Arbeitsgemeinschaft für angewandte Humanpharmakologie
Association for Applied Human Pharmacology
AGAH e.V.

SCHERING
making medicine work

Is Phase I Useful?

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Schering AG, Berlin

Early Drug Development: Scientific and Regulatory Changes

AGAH / Club Phase 1
Joint Annual Meeting 2005
Straßburg, 17-18. March 2005

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How Human Pharmacology evolved

In the 70s:

Single shot approach.

- Study protocols 1 page

- Study reports 1 page
  - ➔ Content: Excellent tolerance, no objections to go ahead....

Duration of Phase I: 4-8 weeks

How Human Pharmacology evolved

In the 80s:

Division of Phase I task, sequencing of activities

- Single dose tolerance
- Multiple dose tolerance
- Pharmacodynamics
- Formulation works

Formalization

- Upcoming Ethical Review Boards
- Standardization of study protocols
- Subject Information and informed consent

Upcoming functional ownership

How Human Pharmacology evolved

In the 90s:

Well established functional division of work

Increasing formalization

- ICH
- GCP
- Exploitation by consultant firms

Development of Phase I as an art of science

- Extended PD modeling
- PK-PD modeling
- Attempts to profile Phase I as a predictor for clinical success
- Virtual drug development

How Human Pharmacology evolved

Around 2000:

- Decrease of numbers of in-house Phase I units
- Increasing outsourcing of clinical trials

- New medical entities often not suited for healthy subjects

- Formal work exceeding scientific work
- Importance and significance of “Phase I” has become questioned: Can we still afford a Phase I unit?
- Benchmarking has shown the impact of speed

How Human Pharmacology evolved

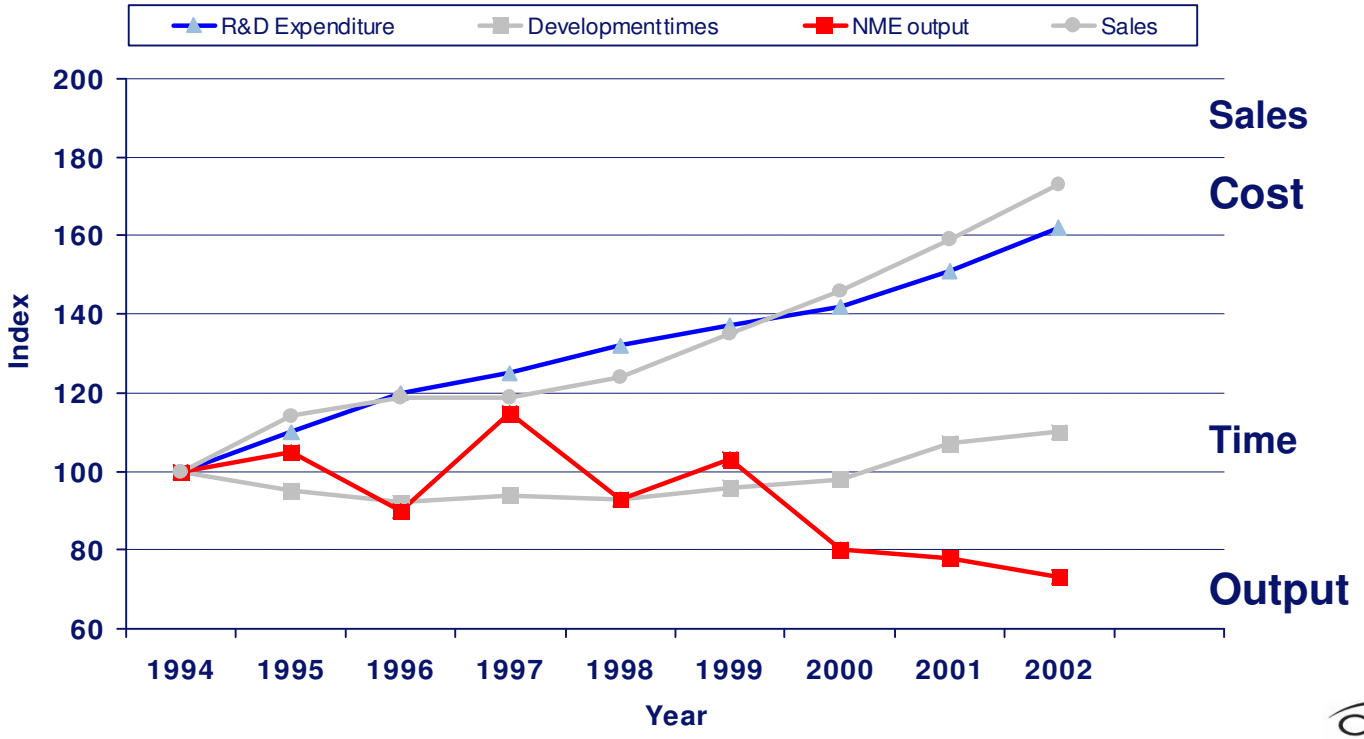
Around 2005:

- Formal work has explicitly exceeded scientific work (EU ClinTrial Directive)
- Academic Clinical Pharmacology continues to struggle

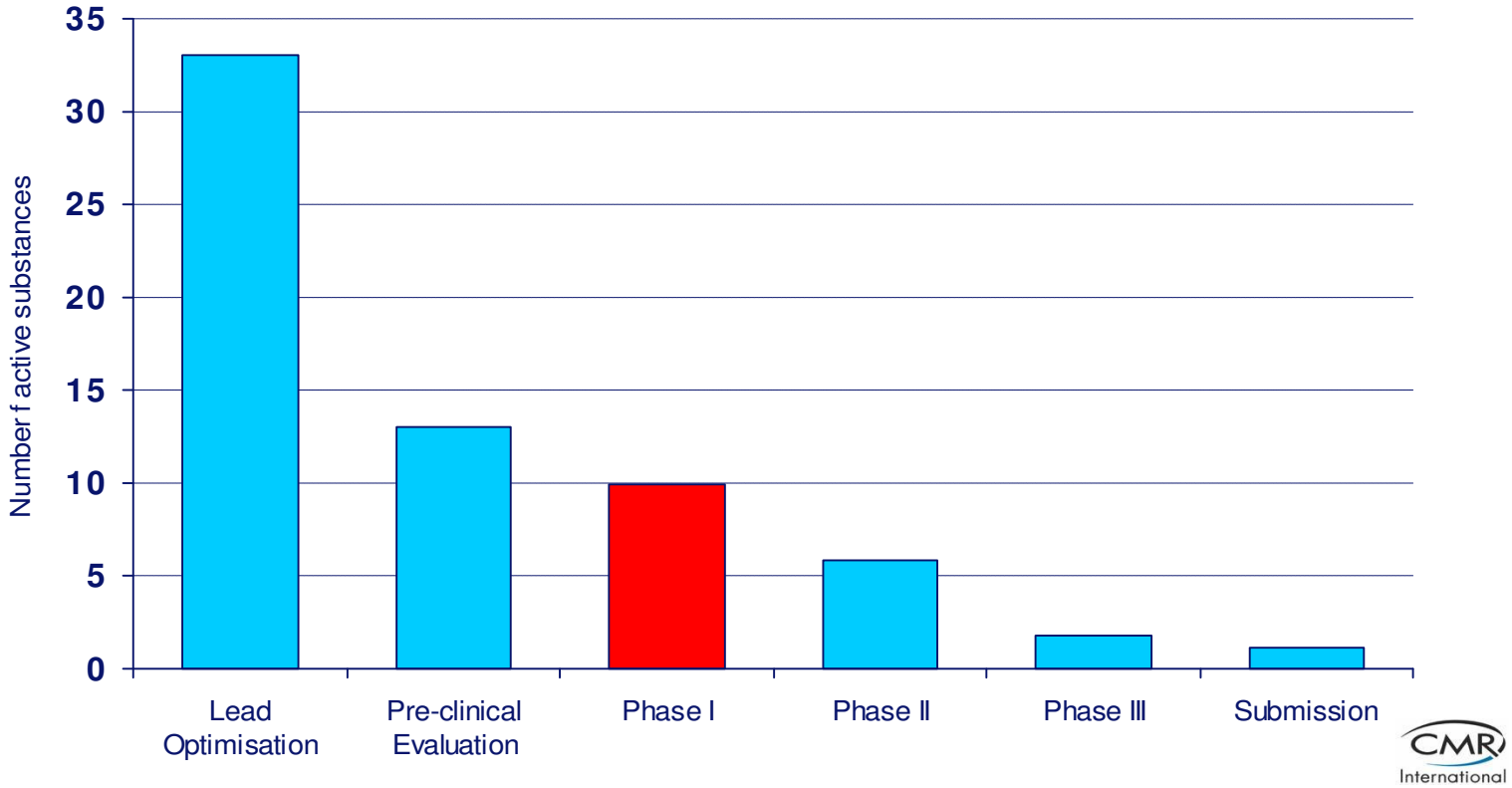
- Increasing impact of economic analyses and cost containment
- Performance metrics systems and benchmarking increasingly established

- Outsourcing and off-shoring rapidly growing
- Hands-on work complemented by transaction management

Global expenditures, development times, sales and NME output



Success rates: Sustainability of development pipeline



Time is an issue

This slide contains proprietory material and cannot be published.

