
The Management of Risk in Pharmaceutical R&D

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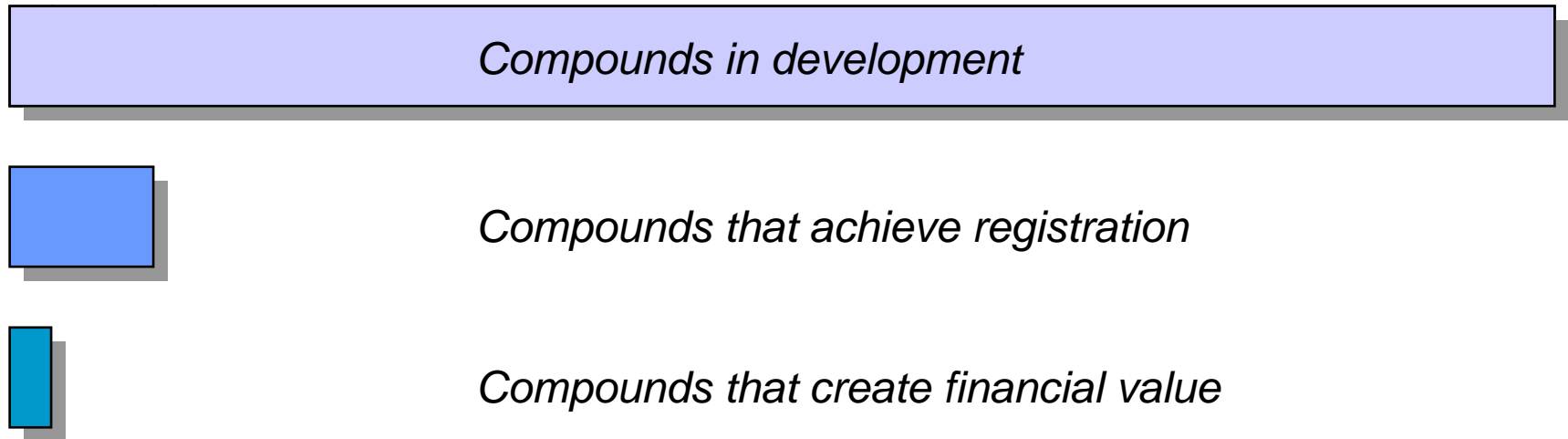
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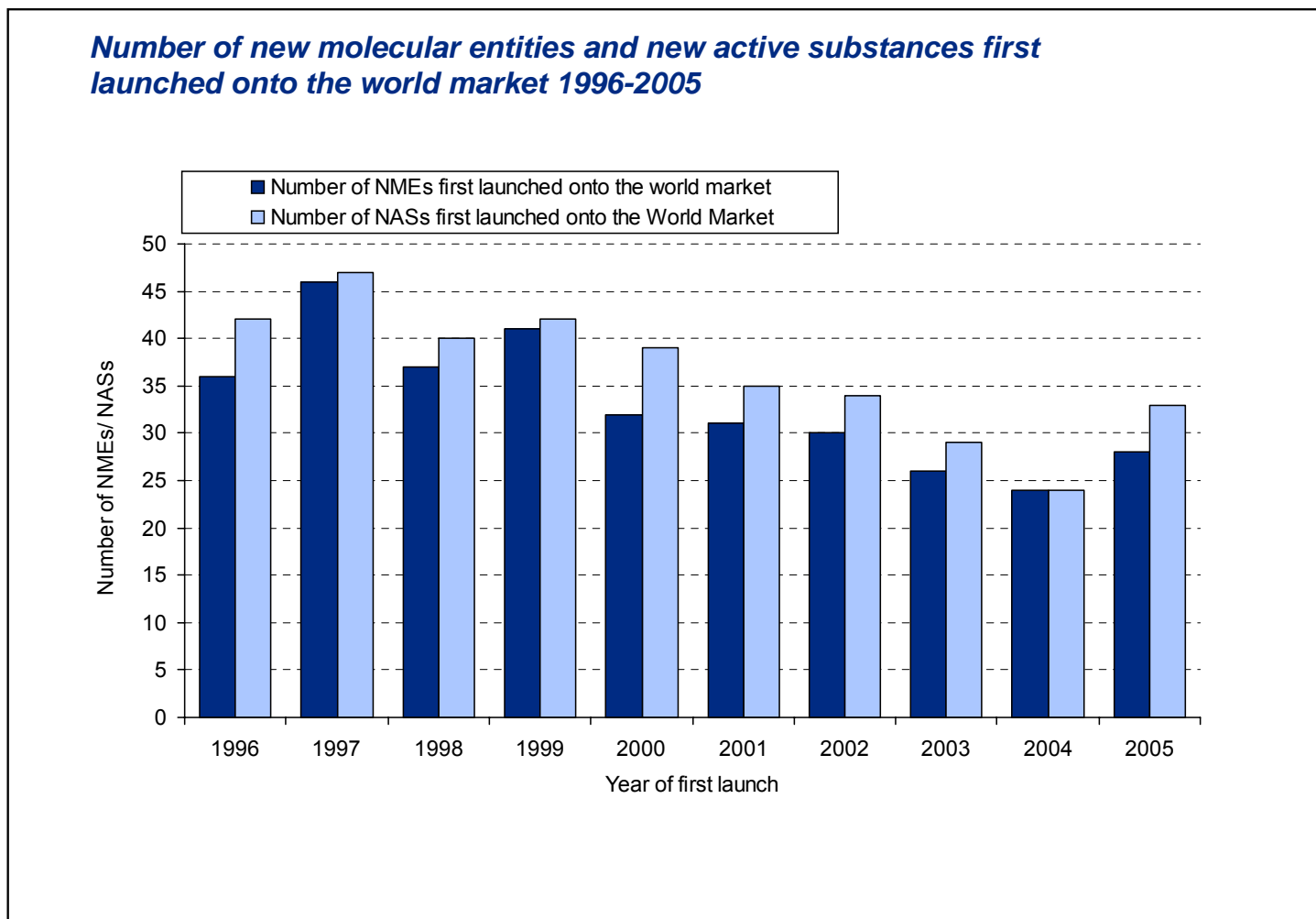
The R&D success ratio in the pharmaceutical industry is low



