Advanced Vaccinology Course

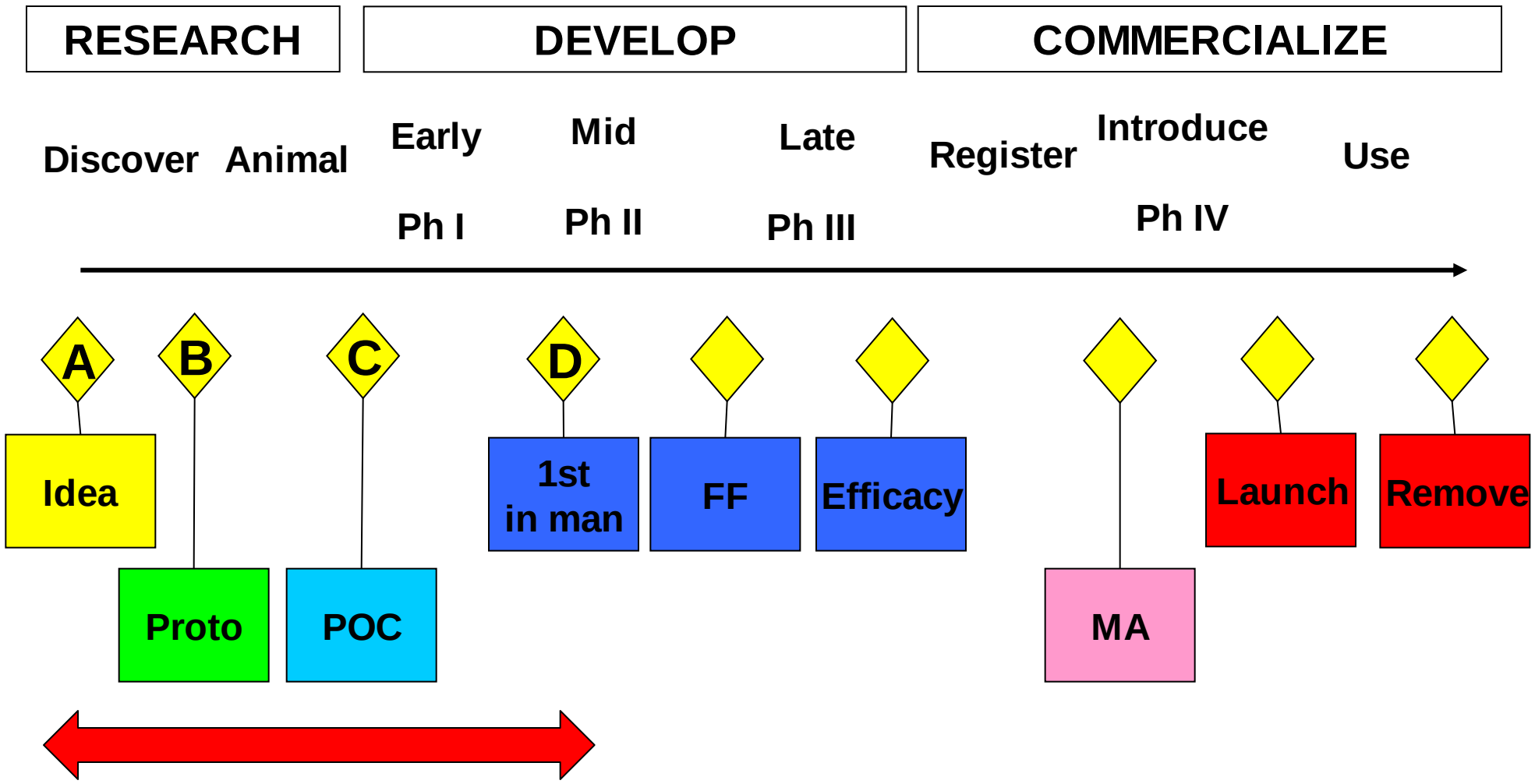
From Pre-Clinical Research to Vaccine Development