It shows as a result of forecasting the time span of future launches from a current development portfolio.

The future launches are related to the stage, a project is currently in.

Time is an issue: reduction of cycle time by 20%

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It shows as a result of forecasting the time span of future launches from a current development portfolio.

The future launches are related to the stage, a project is currently in.

Reduction of cycle times by 20% only increases considerably the number of launches in the near future.

More information about forecasting methods can be obtained from the author.

A new paradigm

Innovation is not alone about the product,

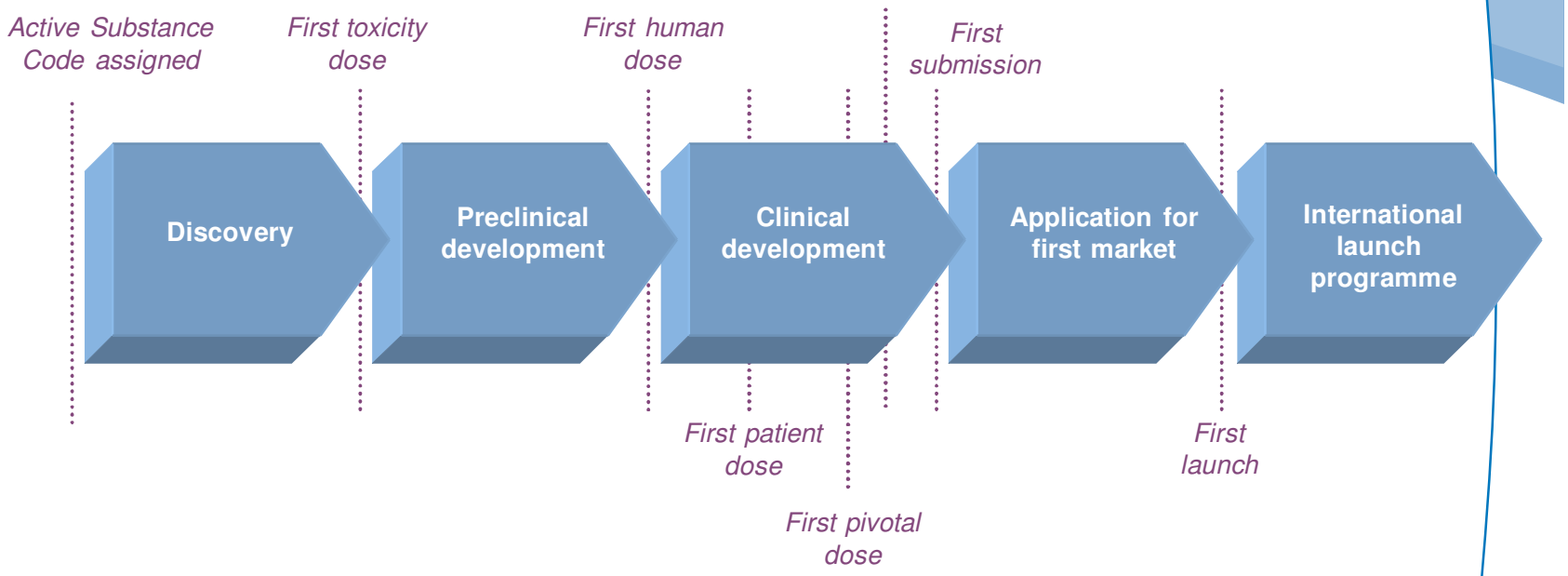
but about **the way the product is produced.**

A new paradigm

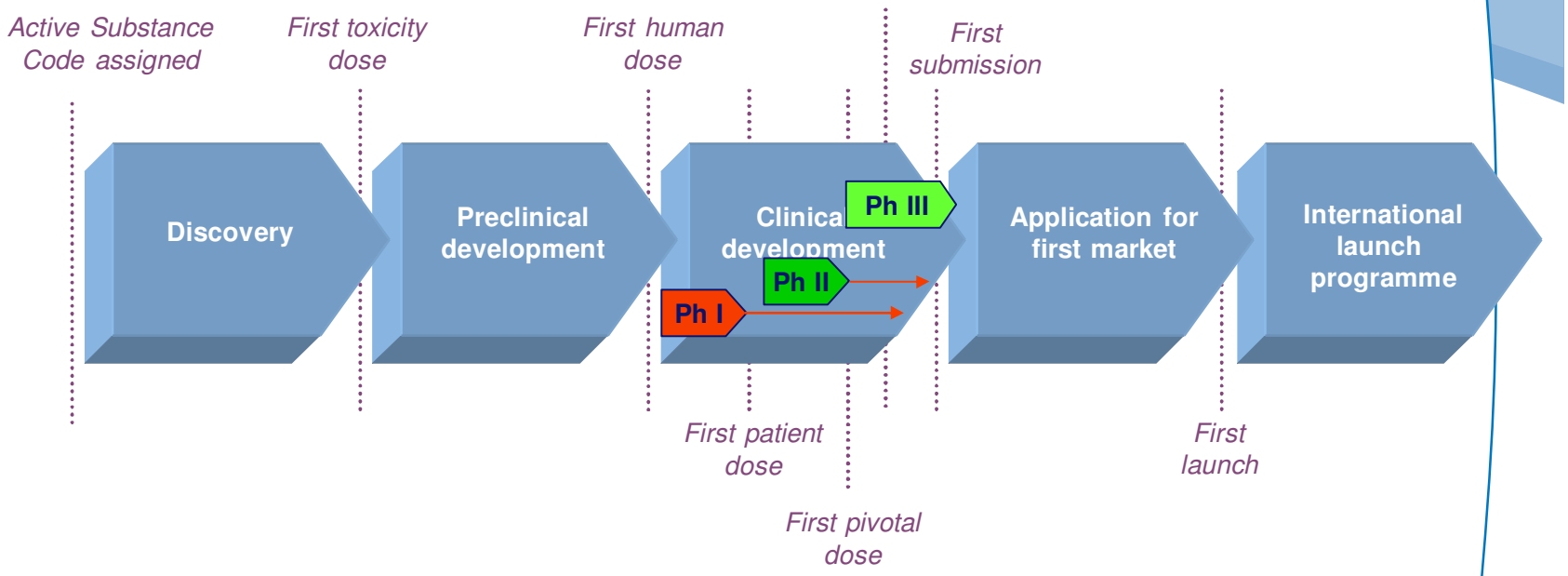
Innovation is not alone about the product,
but about the way the product is produced.

How may the future be looking like?
What will be the role of “Phase I”?

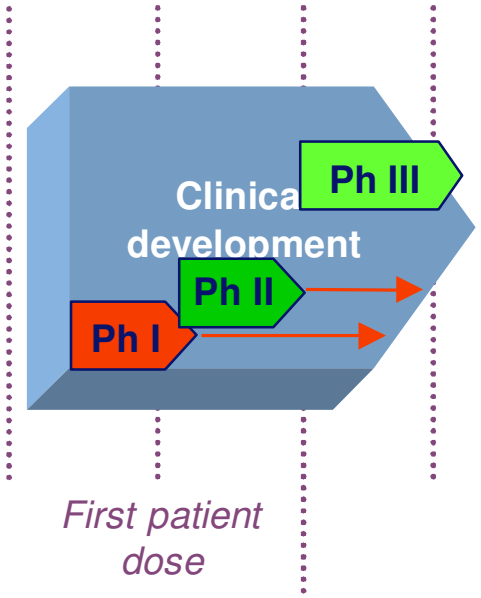
The burdens of “Phase I”: a process view



The burdens of “Phase I”: a process view



The process is function-driven



Quite often, Ph I is a separate, distinct function.

This reflects a development process, which is function-driven.

The function assumes ownership.

Ownership: Advantage

An operative function (Human Pharmacology, Cinical Pharmacology, Institute for ...) owns the process.

Advantages:

- Core competence in the area
- Usually highly educated, trained and motivated teams
- Knowledge, what to do and to what extent
- Organizational transparency

Ownership: Advantage or disadvantage?

An operative function (Human Pharmacology, Cinical Pharmacology, Institute for ...) owns the process.

