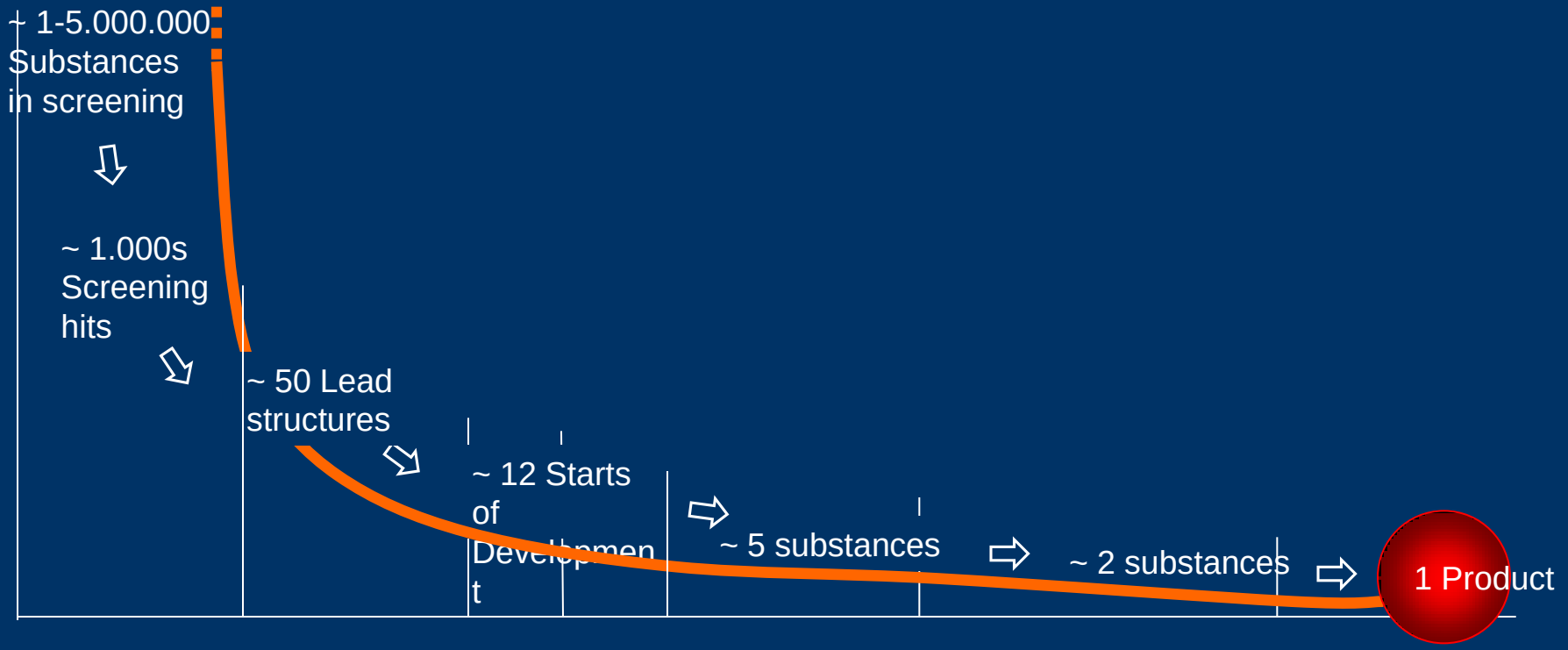
Axel Riedel, Clinical Operations Asia, Middle East & North Africa

Congratulations to the Opening of your new CTC Facility

“恭喜”

The effort to find a drug...