Examples of go / no go decisions

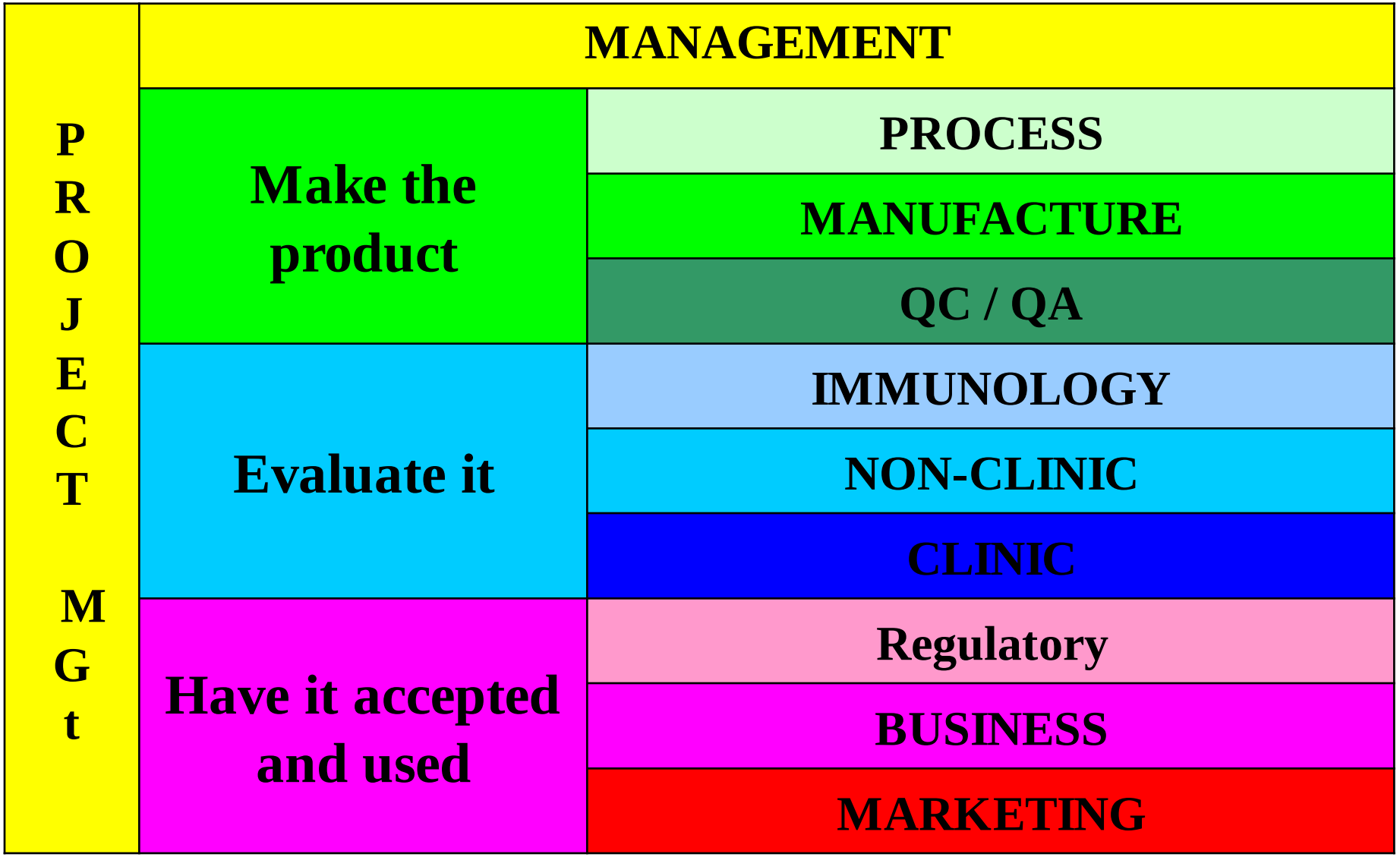
May 14, 2014

Georges THIRY

Life cycle, stages of development and gates



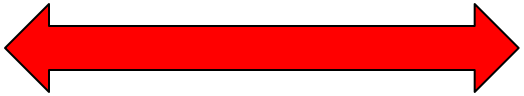
Expertise in Development



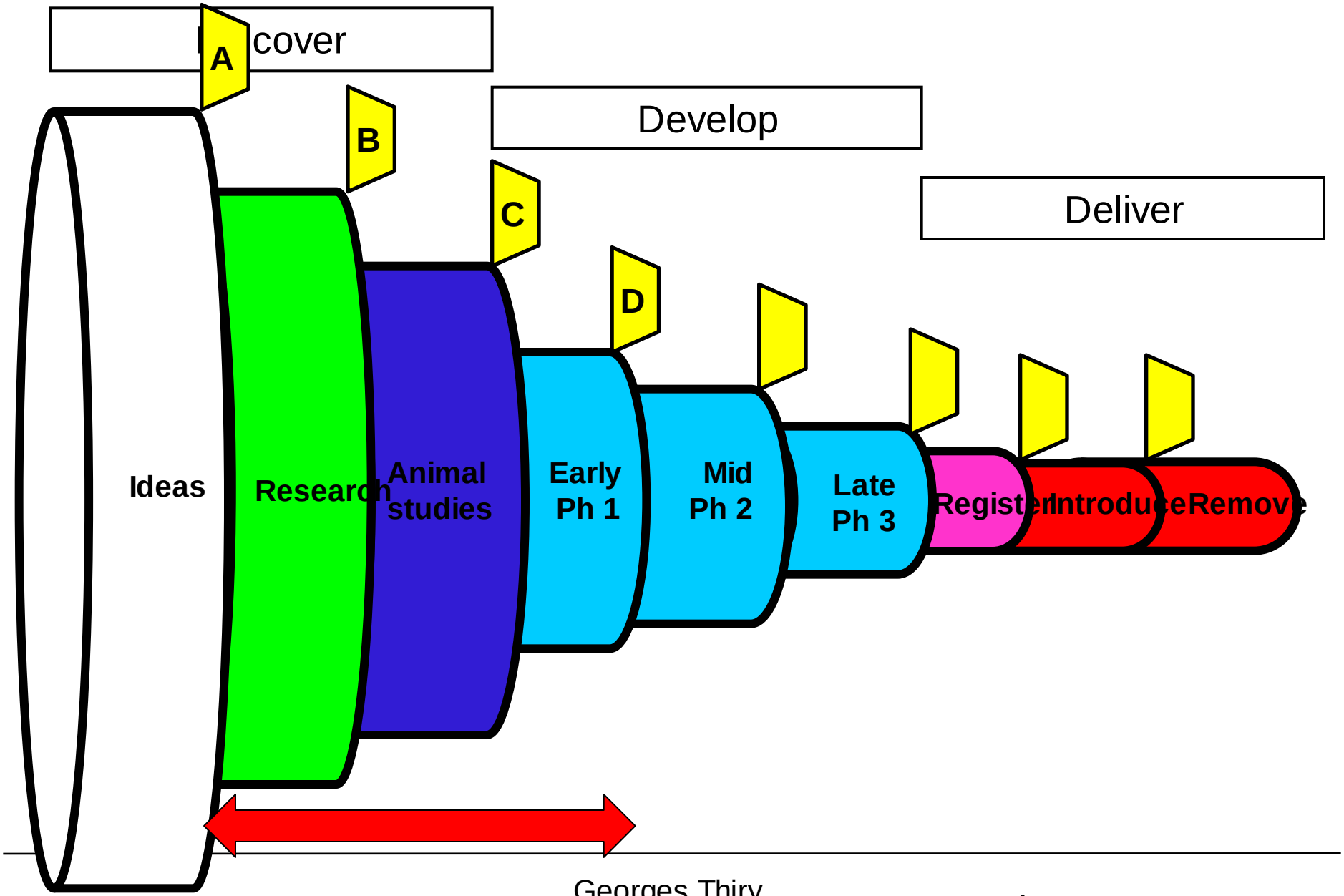
Dynamic between product and evaluation

	MANAGEMENT	Research	Development		Commercialization	
P	PROCESS	Lab				
	MANUFACTURE		Pilot	FP-Cons	FS-Com	FF-Com
	QC / QA					
	IMMUNOLOGY					
M	NON-CLINIC	Animals				
	CLINIC		Phase I/II	Phase III		Phase IV
	RA				Filing	
	BUSINESS					
	MARKETING					Launch

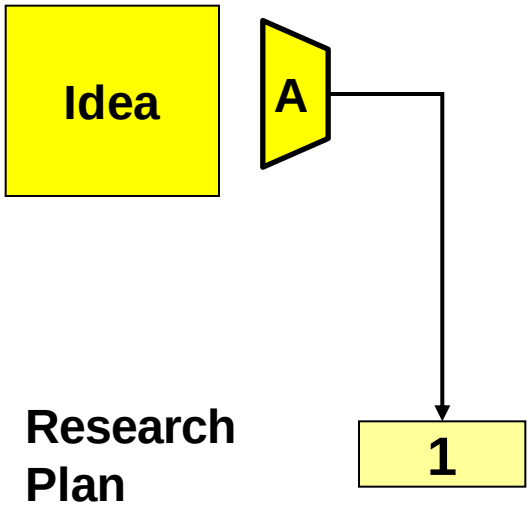
Final Process; Final Scale; Final Facility; consistency; commercial



Pipeline, select candidates through gates



Criteria Gate A: Go / No-Go to a New project



Should we do it?