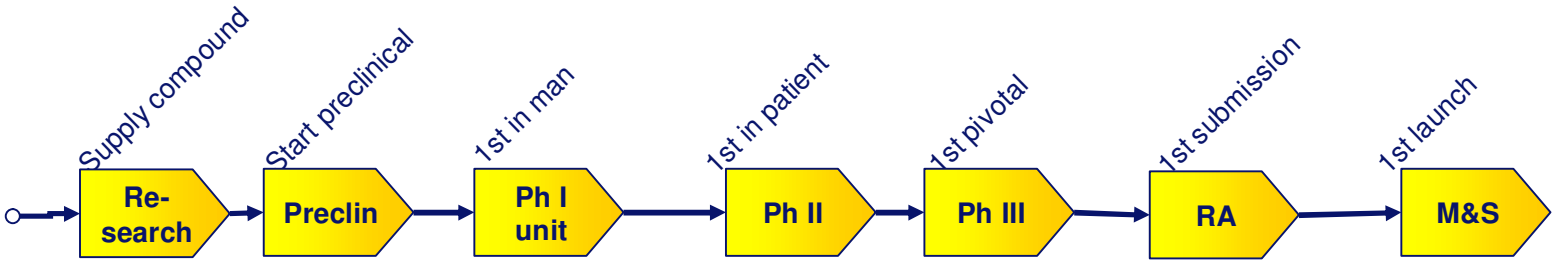
Advantages:

- Core competence in the area
- Usually highly educated, trained and motivated teams
- Knowledge, what to do and to what extent
- Organizational transparency

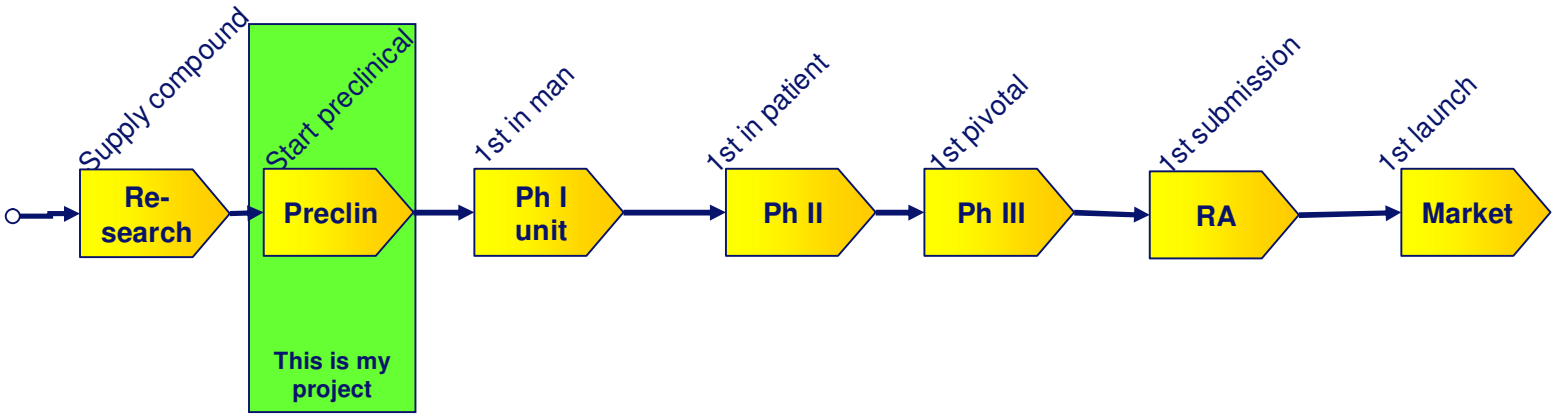
Disadvantages:

- Silo. The process is me.
- Resistant to the outside world (customer views).

Function view of development process



Function view of development process



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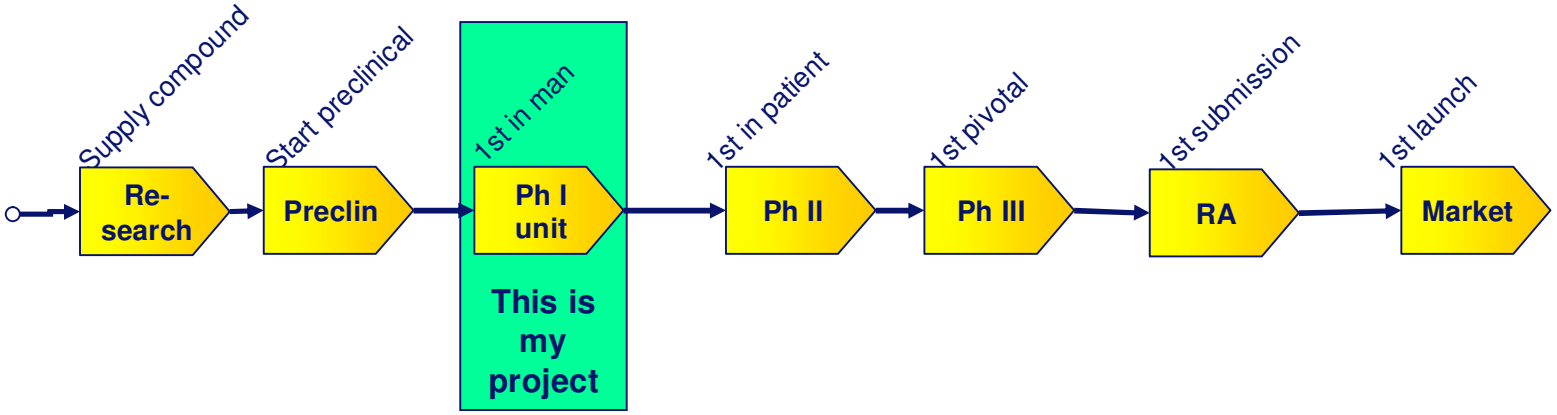

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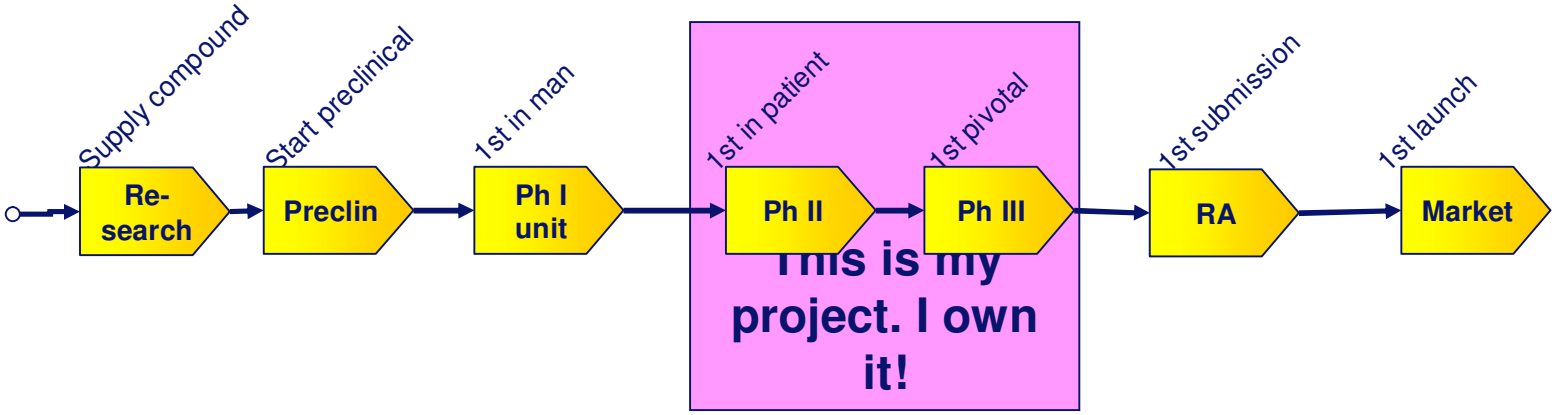
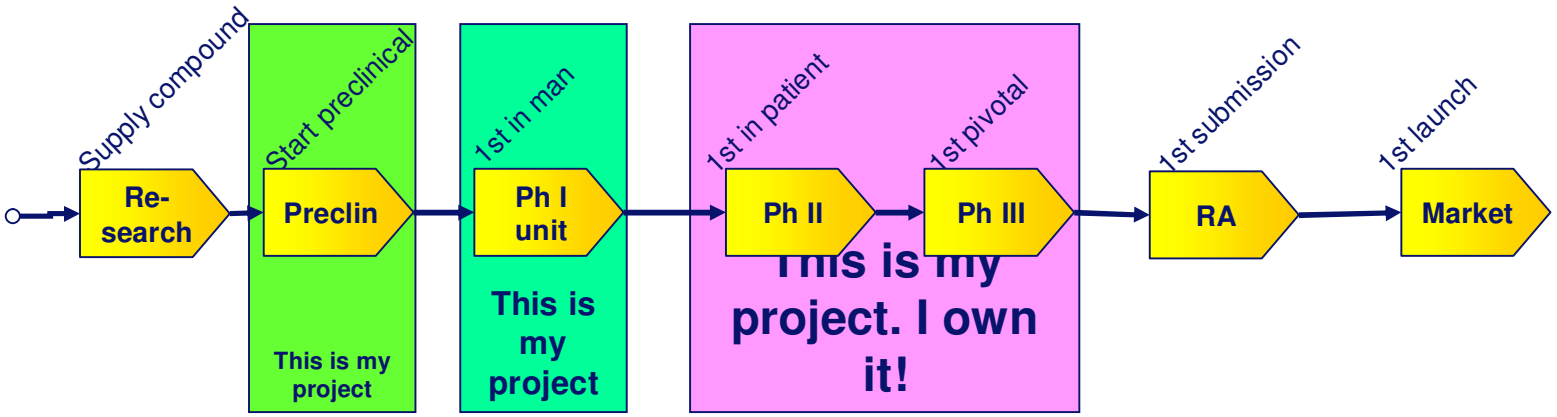