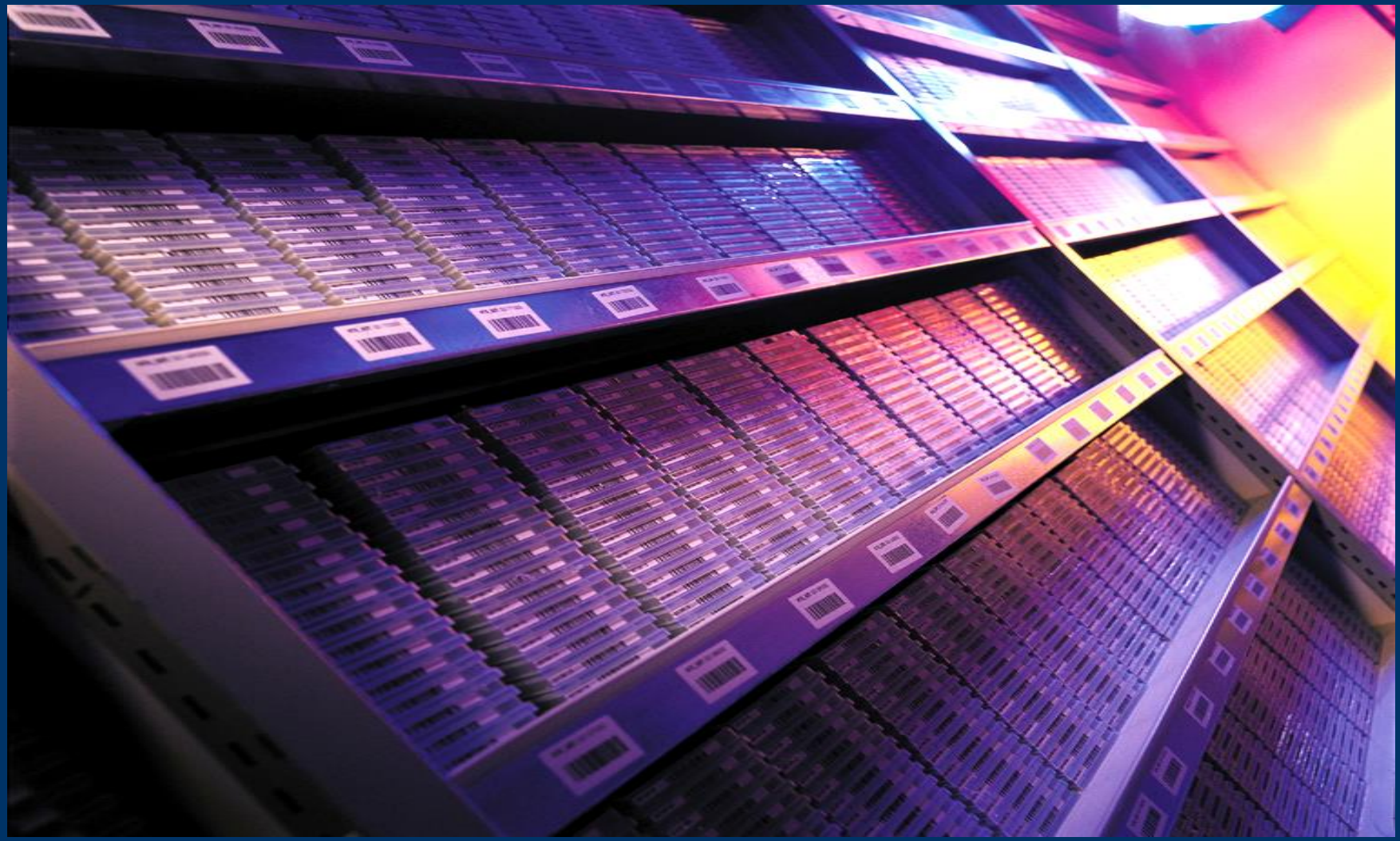
ABCD



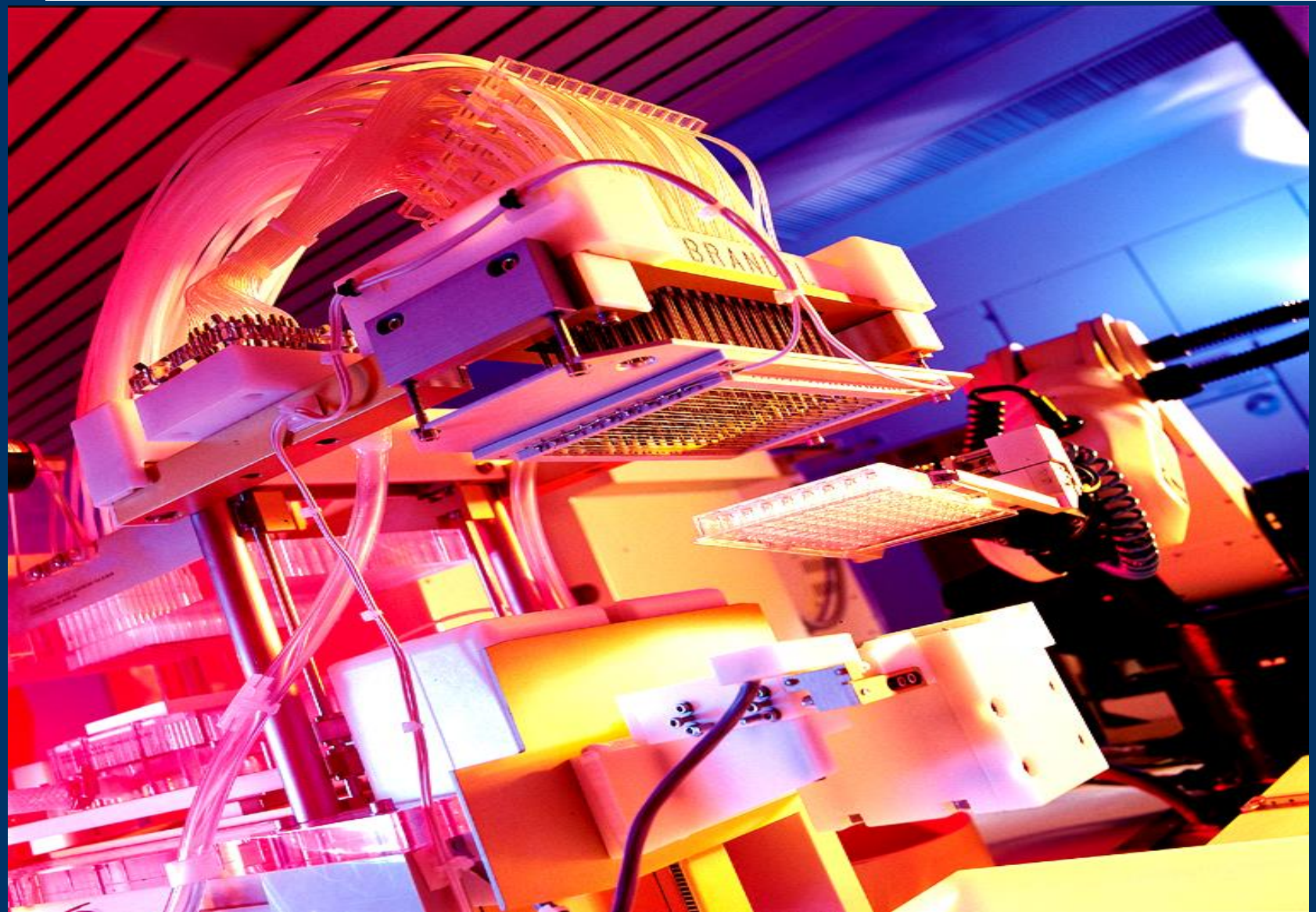
* incl. Costs of non-clinical Development

How to get the huge number of drug candidates ?

ABCD



How to do the selection ?



Cost of Drug Development (1)

ABCD

Table 2. R&D by Function, PhRMA Member Companies, 2009

Function	Dollars (xMM)	Share of Total	Probability of FDA Approval
Prehuman/preclinical	$11,717.4	28.6%	8%
Phase I	$ 3,752.9	9.2%	21%
Phase II	$ 7,123.7	17.4%	28%
Phase III	**$16,300.1**	**39.8%**	**58%**
Approval	$ 2,046.9	5.0%	90%
Total R&D up to FDA approval	**$40,941.0**	**100.0%**	
Phase IV	$ 5,302.7	13.0%	
Uncategorized	$ 197.8	0.5%	