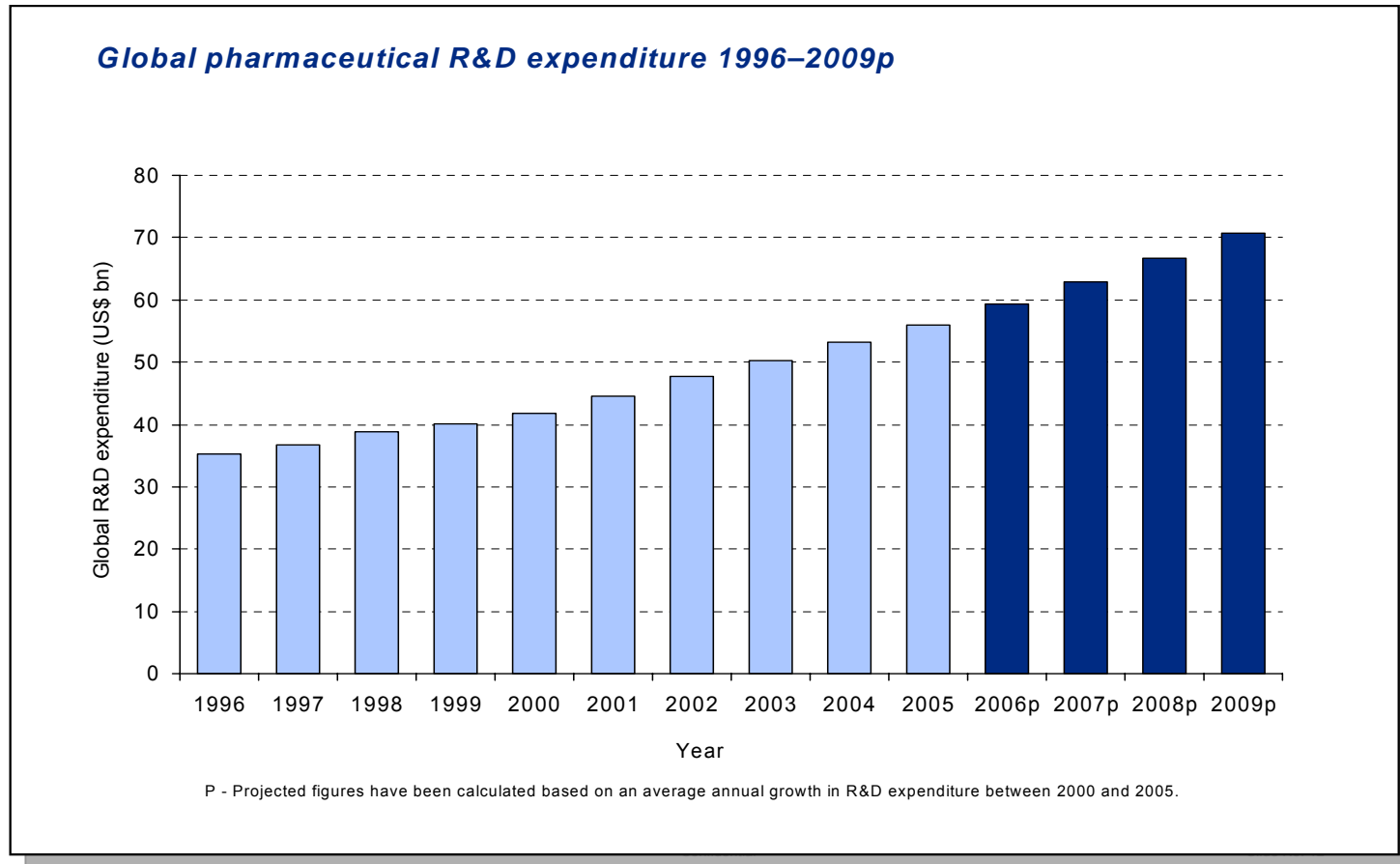
SCRIP, 1997 (referring to an analysis performed by McKinsey)