- ❑ Ethical
- ❑ Fits our mission / objectives
- ❑ Novel, unique
- ❑ Demand, funds

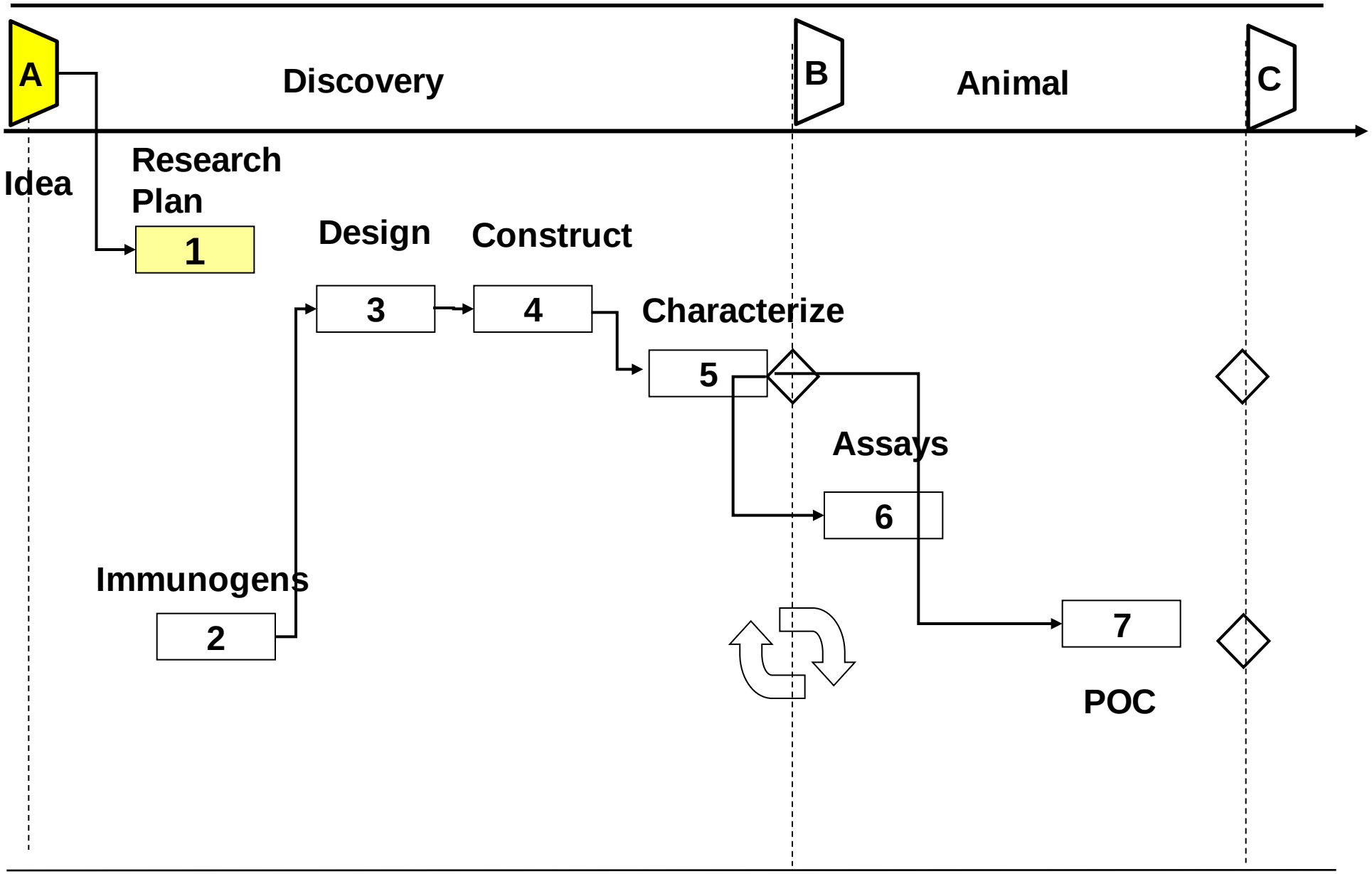
Can we do it?

- ❑ Chance of success, feasible
- ❑ Capability: internal / partnership

What would be the impact, if success?