Function view of development process

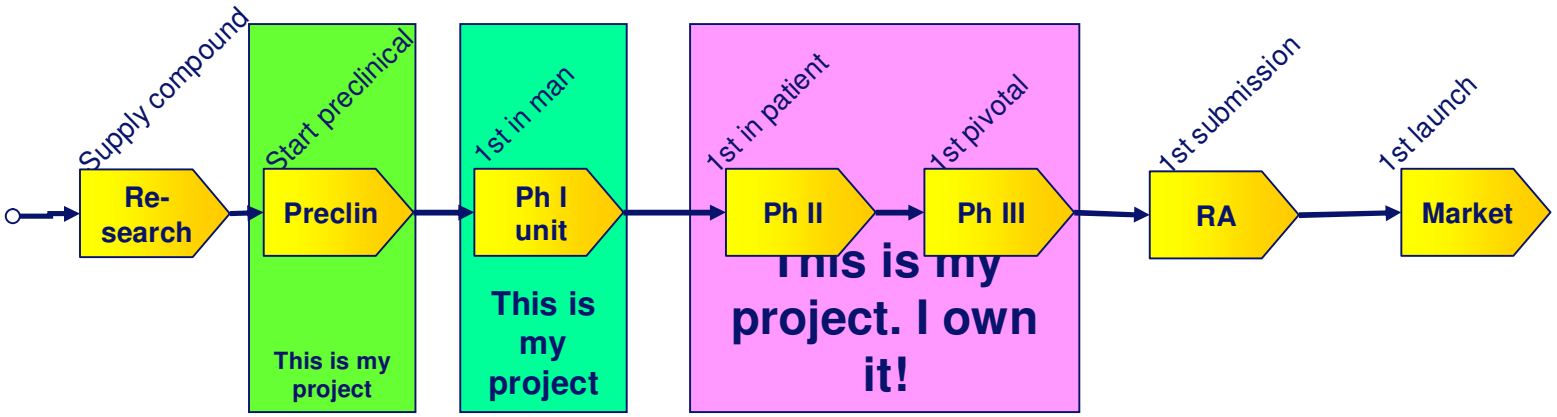


Key questions:

What can I do to answer all the (my) questions?

What can I do else?

Function view of development process



Key questions:

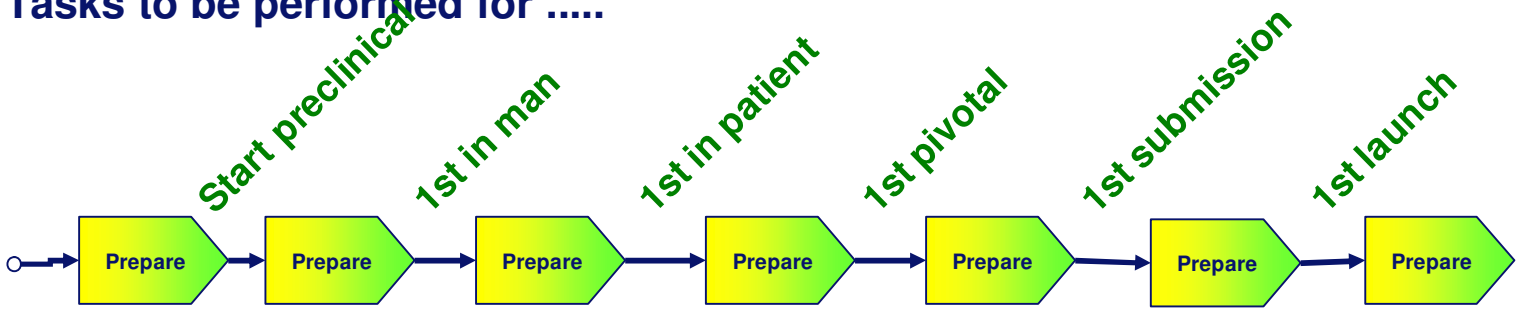
What can I do to answer all the (my) questions?

What else needs to be done?

Project Management has rather a weak, mainly coordinating role

Towards a change of roles and responsibilities

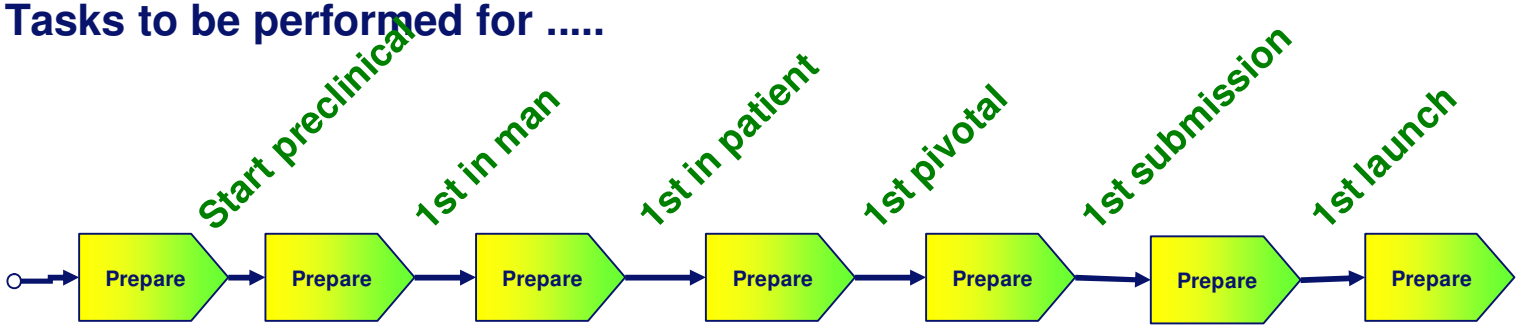
Tasks to be performed for .....



Functions and Process be separated!

Towards a change of roles and responsibilities

Tasks to be performed for .....



Functions and Process be separated!

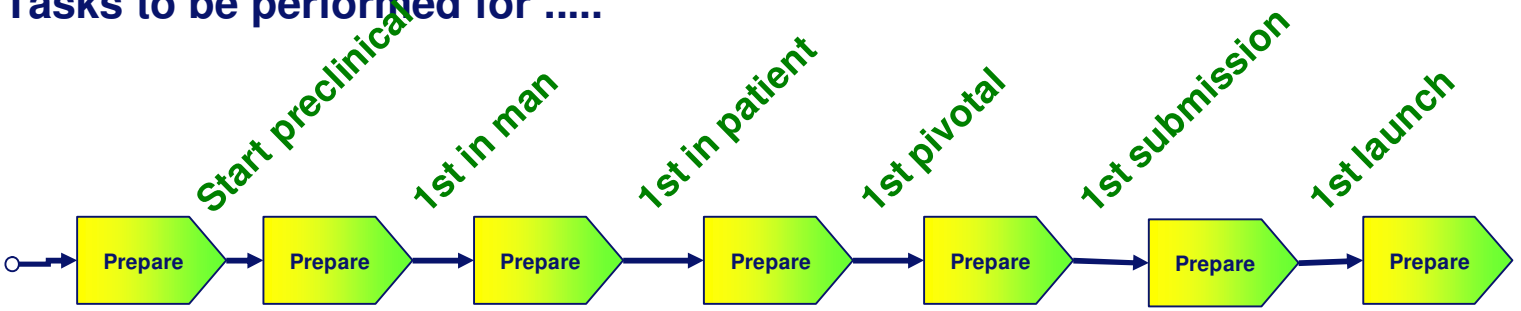
Key questions:

- **What (only) needs to be performed to start the next major task?**
- **Who can contribute to it?**

Functions become **suppliers** to the process (others may too).

Towards a change of roles and responsibilities

Tasks to be performed for .....



Functions and Process be separated!