R&D productivity is declining, despite an increase in R&D expenditures



Global pharmaceutical R&D expenditure

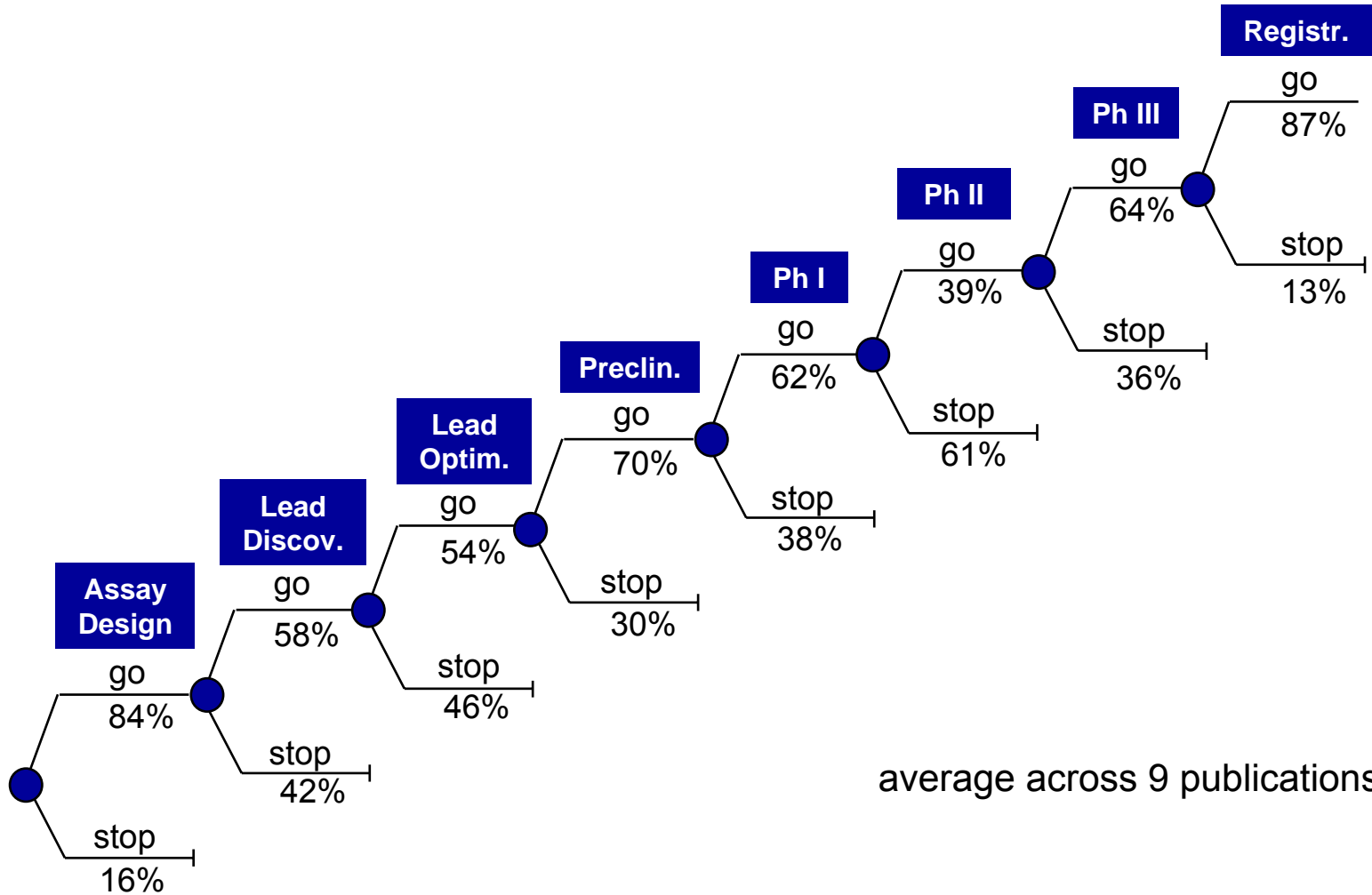


Source: CMR International 2006

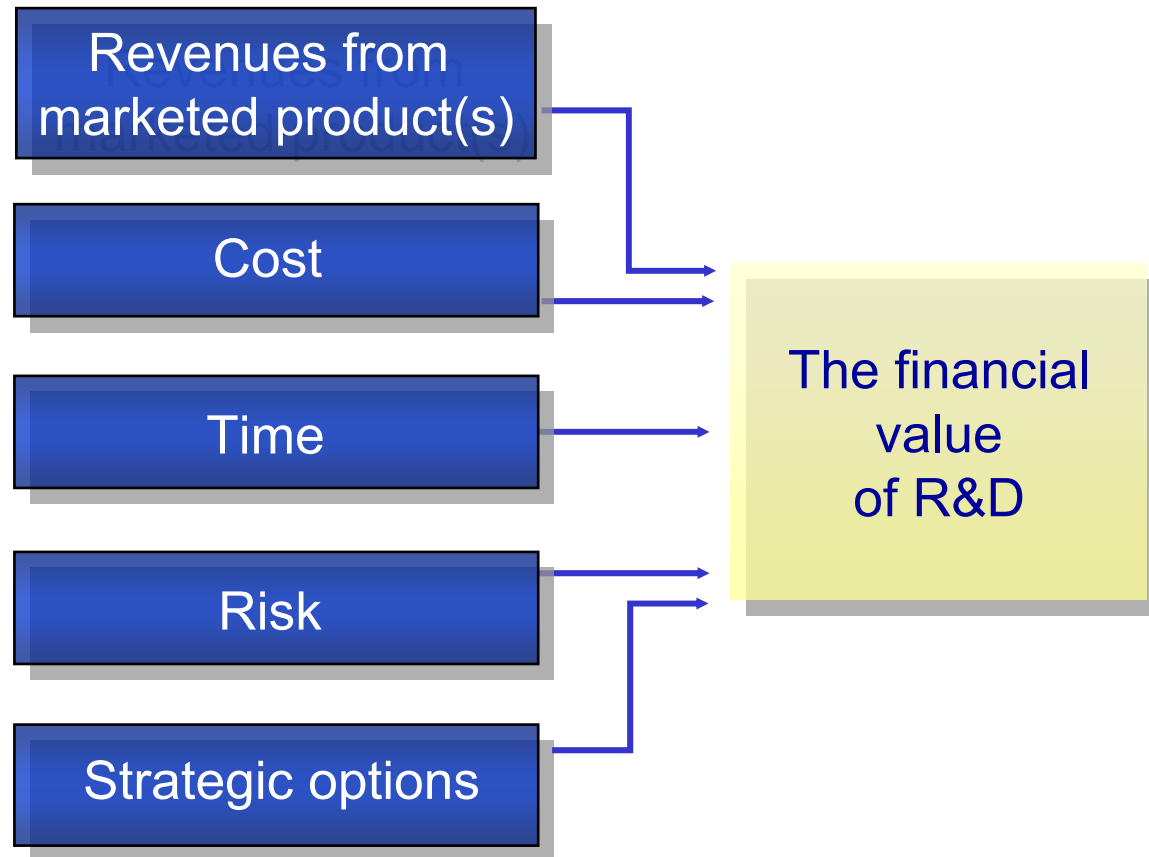
Global R&D expenditures have been – and still are – constantly rising.



Published average success rates (observations in 1995-2005)



The five determinants of value



R&D must be both efficient and effective

Efficiency

'Do the right things'

STRATEGY

Focus on
value creation
and sustained
growth

Strategic perspective
towards risk management

Portfolio Management
Project Management

Successful
Product
Development

Effectiveness

'Do things right'

PROCESS / OPERATIONS

Focus on high
quality and timely
development

Operative perspective
towards risk management

Project Management
Line Functions



Risk management perspectives

Strategic Perspective

Risk comprises events that may result in a significant decrease of project value or to a termination of development

e.g.,

- Minimum/target product profile not commercially viable
- Technical development failure
- Marketing failure
- Significant delay of launch (≥ 6 mths.)
- Significant increase of cost (30% above budget)
- Misalignment between development strategy and TPP
- Misalignment between marketing strategy and TPP
- Unfavorable interactions between multiple therapeutic indications (both in development and in marketing)
- Risks associated with licensing

Operative Perspective

Risk comprises events that may result in an unfavorable deviation from the development plan

e.g.,

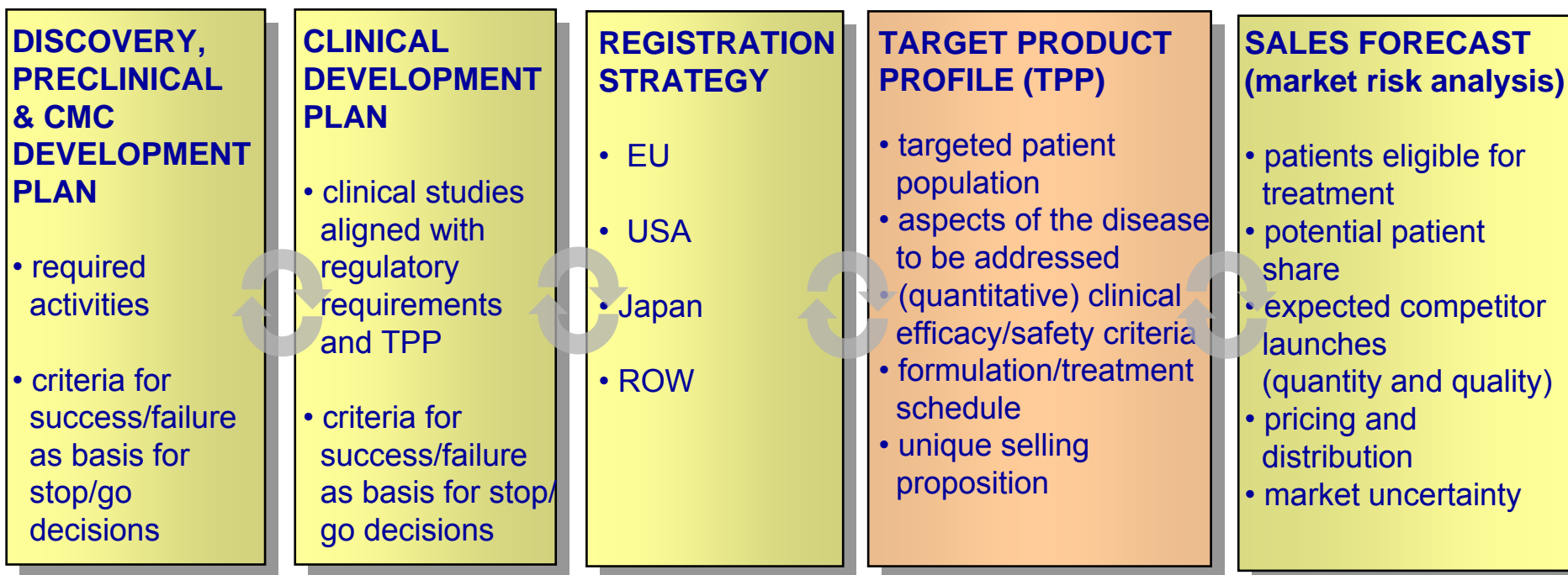
- Drug safety issues
- Regulatory issues
- Issues related to the conduct of clinical trials
- Issues related to the management of cooperation partners/CROs
- Problems of CMC development and production
- Delay of individual activities on the critical path that require attention not to become significant
- Failure of cross-functional cooperation