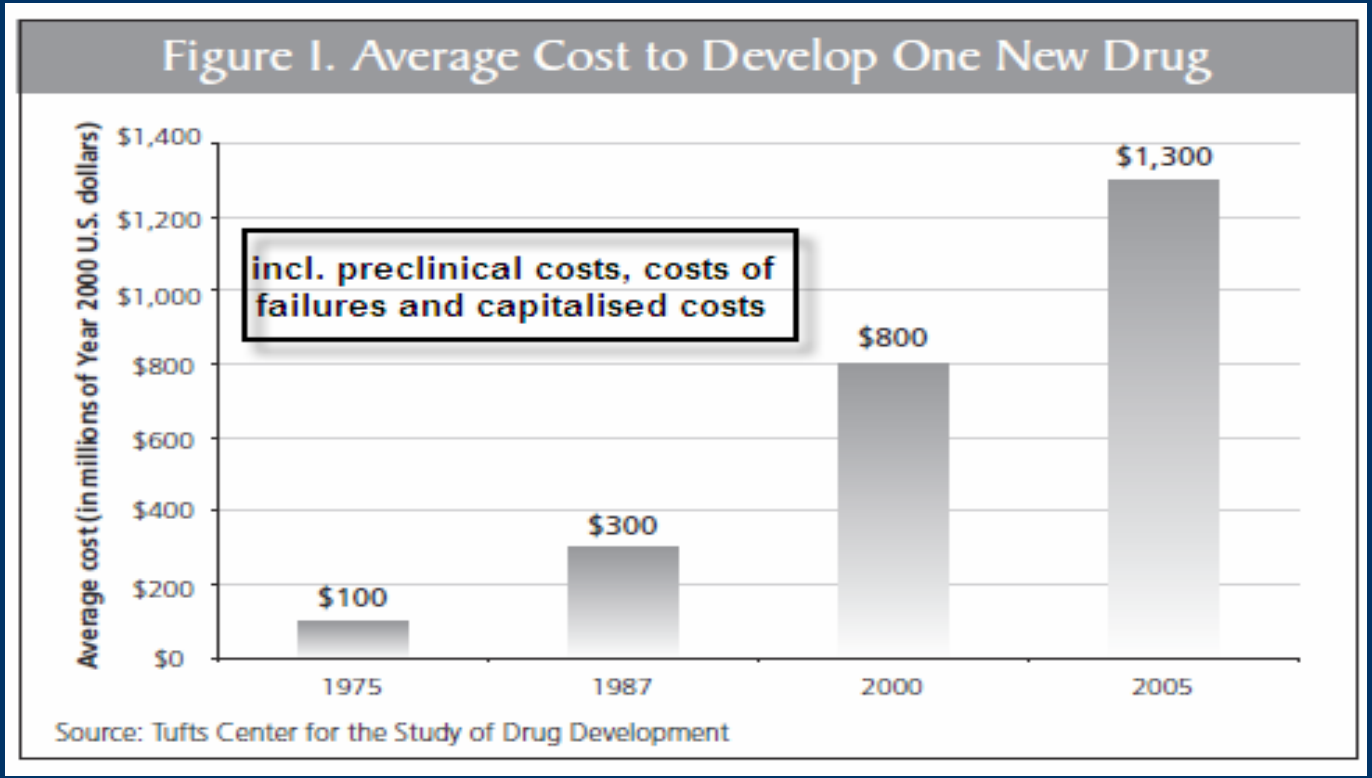
Source: PhRMA Annual Member Survey, 2011; DiMasi et al., J Health Econ 22(2003):151–85

But >= 90% Phase III costs if confined to approved drugs

Avik S. A. Roy, Project FDA Report, Manhattan Institute for Policy Research, 2012

Costs of Drug Development (2)

ABCD



Avik S. A. Roy, Project FDA Report, Manhattan Institute for Policy Research, 2012

- Only 3 out of 10 marketed drugs recover investment made in them (Kola und Landis, 2004)
- No. of successful registrations had been declining over many years

How to deal with this dilemma.....

....apply new strategies in Early Clinical Development with the aim to :

- decide on most promising drug candidates earlier
- to terminate development of less promising drug candidates
- to select best indication and patient population early
- to speed up the development
- to reduce the attrition in later phases

What does this mean for Phase I

-Do critical phase I studies with go/no go decision potential early
(selected DDI studies, TQT study...)