Key questions:

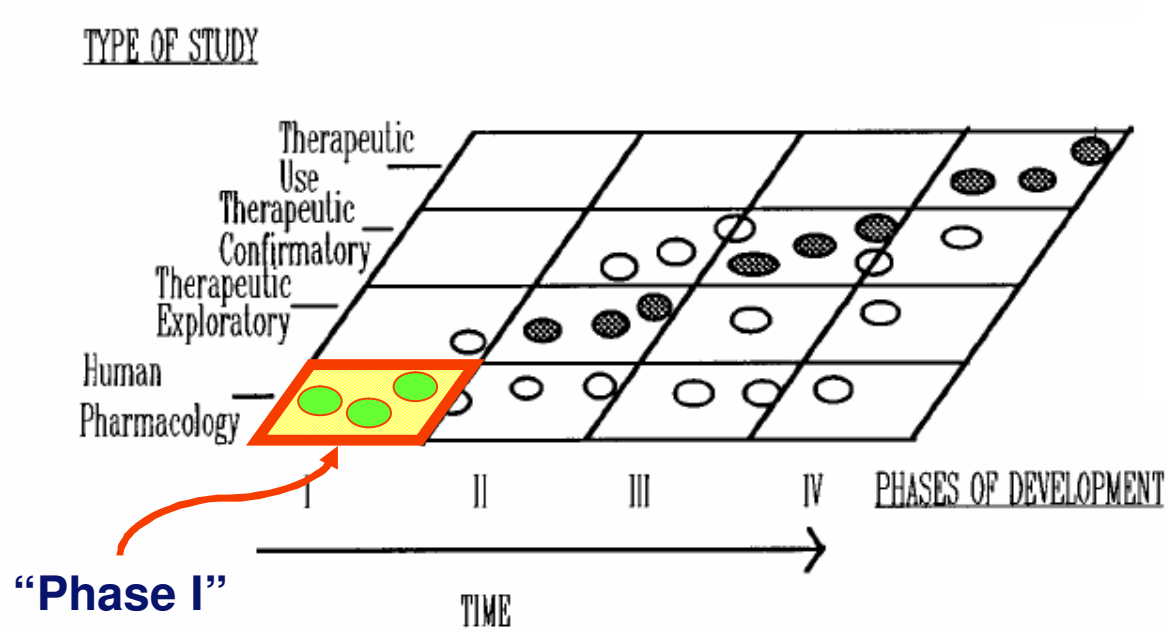
- **What (only) needs to be performed to start the next activity?**
- **Who can contribute to it?**

Functions become **suppliers** to the process (others may too).

Driver of the process: Project Management

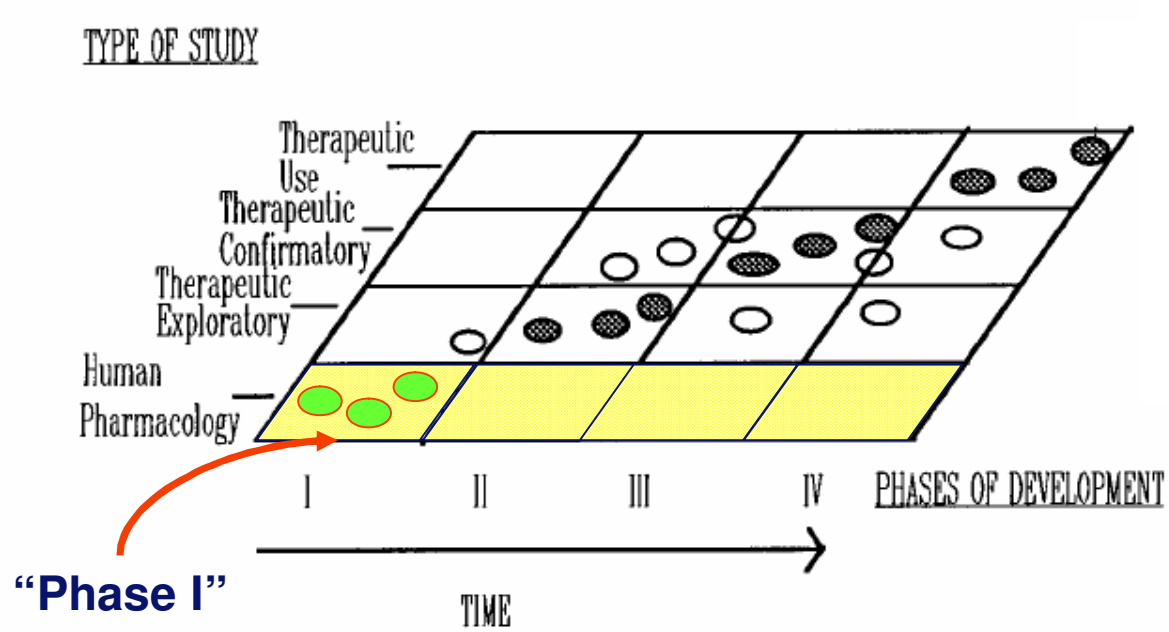
What would that mean for “Phase I”?

The development landscape

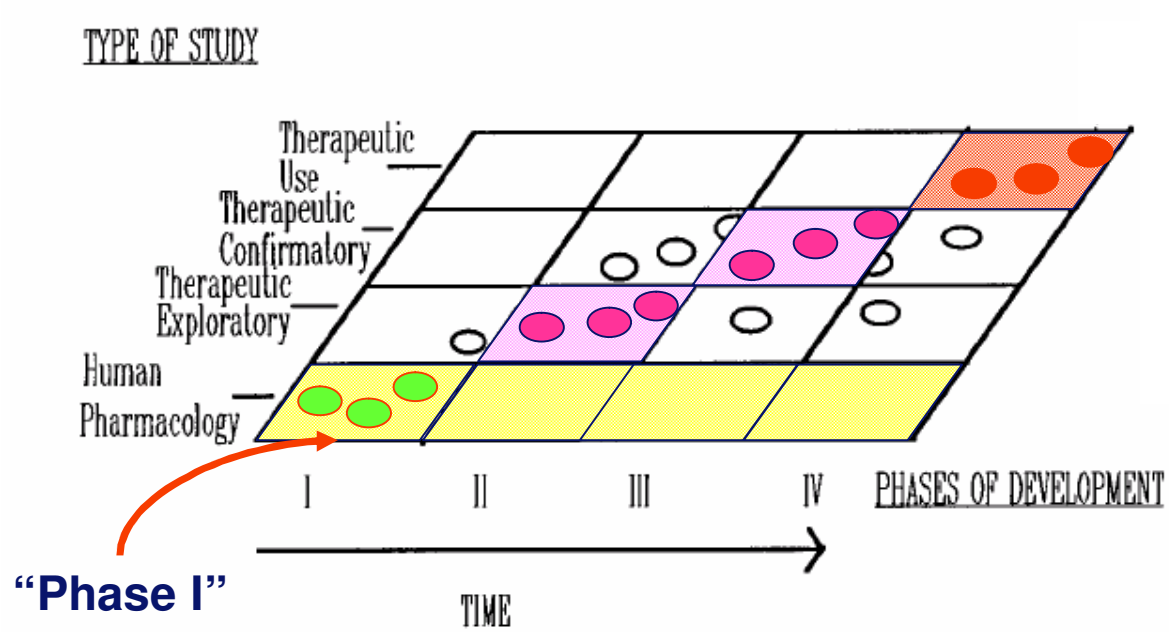


ICH E8; Federal Register / Vol. 62, No. 242 / Wednesday, December 17, 1997 / Notices
"General considerations for clinical trials..."