- Issues that are usually not related to stop/go decisions



Target product profile (TPP)

The TPP defines the scope and deliverables of a project (aligned with marketing objectives and corporate goals):



The TPP reflects the required development activities, whereas the minimum product profile (TPP) reflects criteria for STOP/GO decisions.



Augmented NPV ('risk-adjusted', 'expected' NPV)

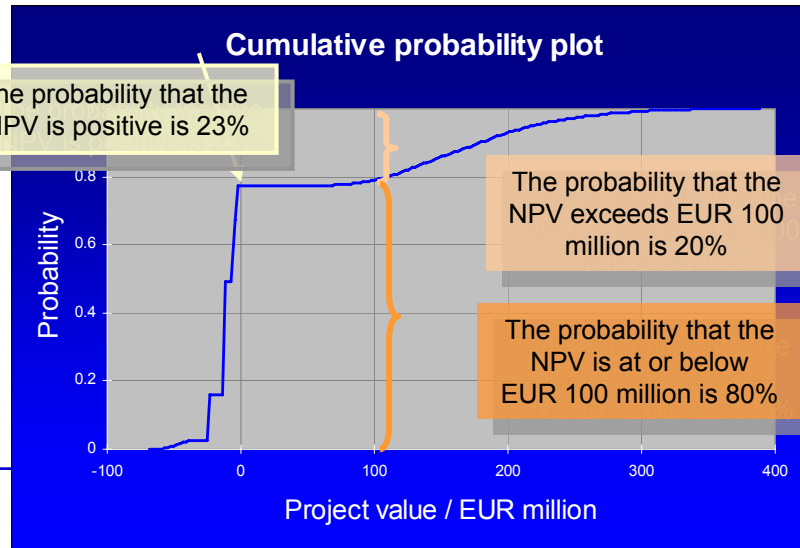
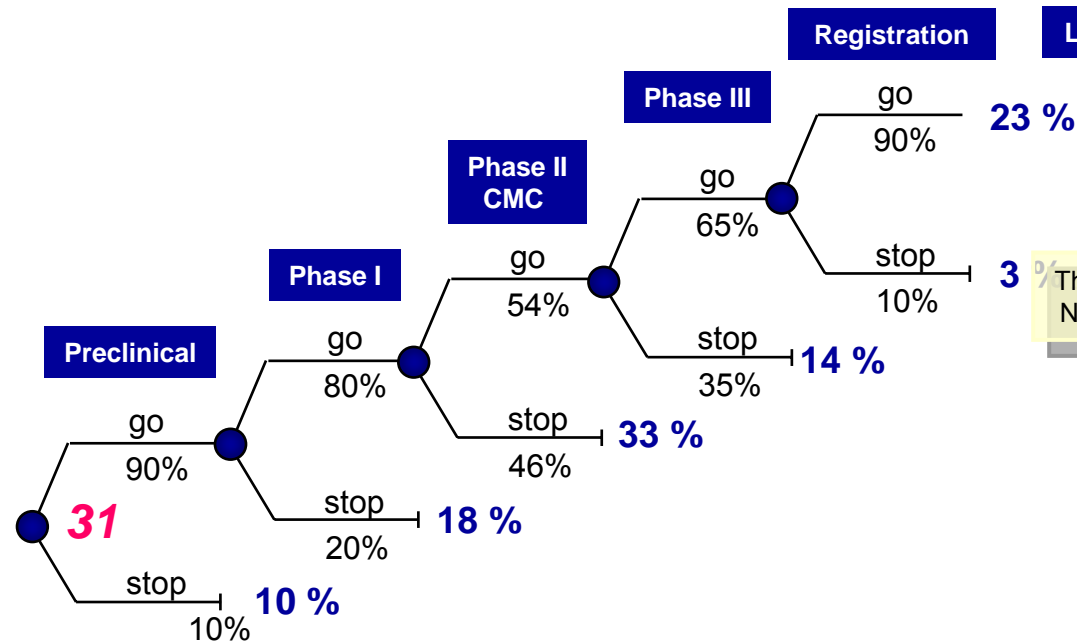
Expected Project NPV = EUR **31 million**

Scenario	Probability	Scen. NPV (EUR thousands)	Exp. Scen. NPV (EUR thousands)	
1	23%	177,600	40,395	Launch
2	3%	-49,305	-1,246	STOP after failure of Registration
3	14%	-23,923	-3,255	STOP after failure of Phase III
4	33%	-11,627	-3,851	STOP after failure of Phase II
5	18%	-6,143	-1,106	STOP after failure of Phase I
6	10%	-2,841	-284	STOP after failure of Preclinical

Example

Assumptions for Sales Forecast

	Presence	Future
Prevalence/incidence	min - likely - max	
Diagnostic rate	min - likely - max	
Treatment rate	fixed value	
Compliance rate	fixed value	
Patient share	min - likely - max	
Price	min - likely - max	