- ❑ On outside world / our organization

Research: from an idea to a proof of concept



Identify immunogens, understand protection

Pathogenicity

Natural immunity

Mechanism of protection

Protective antigens

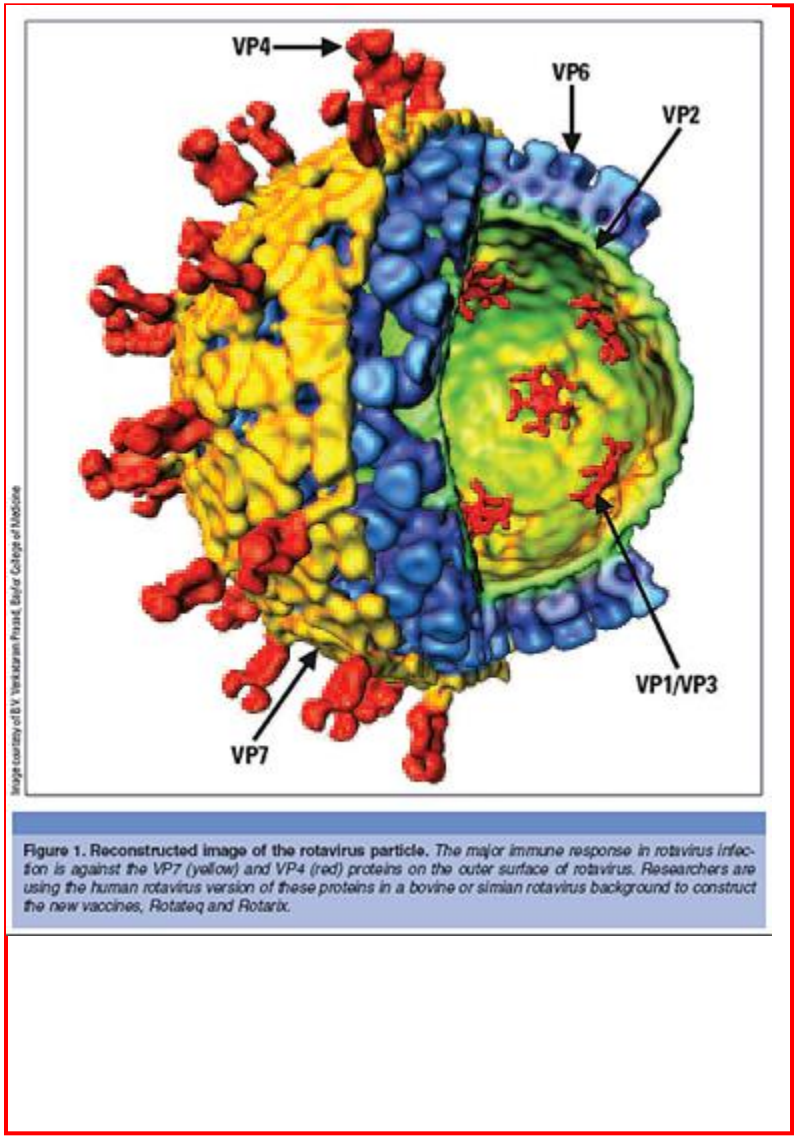


Figure 1. Reconstructed image of the rotavirus particle. *The major immune response in rotavirus infection is against the VP7 (yellow) and VP4 (red) proteins on the outer surface of rotavirus. Researchers are using the human rotavirus version of these proteins in a bovine or simian rotavirus background to construct the new vaccines, Rotateq and Rotarix.*

Design candidates on paper

Live, killed, sub-unit?

Adjuvant?

Formulation?

=> Composition

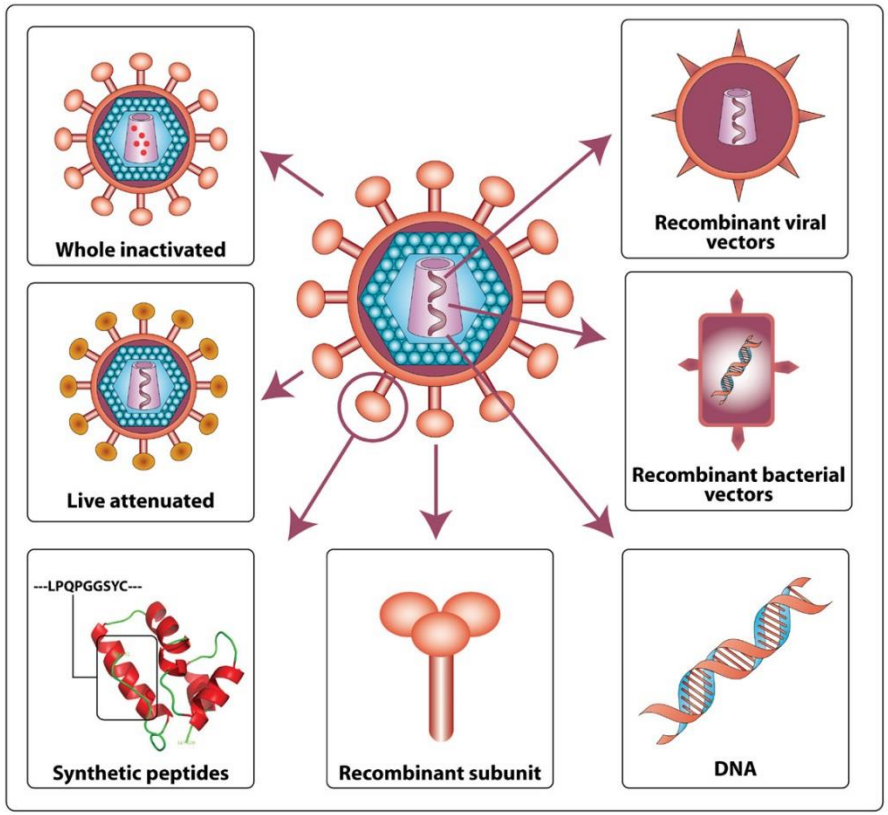
Liquid, lyo?

Nb of administrations?

Route of administration?

Vials, device?

Population?



=> Target Product Profile

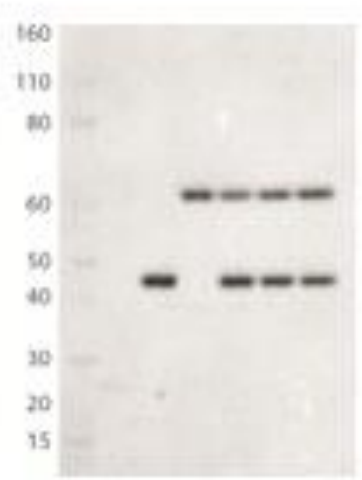
Construct & characterize prototypes

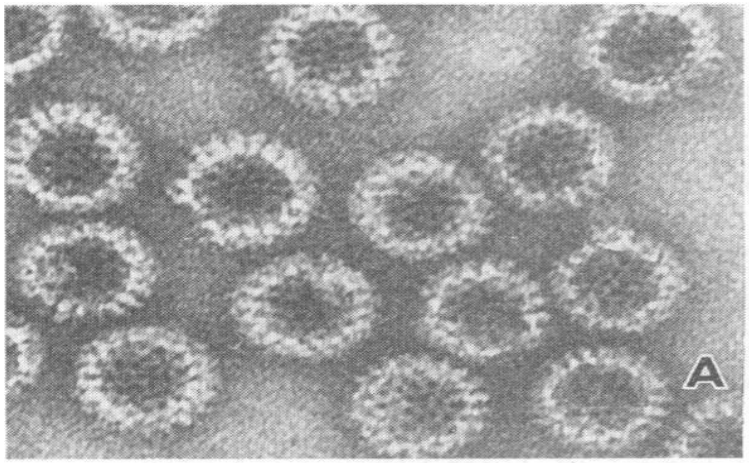
Lab scale

- Produce bulk (USP)
- Purify (DSP)
- Formulate (stabilizer)
- Yield

Characterize

- Identity
- Concentration, potency
- Purity
- Stability
- Sterility





L. Lua, pc; Crawford, 1994

Set up assays - Perform animal studies

Assays

- Immunogenicity
  - Antibodies
  - T-cell
- Protection
  - Challenge
  - Weights
  - …