The development landscape



The development landscape



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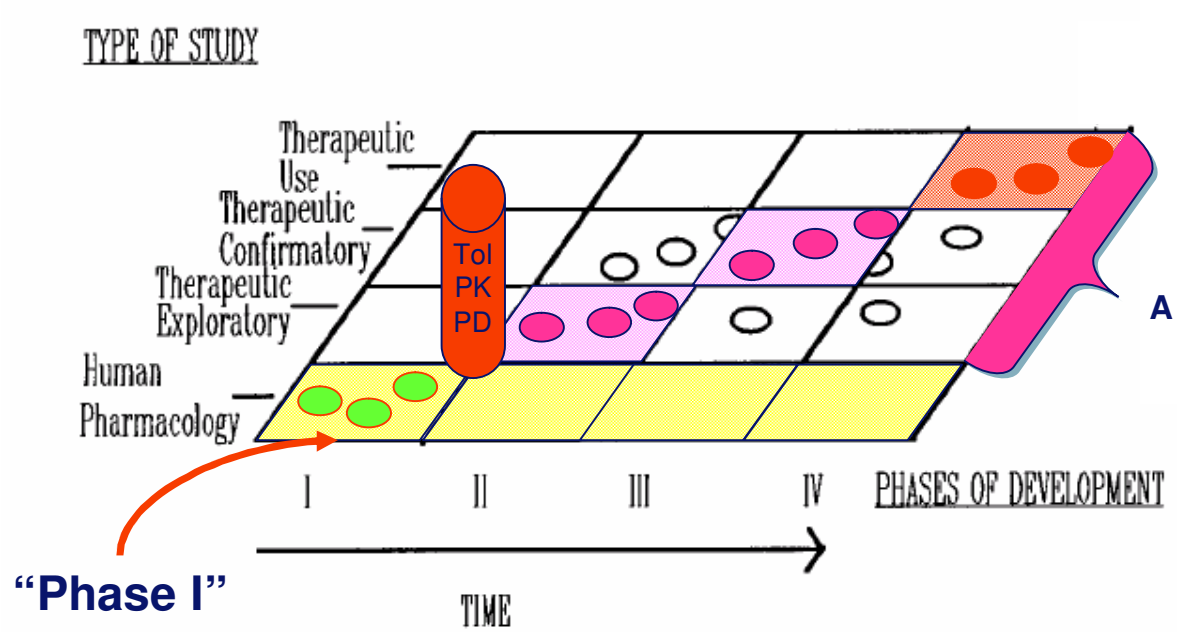
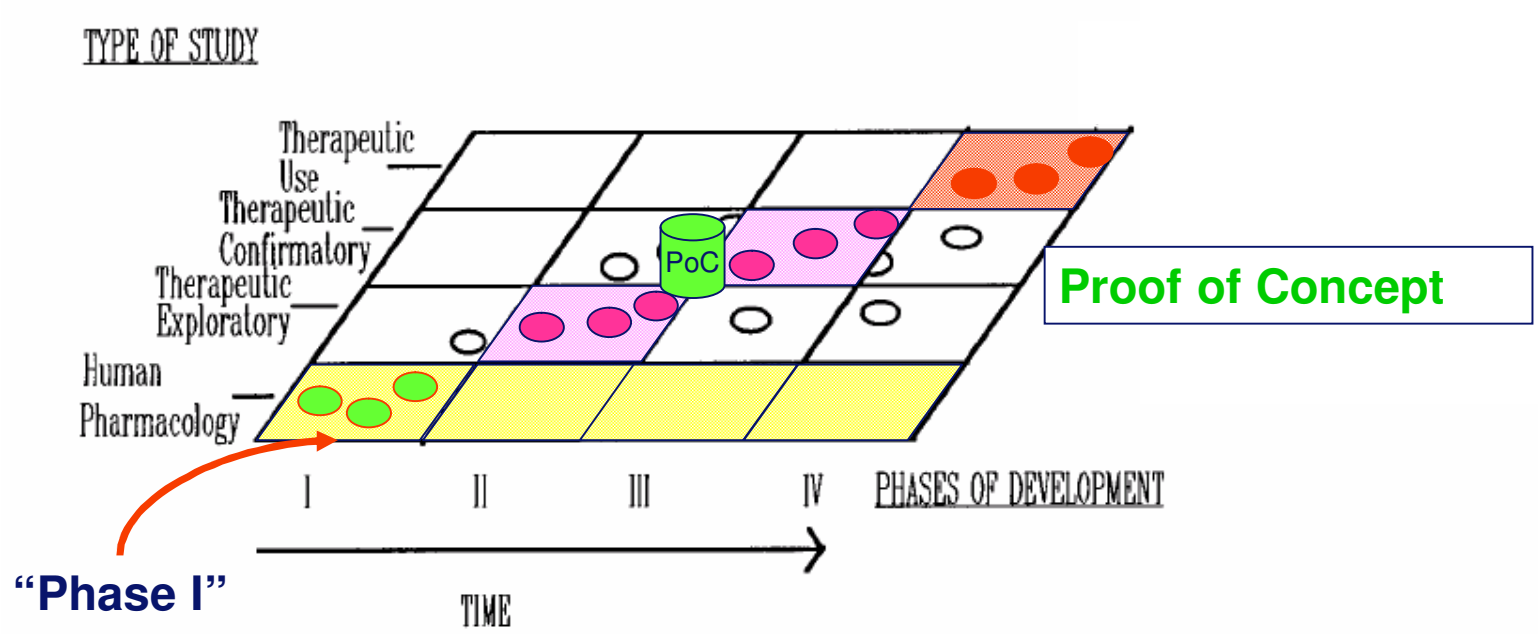


A clinical domain

"Phase I"

The development landscape



Proof of Concept: Definition

General

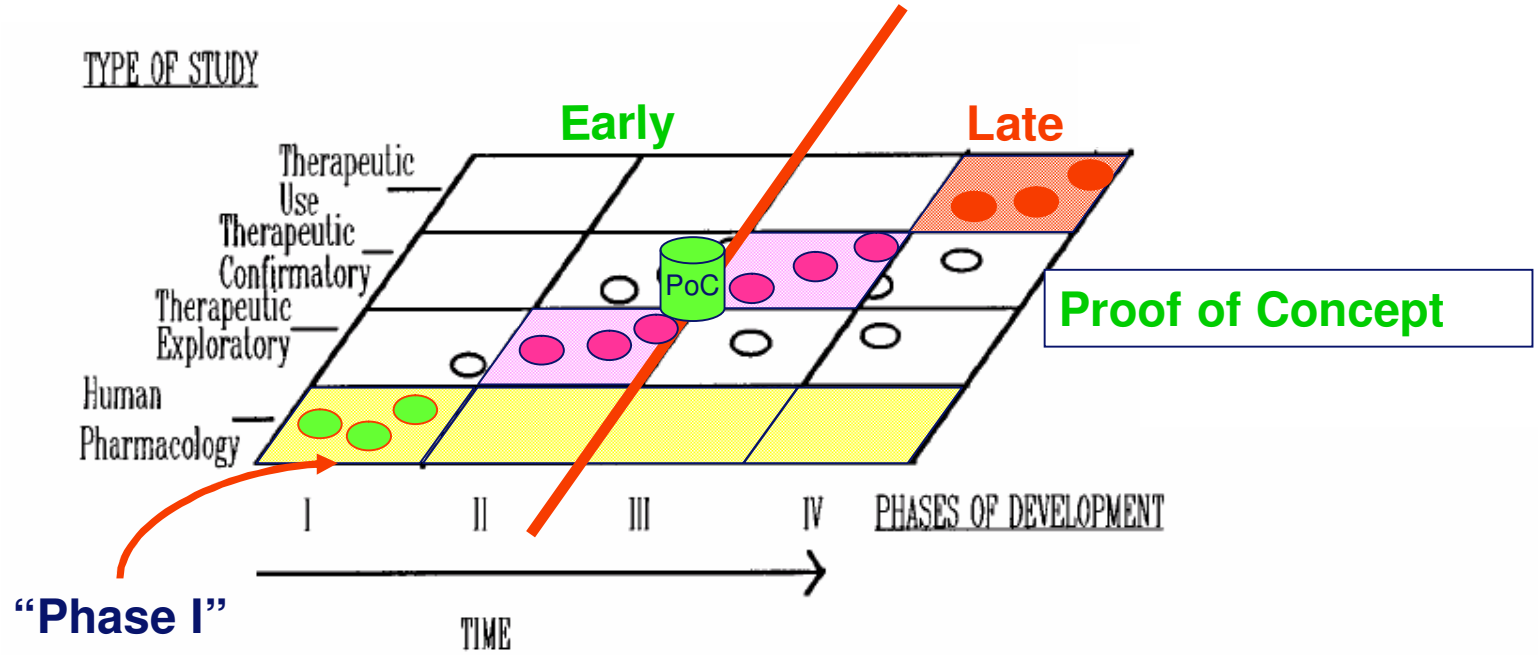
- Evidence, that a business model or idea is feasible. (Investorwords.com)

Pharma

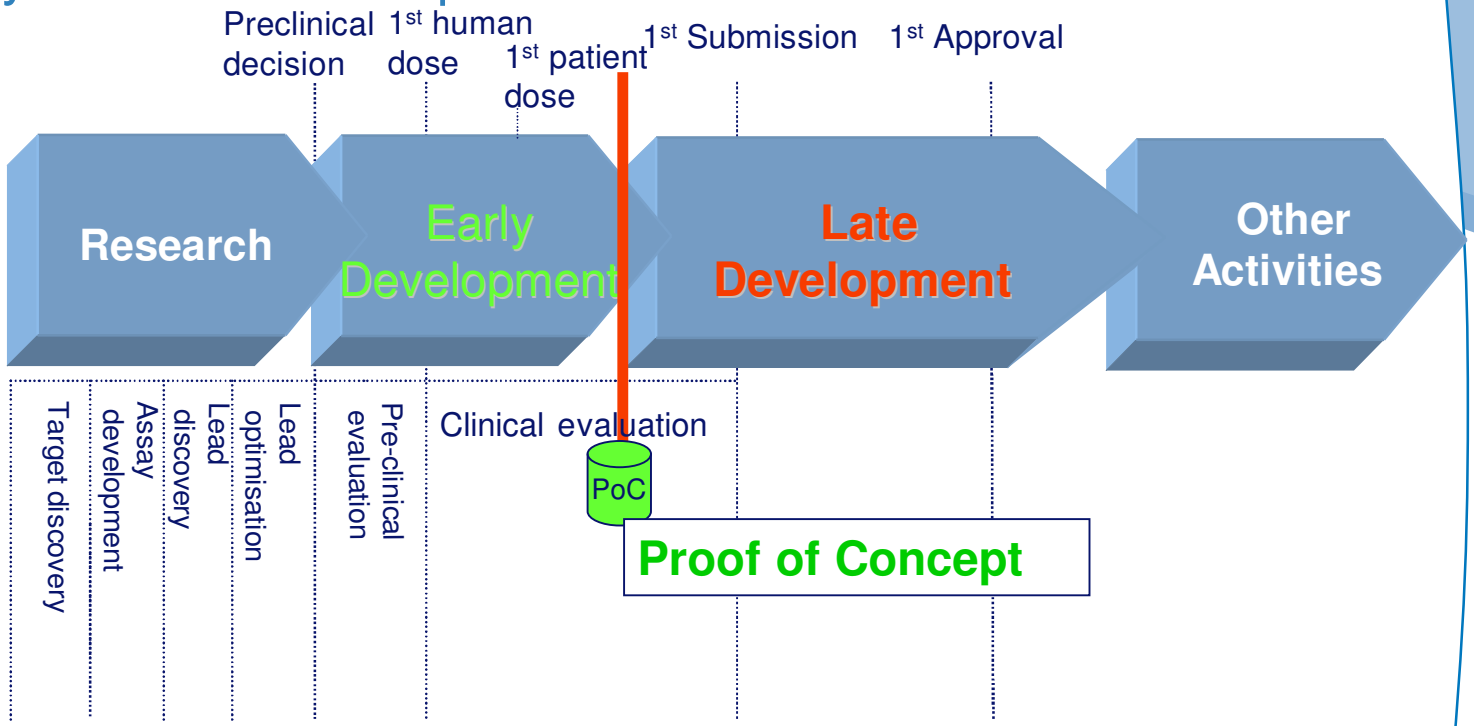
- Definitive clinical evidence has been gathered to allow recommendation to continue development of the project.