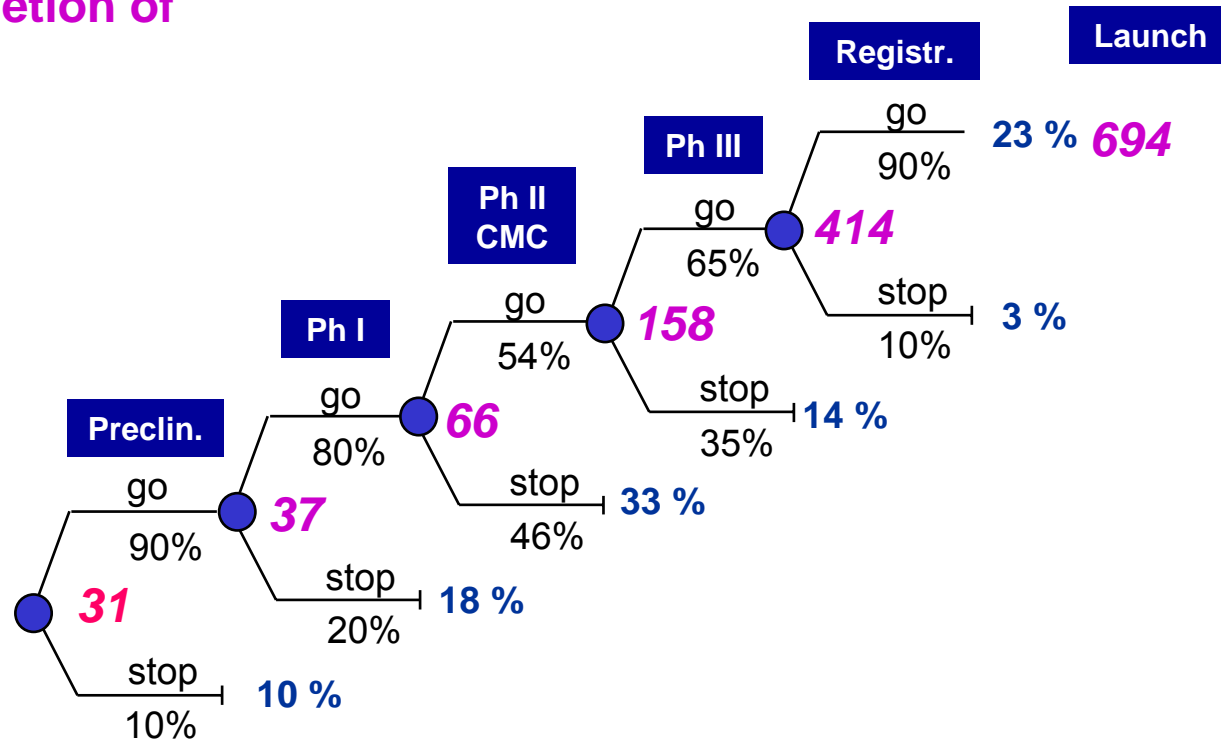
Risk analysis process and assessment of probability of success

- The assessment benefits from an experienced moderator and a cross-functional interactive process.
- Use published success rates from different sources as orientation, but make your own judgment.
- Explain reasons for your judgment (arguments for both optimism and pessimism).
- Exchange existing knowledge.
- If a common view is not emerging, opinions are collected and the sensitivity of the outcome to individual judgments is investigated.
- If the decision is highly dependent on the uncertain assumption, additional research may be initiated to reduce uncertainty.



The ,optionality' of R&D investments

Expected value uptake at successful completion of development MS (€million)



R&D investment to progress to next MS (€million)

0.5 7.2 15.5 36.6



Risk affects value

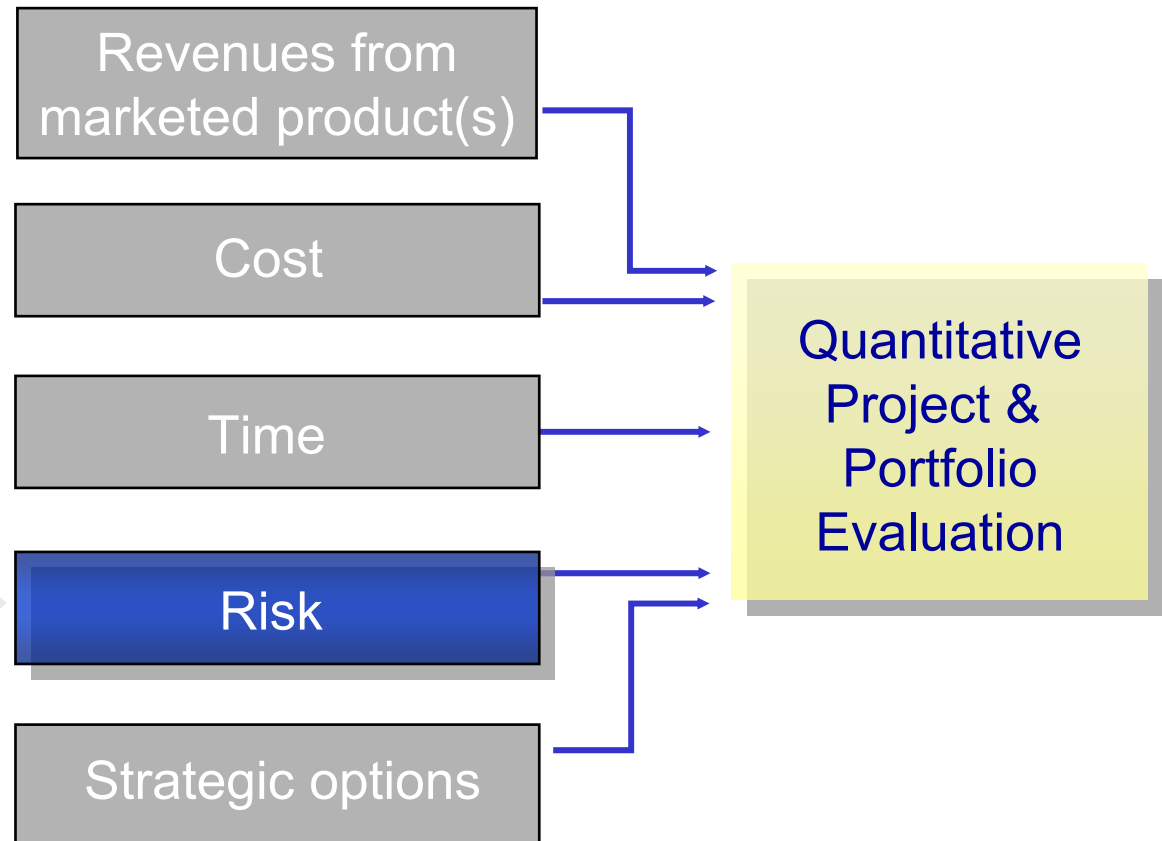
R&D risk:

Compound or target related uncertainty, e.g.:

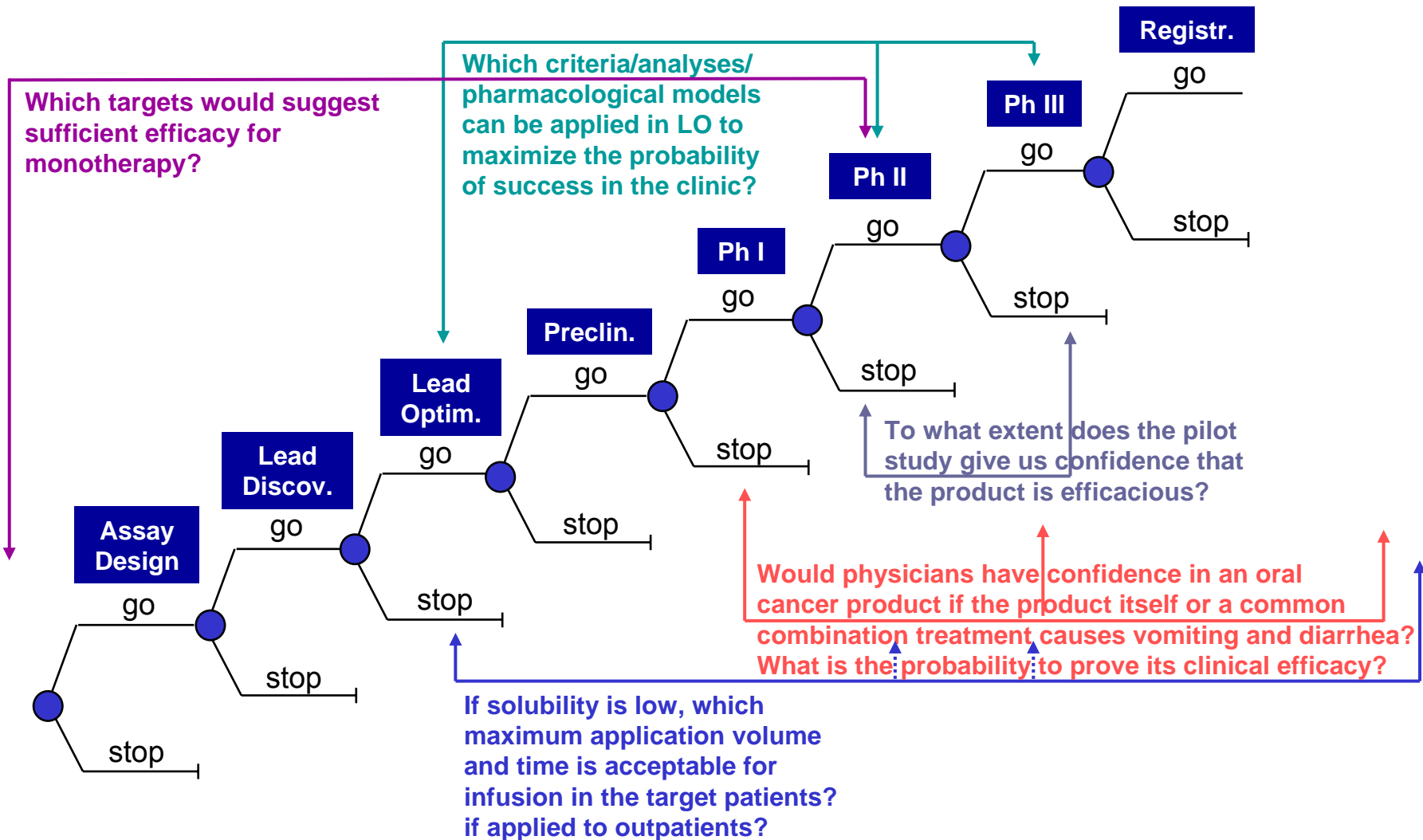
- insufficient efficacy/safety
- unexpectedly positive effects

Uncertainty associated with development strategy, e.g.:

- selected study endpoints
- selected study population
- front- versus backloaded risk structure
- validity and reliability of 'pilot' studies

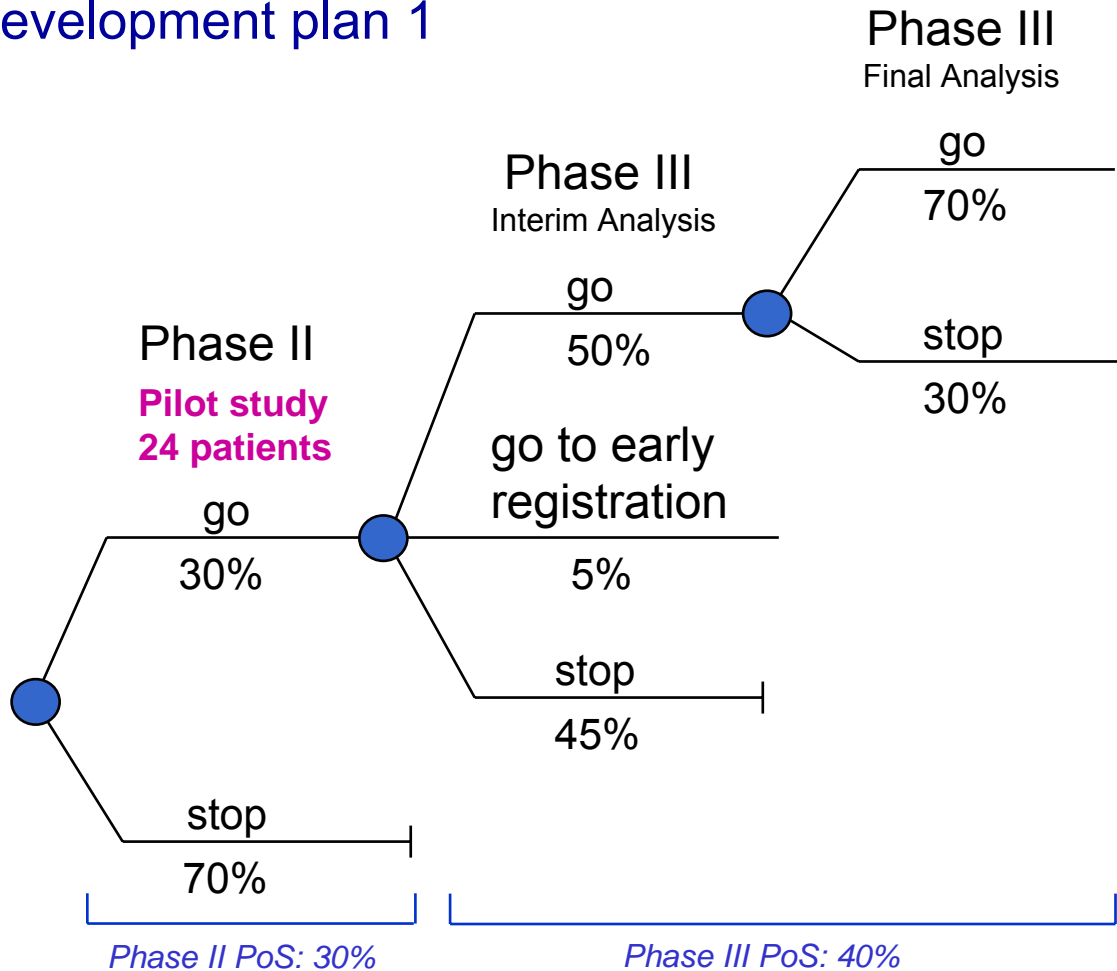


Analysis of R&D risk structure will lead to more robust probability assessments



Project risk management – alternative development plans may differ in risk

Hemorrhagic shock development plan 1



Launch: 2010
(at the same time or 1 year after strong competitor)