-Include proof-of-concept assessments (e.g. biomarkers)

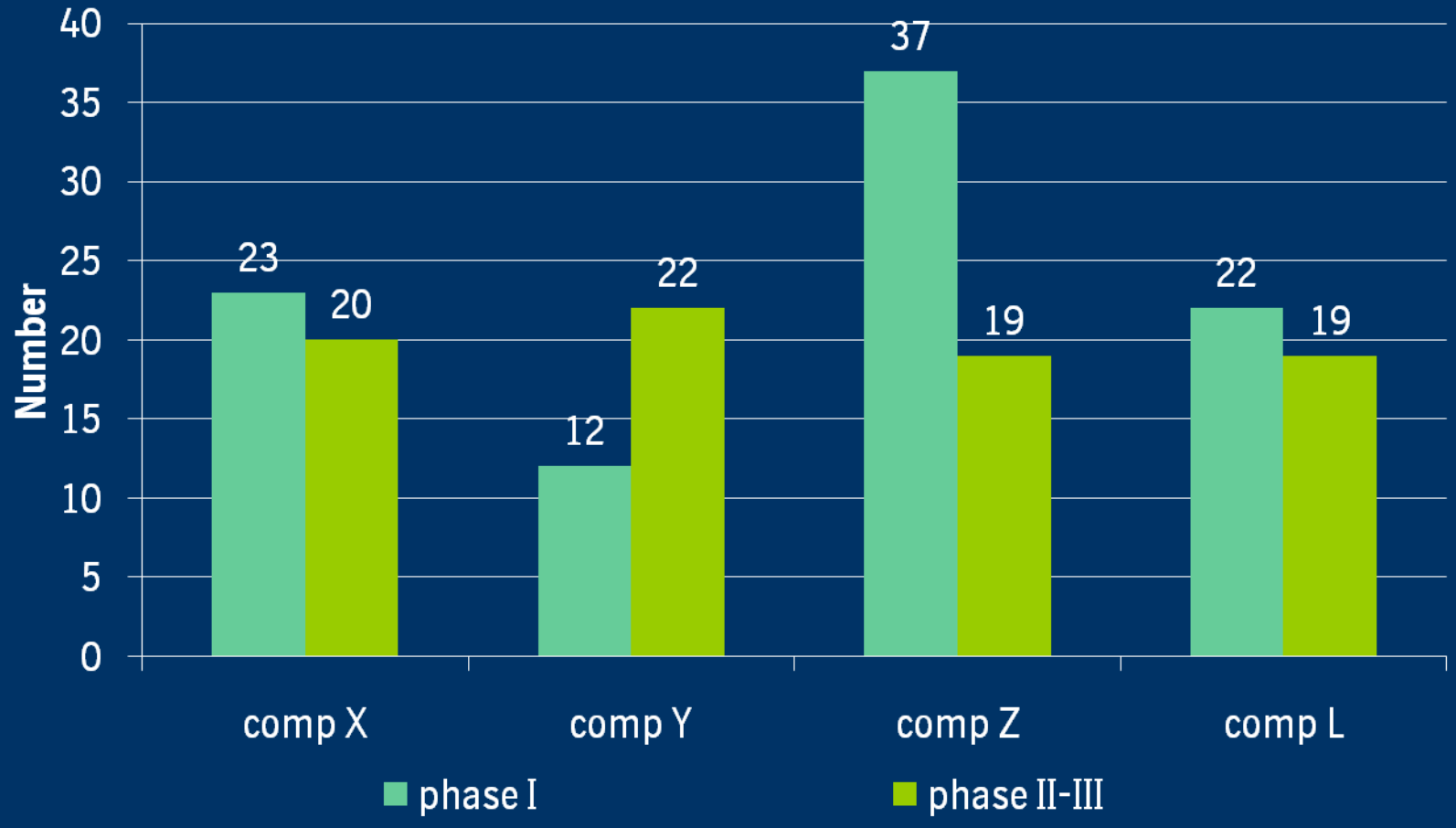
-Consider inclusion of target population in phase I, either at MRD stage or do Phase I c

-Integrate comparison of formulations and food effect exploration in SRD study

-Do interim PK/PD in SRD and prepare MRD protocol in parallel to SRD study execution
(Combined SRD/MRD ?)