Mice

Rats

Cotton rats

Guinea pigs

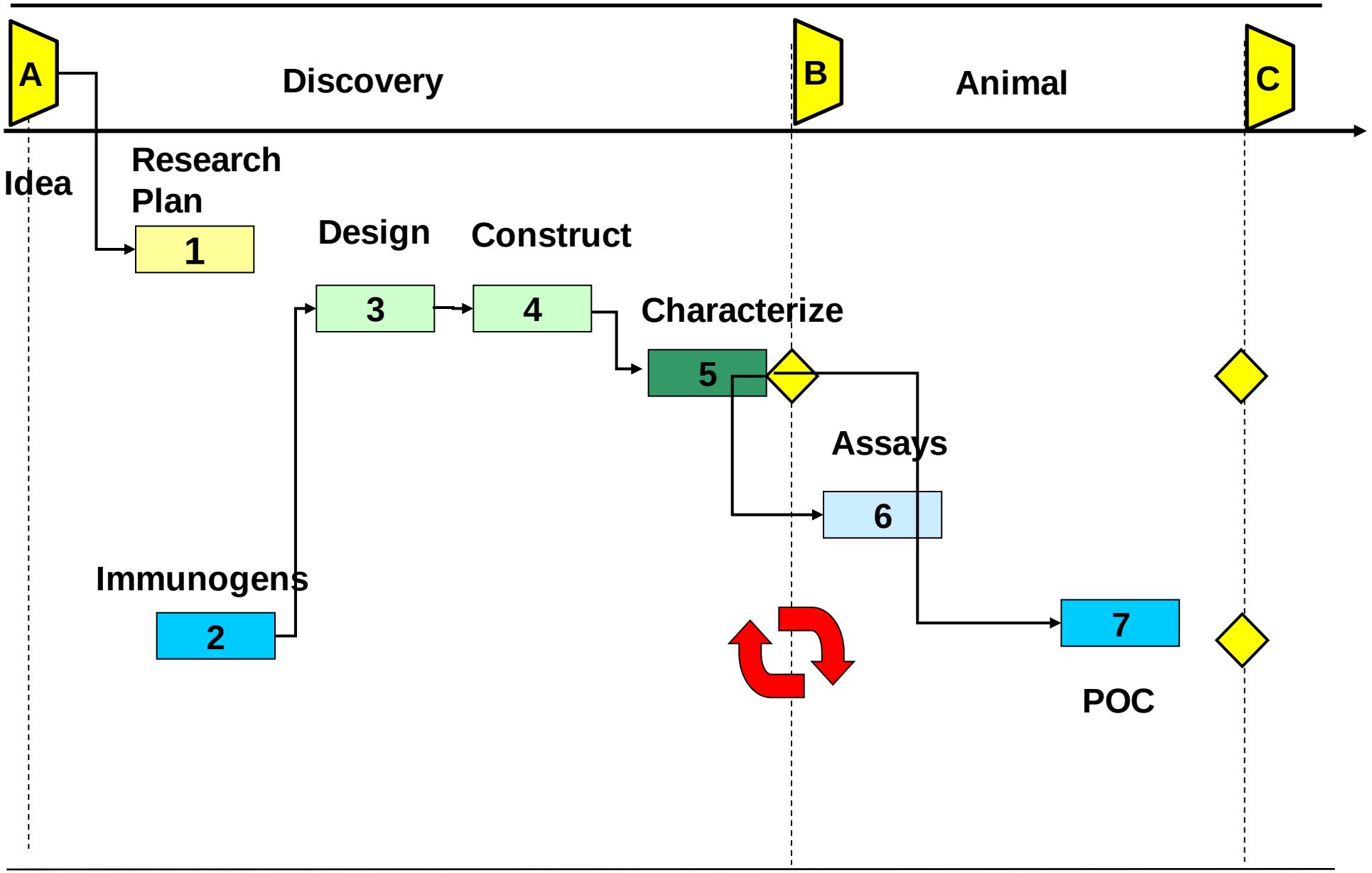
Rabbit

Ferrets

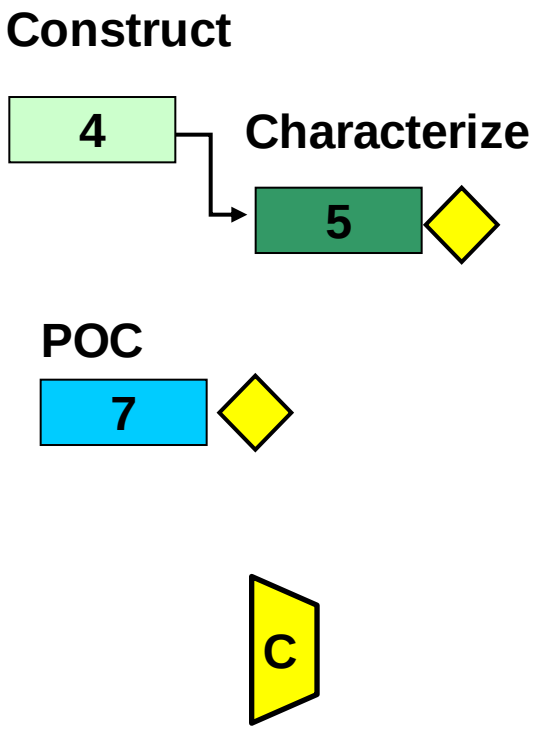
Mini-pig

Monkeys

Research: from an idea to a proof of concept

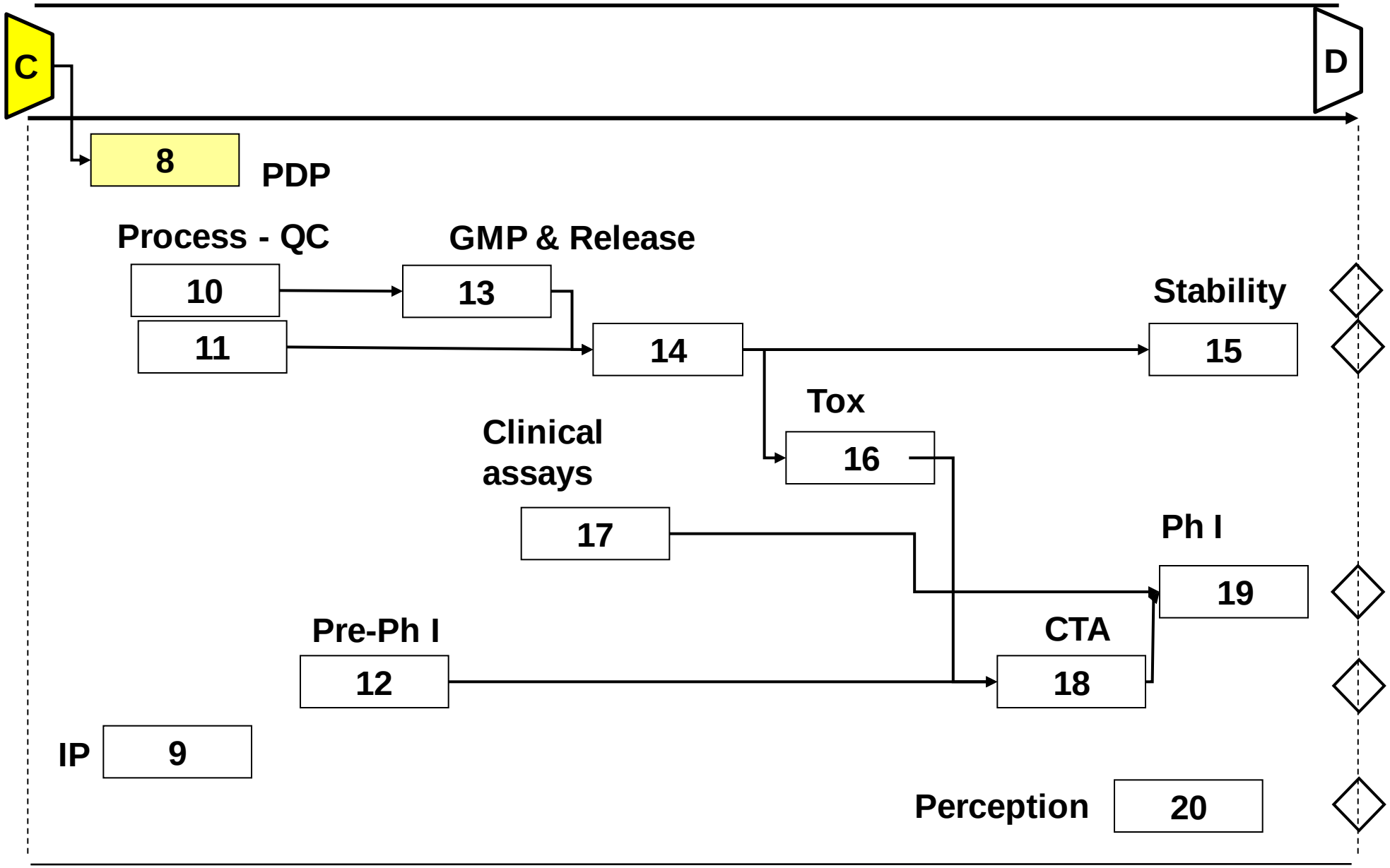


Criteria Gate C: Go / No-Go to Ph 1



- Process
  - ❑ Yield, feasible at Pilot scale
  - ❑ Stable
- Animal studies
  - ❑ POC demonstrated
- Management
  - ❑ Capability, cost
  - ❑ Competition
- Clinic and RA
  - ❑ Safe
  - ❑ Acceptable for human

Early development – from POC to 'first-in-man'



Review IP

Landscape of patents

Freedom to operate

React:

- ❑ Write patent applications