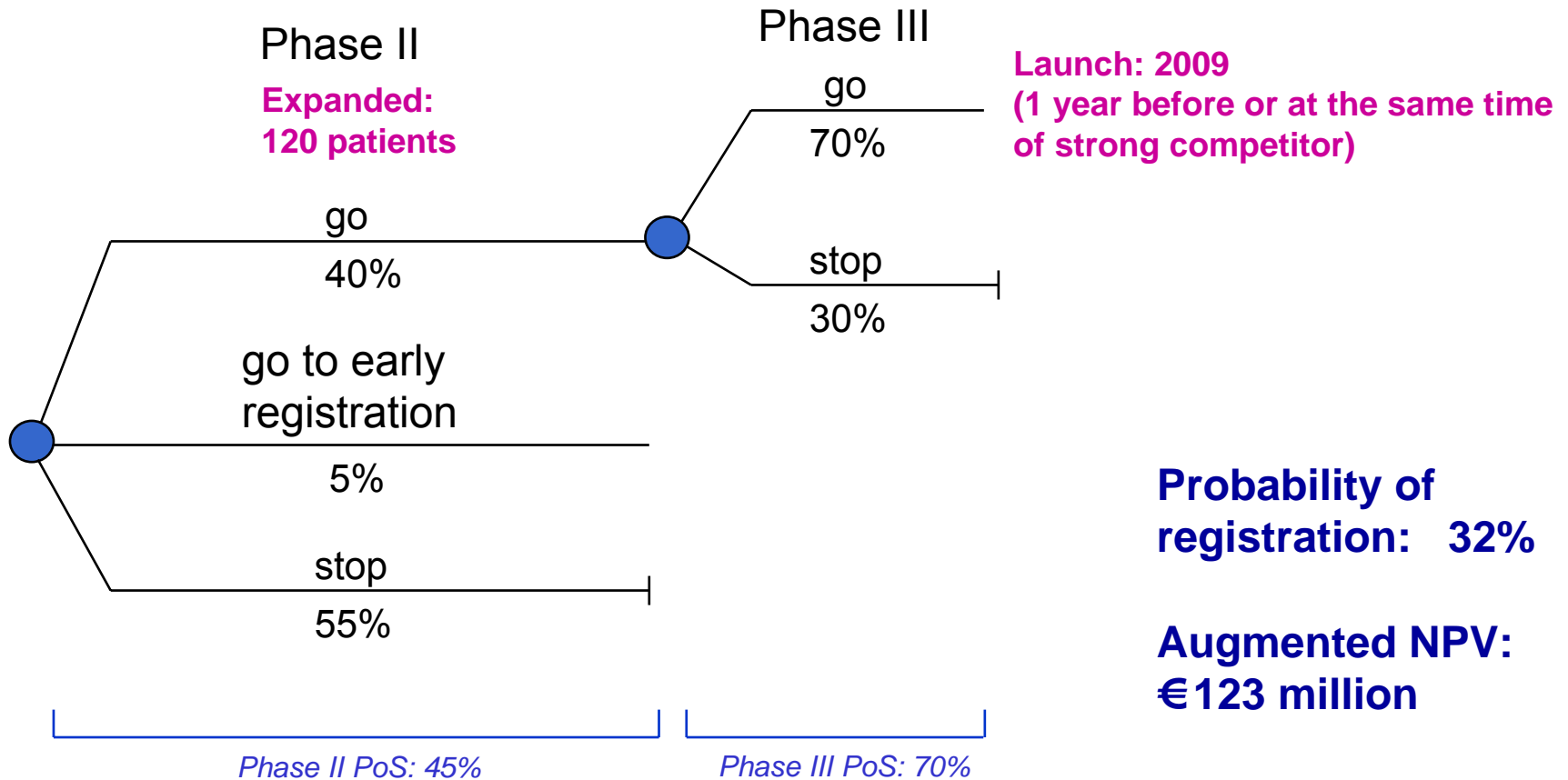
Probability of registration: 12%

Augmented NPV: €61 million



Project risk management – alternative development plans may differ in risk

Hemorrhagic shock development plan 2



Portfolio risk management

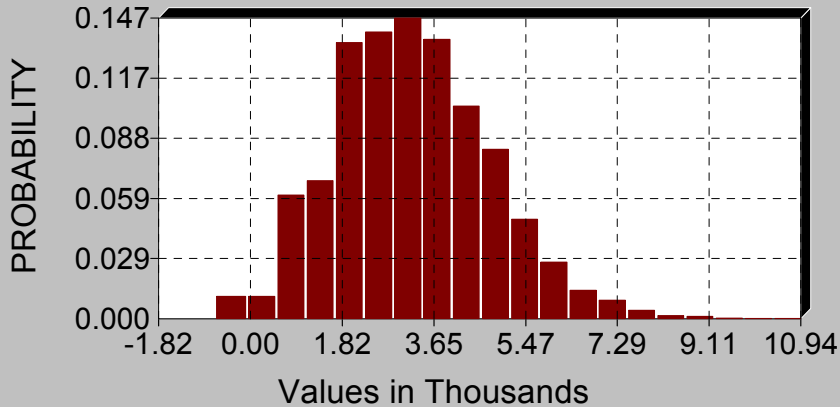
- Portfolio risk is driven by the number and the risk structure of individual projects, including the uncertainty of achieving sales targets. In addition, portfolio risk is related to the degree of dependency and covariance among projects.
- Portfolio productivity can be enhanced by conducting thorough project risk analysis and by identifying potential reasons for project failure that can be avoided. Such analyses generate insights for optimizing the risk structure of individual projects, revealing opportunities for portfolio risk management.
- It is suggested to proactively design the portfolio, taking advantage of complementary value/risk structures of different types of projects.