Number of Studies for Registration – Examples

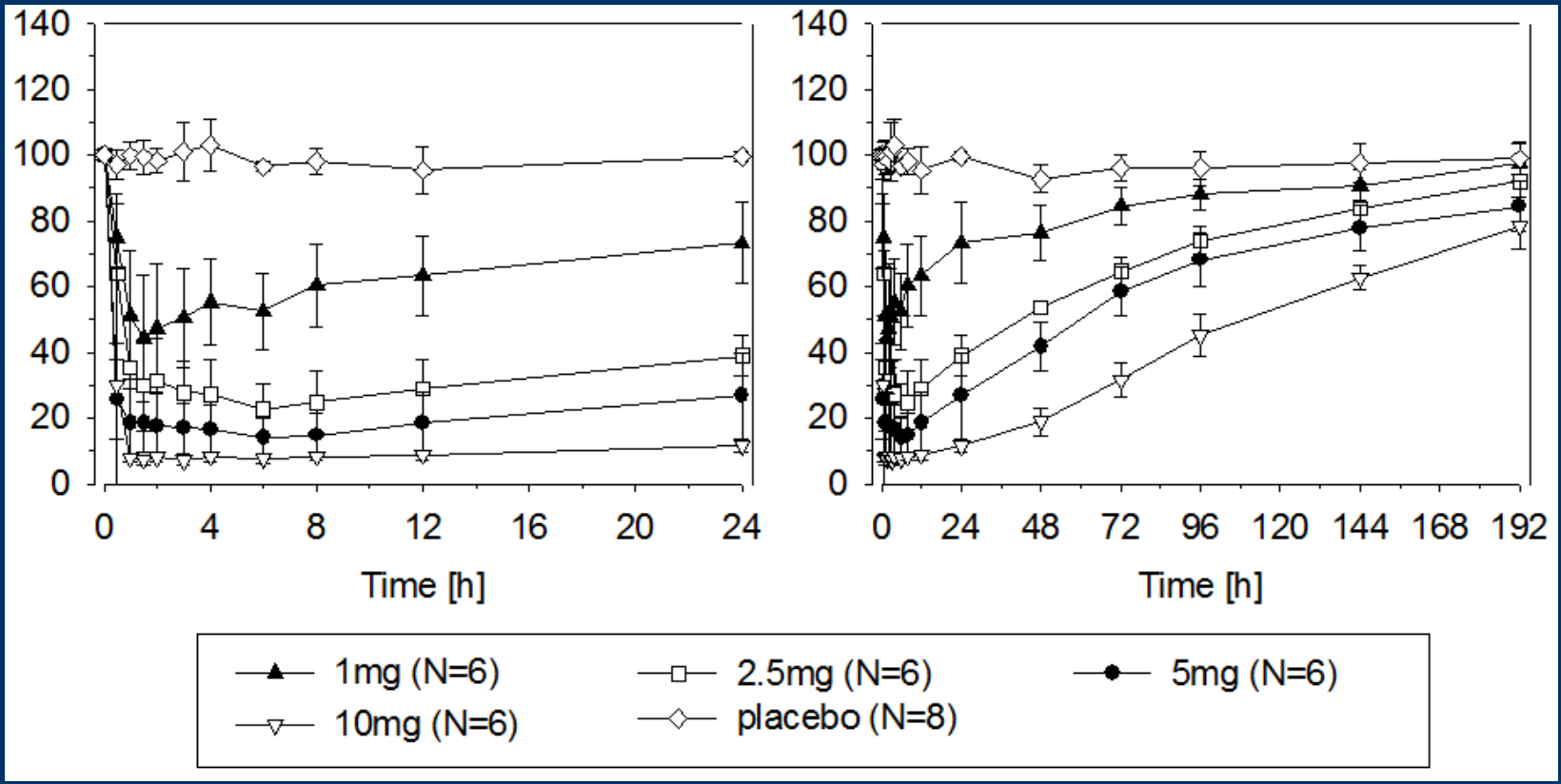
ABCD



Phase I Lab Biomarker (Example)