  The evidence should comprise scientific data (i.e. clinical endpoints, or clinical surrogate markers of such endpoints, or resulting biomarkers that provide a good indicator of clinical efficacy) and support the scientific concept for a project.
  (CMR intl)

The development landscape: divided into early and late

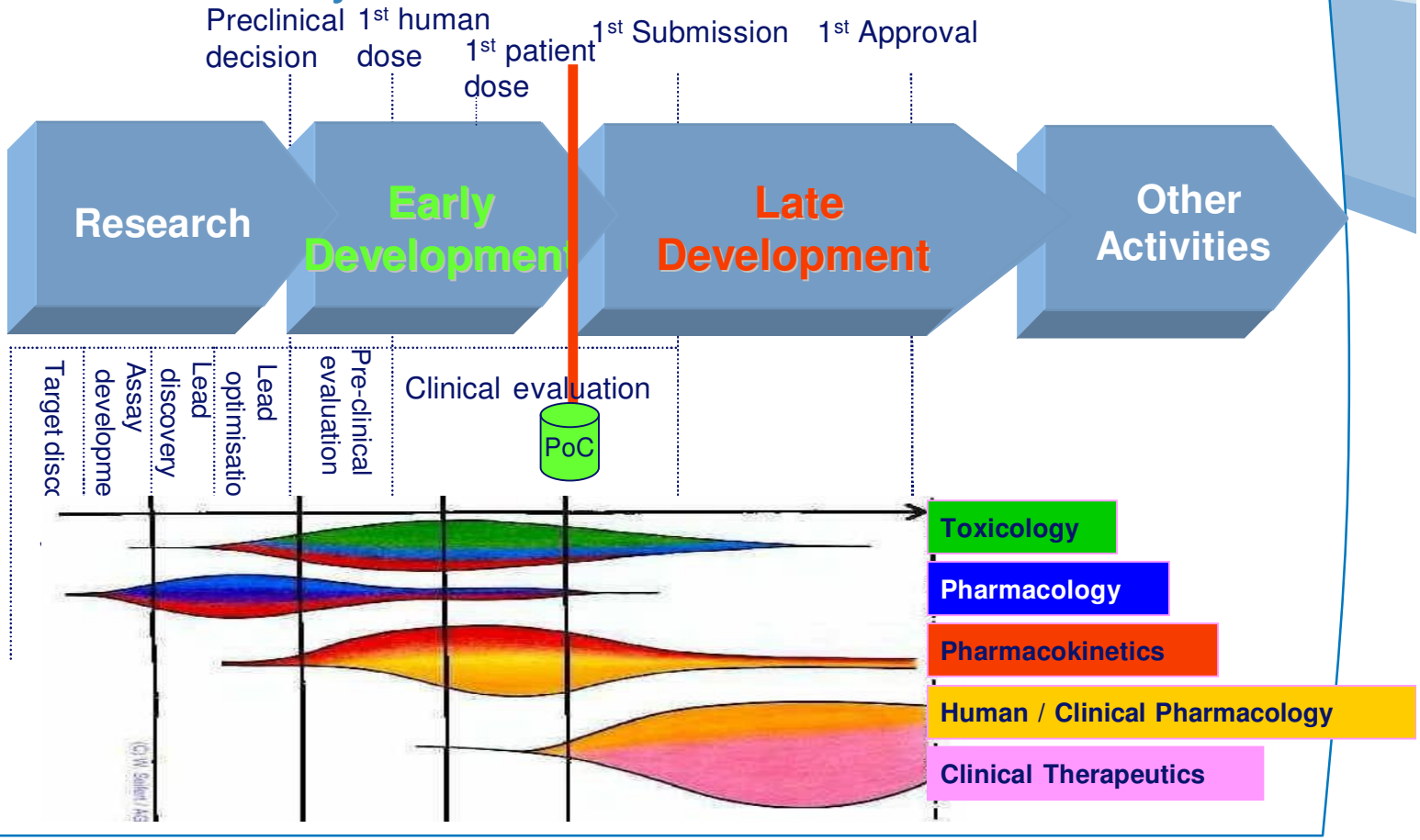


Early and late development



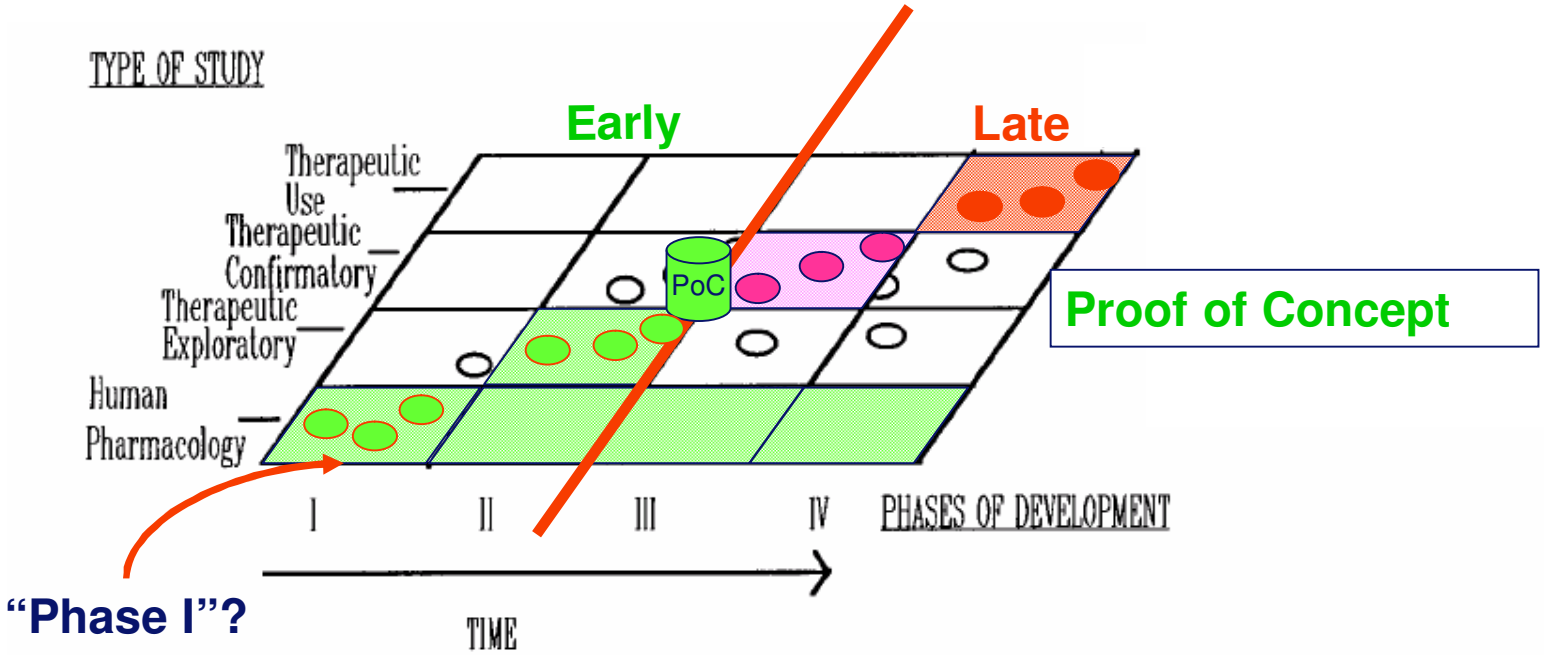
Source: CMR / AGAH Platform 2000

How "Phase I" may evolve?