Portfolio risk assessment – *value per unit of risk*

Value-risk ratio (‘Sharpe’ ratio): portfolio 1 offers more value per unit of risk than portfolio 2

**9 Preclinical, 3 Phase I, 2 Phase II Projects,
1 Phase III Project**



Portfolio 1

Mean: \$ 3,191 million

SD: \$ 1,550 million

value-risk ratio: 2.06

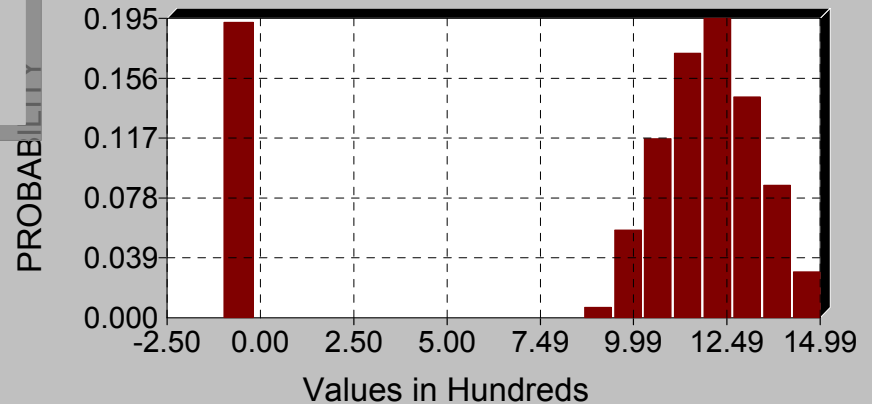
Portfolio 2

Mean: \$ 955 million

SD: \$ 513 million

value-risk ratio: 1.86

1 Phase III Project



The management of portfolio risk

- Characterize the risk/cost/value profile of R&D projects, e.g.,
 - I. innovative NCEs (*high risk, high cost, blockbuster potential*)
 - II. fast follower (*lower risk, high cost, blockbuster potential*)
 - III. molecular variants of existing successful products (*low to moderate risk, cost as me-too's, sales potential moderate to high*)
 - IV. supergenerics, standard generics (*low risk and cost, low to moderate sales*)
 - V. patentable fixed drug combinations

- Complement highly innovative and uncertain projects with lower risk projects in alignment with the corporate risk preference.

- Lower risk products with known MoA often require less resources than NCEs, leaving room for increasing the number of projects, i.e., diversification.

- Increase the number of projects by partnering programs and use the regained resources for acquisition/development of other projects.



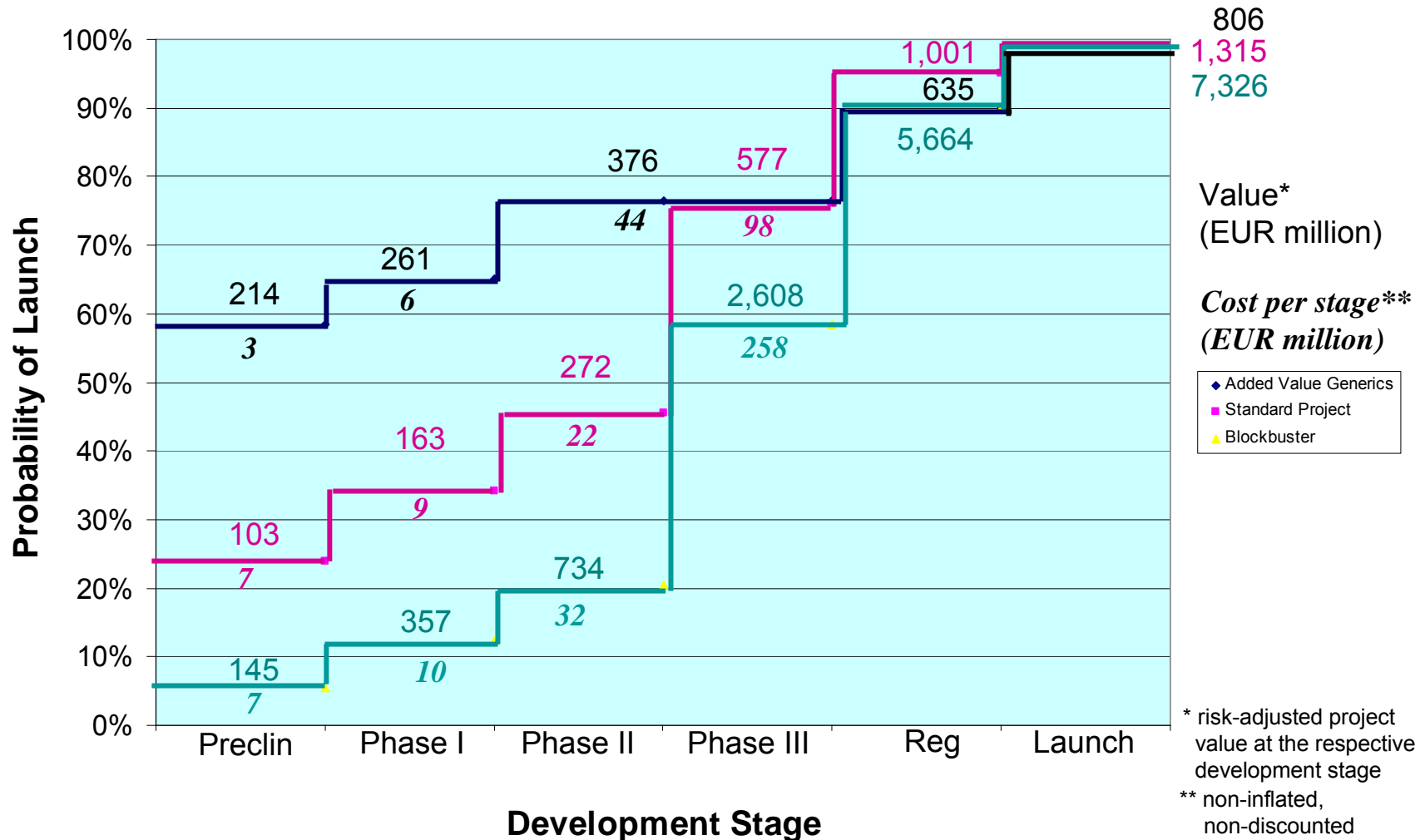
Illustrative example - assumptions

discount rate: 10% tax rate: 40%	Peak sales (EUR mill.)	Years to peak	COST (EUR mill.)* / probability of success								% sales reduction in year of patent expiry
			Preclin	Phase I	Phase II	Phase III	Reg	Phase IV	CMC/ Product devel.	Marketing (year of launch)	
Added value generic	250	5	3	6	44	39	-	5	38	-	
			90%	85%	85%	90%					
Standard product	500	5	7	9	22	98	66	5% of peak sales (years 1-5 after launch)	13	125	75%
			70%	75%	60%	80%	95%				
Blockbuster product	3,000	7	7	10	32	258	452	5% of peak sales (years 1-5 after launch)	13	450	90%
			45%	60%	35%	65%	90%				

* total stage-related costs, non-inflated and non-discounted



Risk structure and value uptake of 3 categories of R&D projects



Summary and conclusions

- Systematic risk analysis facilitates the establishment of robust and productive R&D portfolios through
 - an improved understanding of risk structure and the expected productivity and value uptake,
 - the avoidance of projects with correlated risk
 - the identification of actions that reduce risk or reduce the impact of potential unfavorable outcomes.
- Proper risk management can enhance the output and value of R&D.
- Outlining the relationship between the probability of success, the required investment, and the expected value increase of R&D projects facilitates the communication between scientists and investors and increases the chance of successful financing rounds.