- ❑ Change process
- ❑ License

Patent landscape, WIPO, 2011

Fix process for manufacturing and fix QC

Process

- Assess
- Fix process
  - Write methods

QC assays for release

- Assess
- Fix

Develop stability plan

Lab scale

GLP

⇒ Pilot scale

⇒ GMP

Consult RA

Present

- ❑Vaccine candidate
- ❑Rational
- ❑Production
- ❑Animal study
- ❑Design of Tox study
- ❑Synopsis Phase 1

Benefits

⇒ Internal review and team work

⇒ Share knowledge

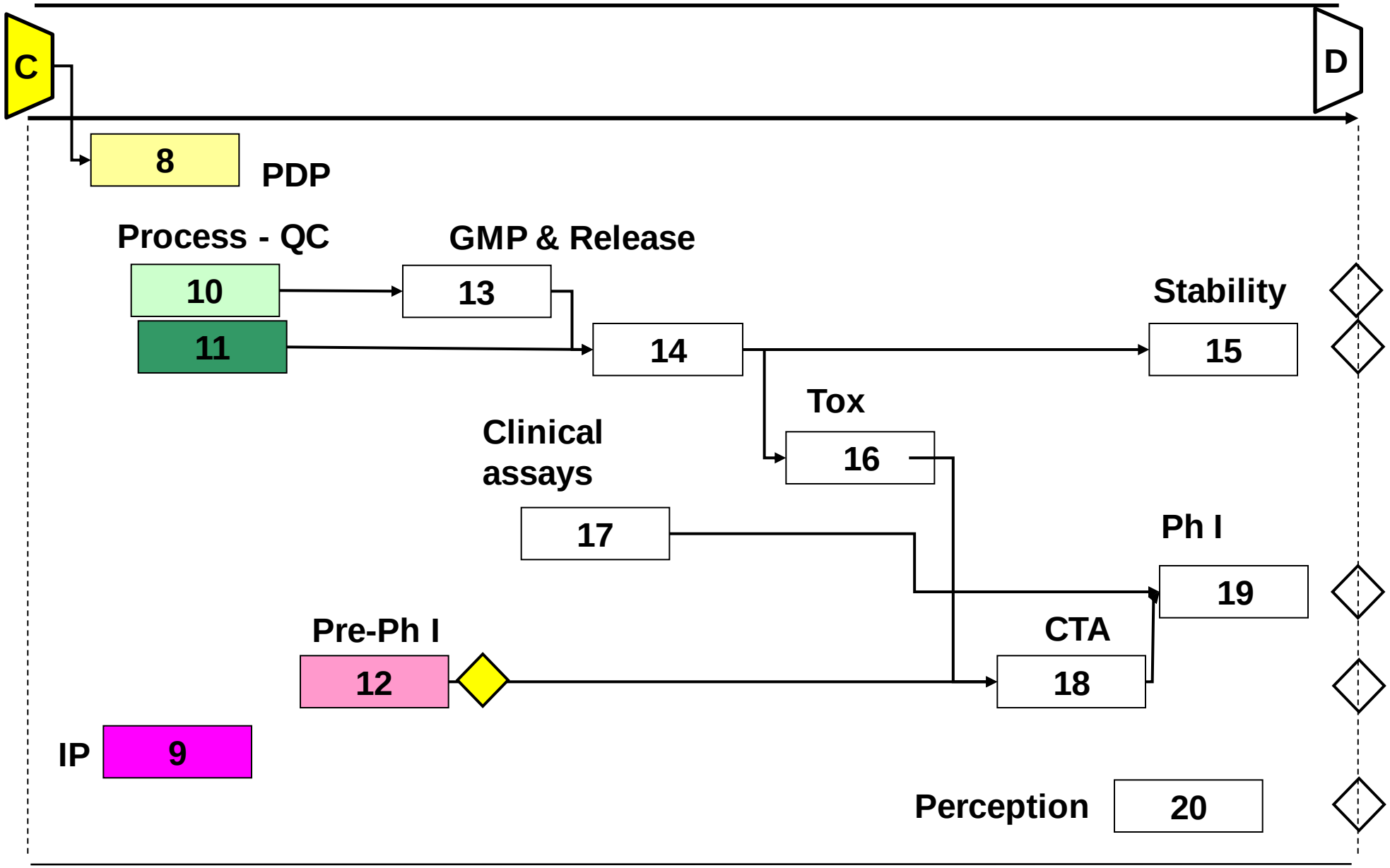
⇒ Questions raised by RA

⇒ Obtain opinion and advises

⇒ Establish relationship

⇒ Prepare for CTA

Early development – from POC to 'first-in-man'