ABCD

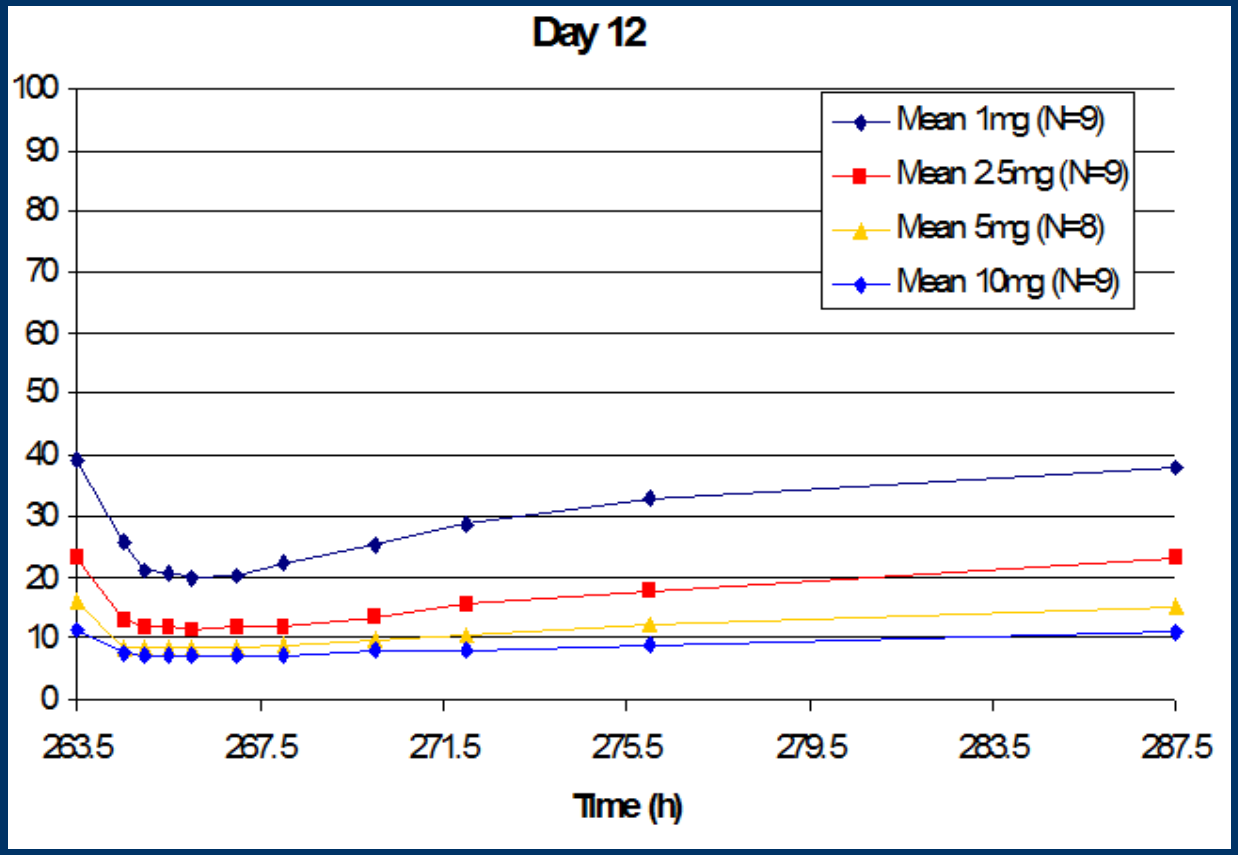
Information about potentially therapeutic dose range can already be obtained from FIM / single dose data: goal 80% activity inhibition



Phase I Lab Biomarker (Example)

ABCD

From single to multiple dose: goal 80% activity inhibition



Phase I PD Biomarker -Exercise Testing (Example)

ABCD

- To test PD effects of a bradycardic drug
- Test drug po once daily for 14 days @ 5 doses
- Metoprolol 190 mg (active control)
- Placebo controlled (double blind)
- Screening: for each subject individual workload (Watt) and duration of exercise (1 to 3 min) required to reach pre-specified target heart rate (+/- 10 bpm)

What does this mean for Phase II a

-Combine Proof-of-Concept and Dose-Finding

-Do a thorough Dose-Finding reducing the effort in phase III

-Explore more than one potential indication and patient population in parallel

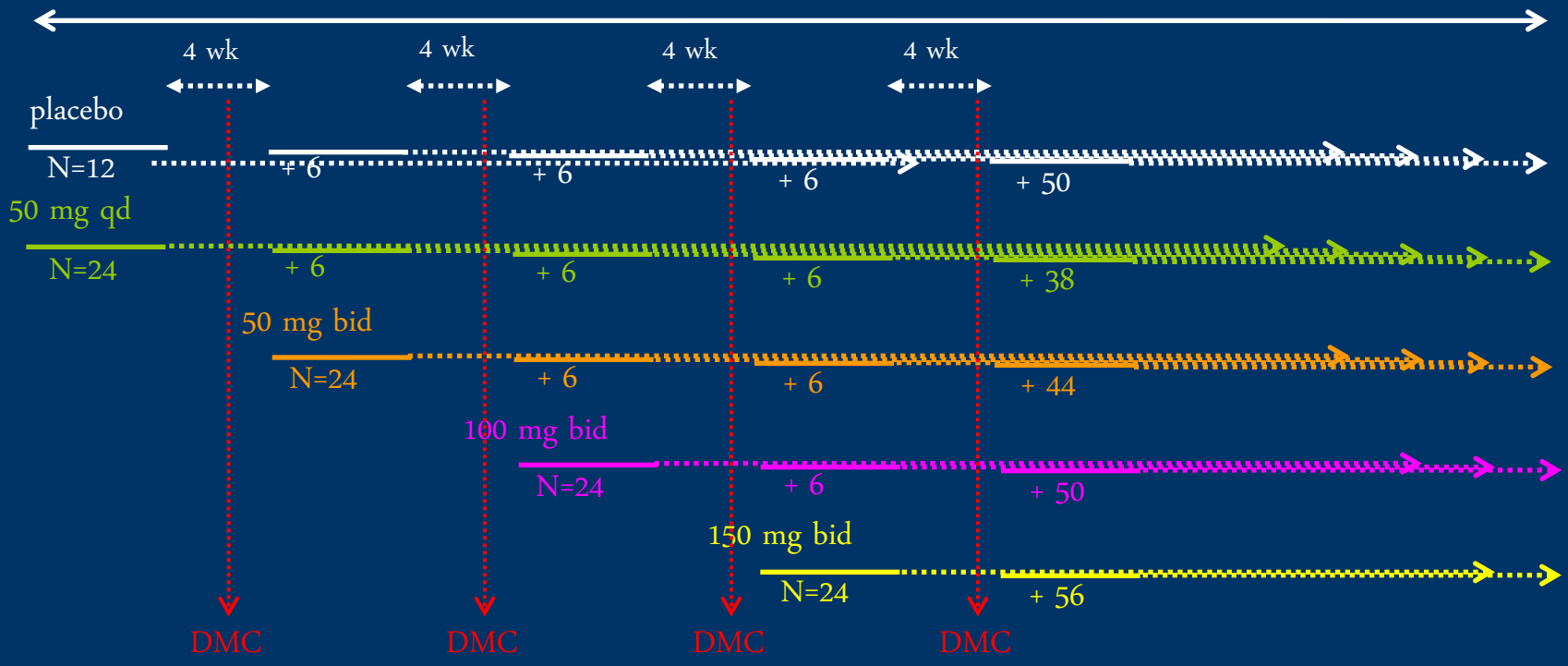
-Consider the inclusion of a comparator early as benchmark

-Use innovative study designs that save time and cost and provide as much information as needed
(see some examples)

Phase II design with dose escalation scheme....

ABCD

XXX in severe chronic pulmonary indication



-cumulative design- all treatments continue

-DMC decision based on AEs and key efficacy parameter

Factorial Design X+Y

16 Treatment Cells:

	Placebo	X-Compound 2.5 mg	X-Compound 5 mg	X-Compound 10 mg
Placebo	40	40	120	120
Y-Compound 20 mg	40	40	40	
Y-Compound 40 mg	120	40	120	120
Y-Compound 80 mg	120	40	120	120

Cells of Interest

Evaluation of data by "Surface Analysis"

Many Thanks