GMP manufacture and release

Transfer

- ❑ Seeds, reagents
- ❑ Methods

Vials for

- ❑ QC
- ❑ + Archive
- ❑ + Stability
- ❑ + Tox
- ❑ + Ph ½

Placebo

Perform toxicity studies

Guidelines: pyrogenicity, single & repeat dose acute toxicity, local tolerance

DNA: bio-distribution, persistence, integration.

Live: attenuation; reversion to virulence; recombination; shedding;

Develop / fix immunological assays for Ph I

Immune response

- Antibodies …
- Cellular …
- Mucosal …

Assays

- SOP's
- Training
- Towards validation

From assays in the Lab

=> toward cGLP

Submit Clinical Trial Application; obtain approval

CTA

- Product, rational, need
- Chemistry, Manufacturing & Control (CMC)
- Pre-clinic: Tox, Immuno
- Previous clinical experience with similar vaccine
- Ph 1 protocol

Submitted to :

- NRA
- Ethics Committee, MOH
- Genetic recombinant committee
- Scientific committee …

Perform Ph I – First-in-man

Classical Ph 1:

- 20 healthy adults
- 25 - 45 years
- 1 administration
- Lowest dosage
- Placebo controlled

End points

- Safety
- Immunogenicity

Review marketing

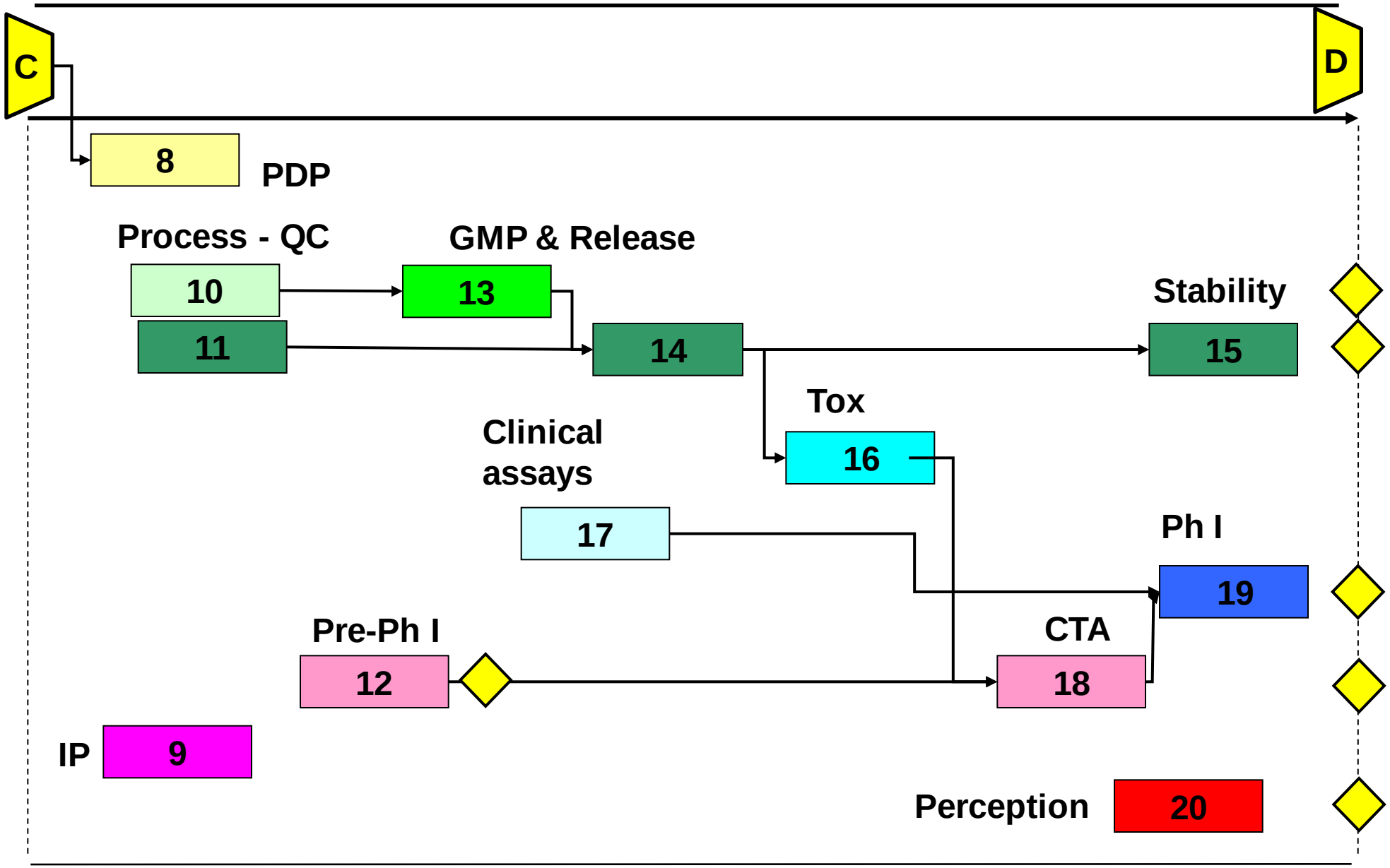
Perception of disease

Perception of vaccines

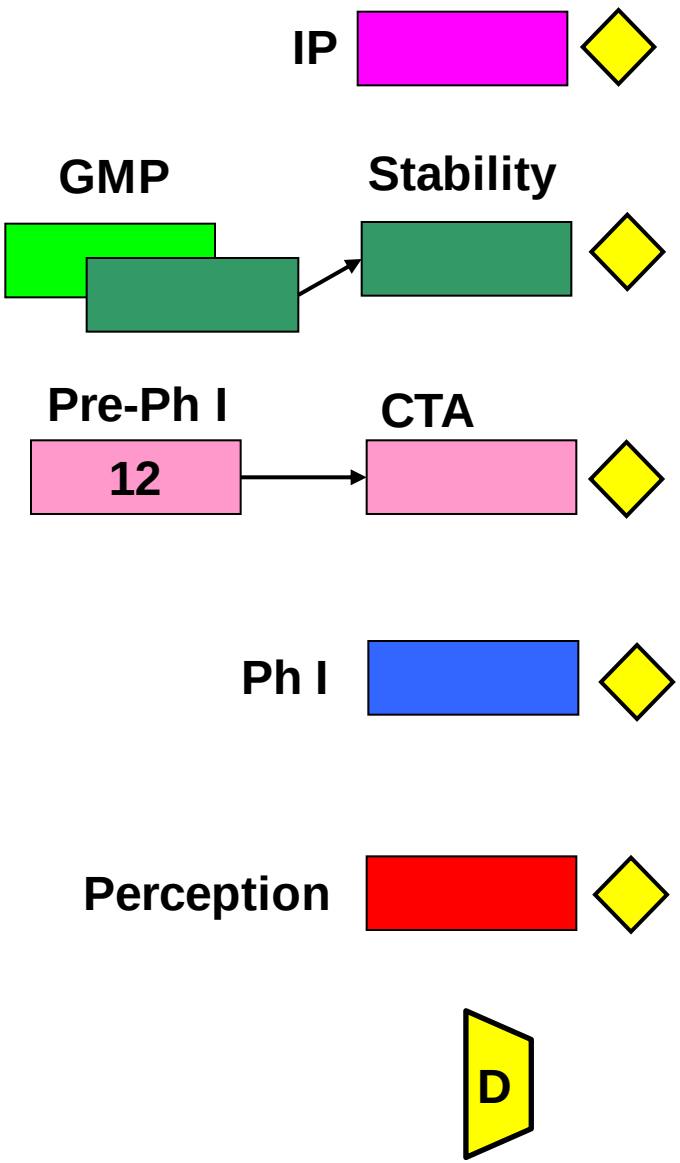
Survey

=> Marketing efforts

Early development – from POC to 'first-in-man'



Criteria at Gate D – Pursue to Ph 2?



IP position, competition…

Process, feasibility, stability, scale up

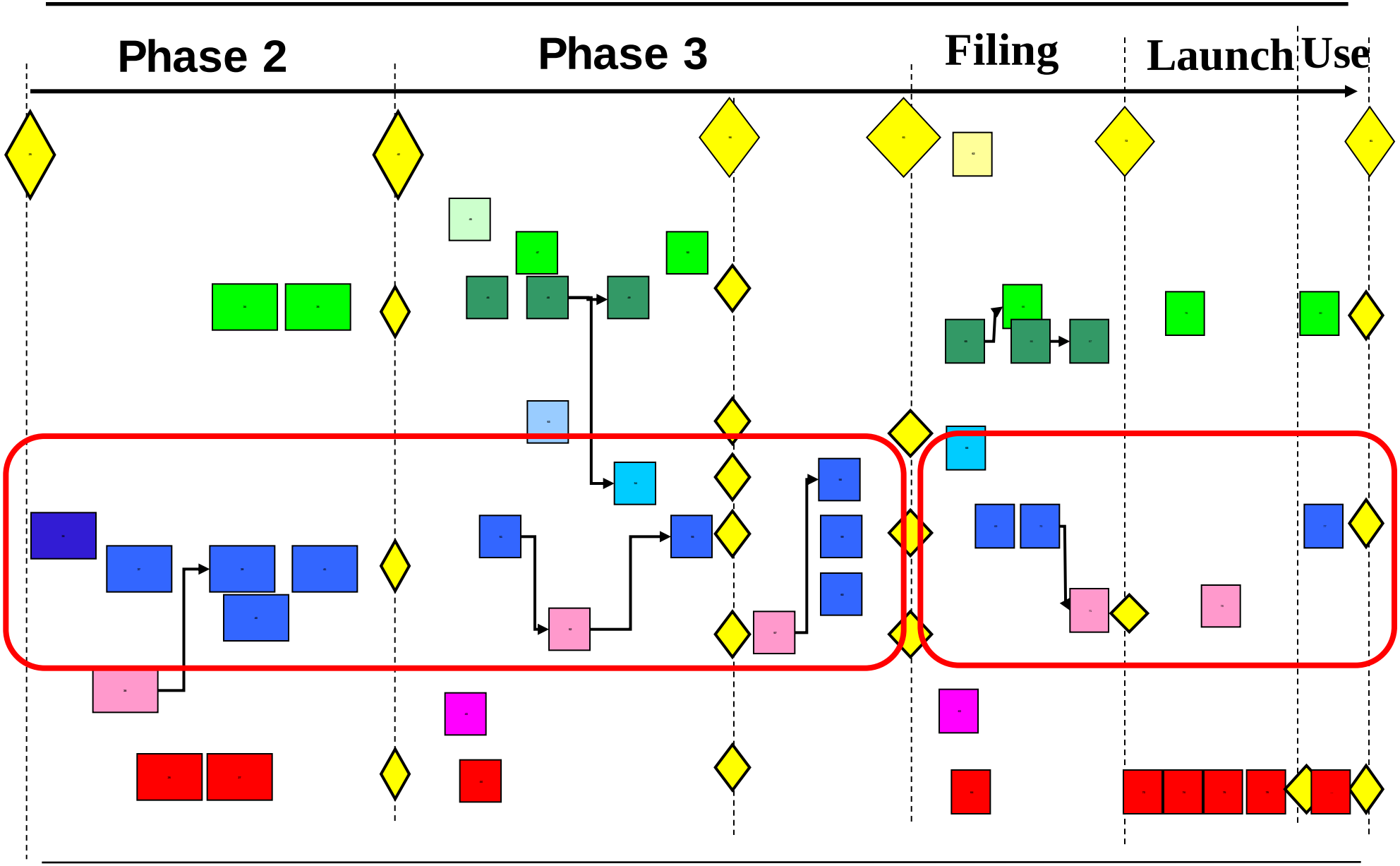
Questions from RA

Safety in man, immuno; Plan Ph2

Market review

Feasibility, cost, funding, portfolio

Ph 2, 3, 4



Conclusions

There is a methodology in vaccine development, with sequence of events, data generated, review and decision-making points.

Development is long (15 + years), risky (1% ideas become products), complex (multiple expertise), complex (management of // activities), complex (changes in epidemiology, competition, political, …) and complex (global).

A decision to “stop or go” depends on the quality of information and cleverness of analysis, experience, entrepreneurship, risk taking, and intuition.

Merci beaucoup

Thank you much

감사합니다

ขอบคุณ

Gracias

Terima kasih

谢谢您