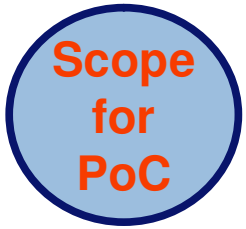
Sources: CMR; AGAH Platform 2000

...and the work area of “Phase I”



Method: Reverse engineering for PoC

1. Scope definition

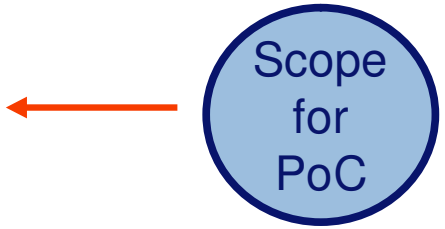


After K. Breithaupt-Grögler, M. Zühlsdorf and W. Seifert, 2004

Method: Reverse engineering for PoC

2. “Reverse engineering”

1. Scope definition



What is the essential
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immediate next step?
(fit for purpose)

Method: Reverse engineering for PoC

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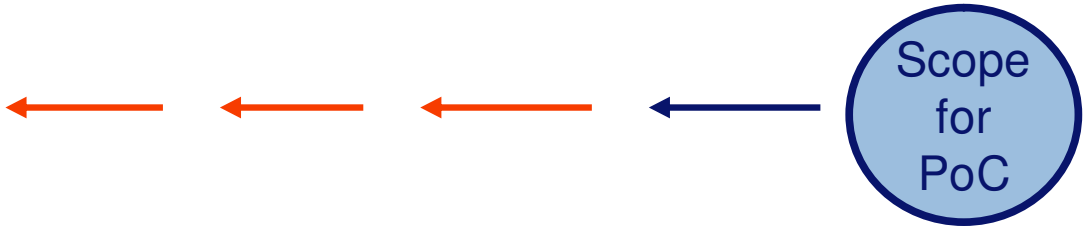

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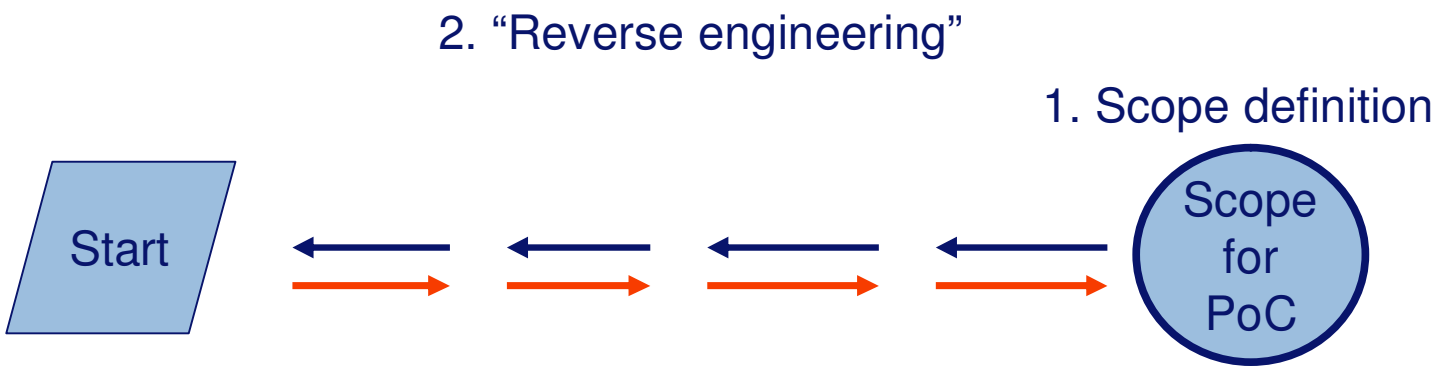
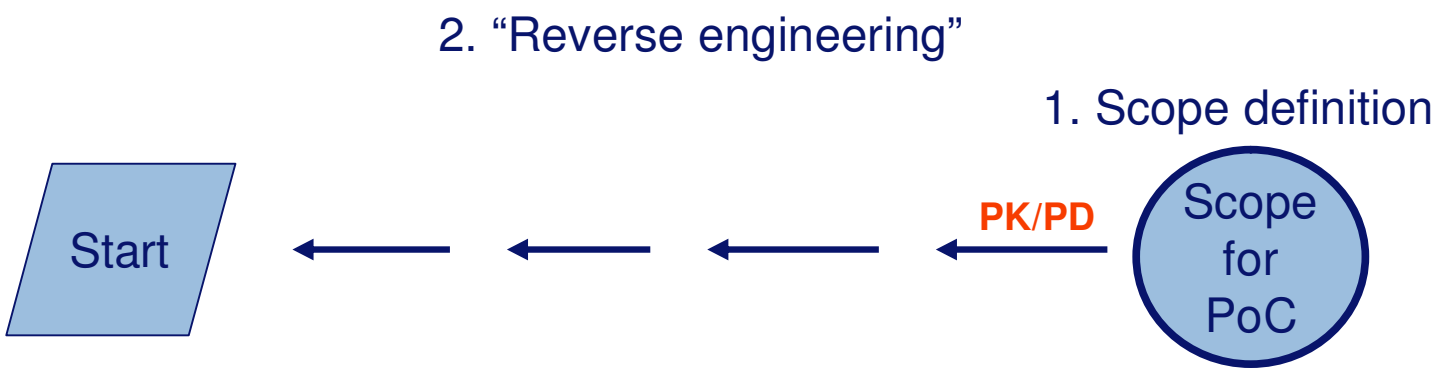
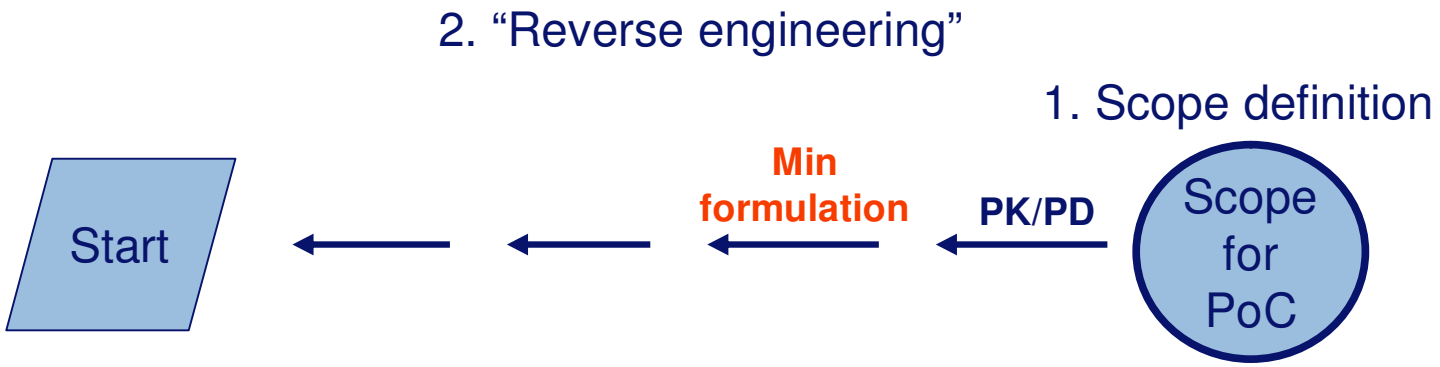


Result: A set of essential tasks to perform the next step

Method: Reverse engineering for PoC



Method: Reverse engineering for PoC



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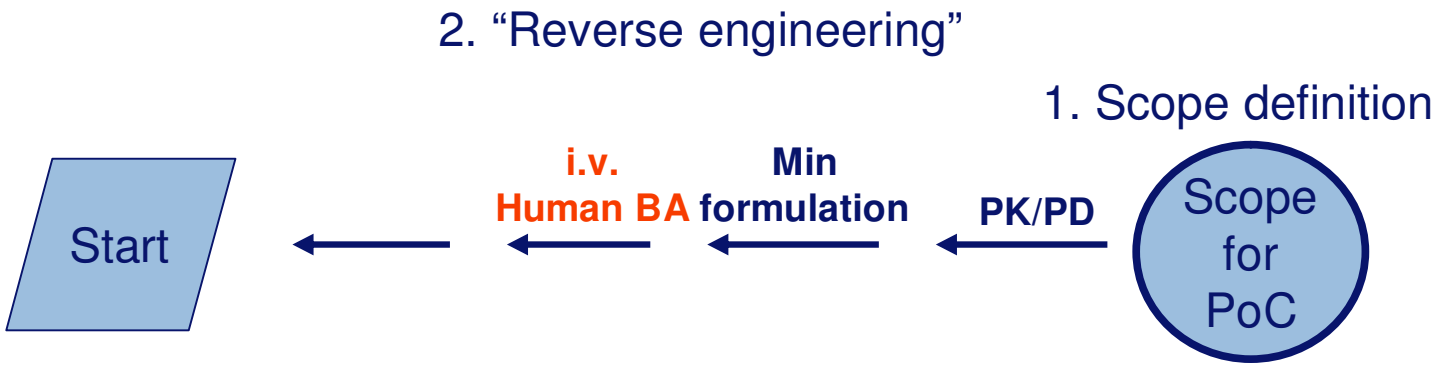

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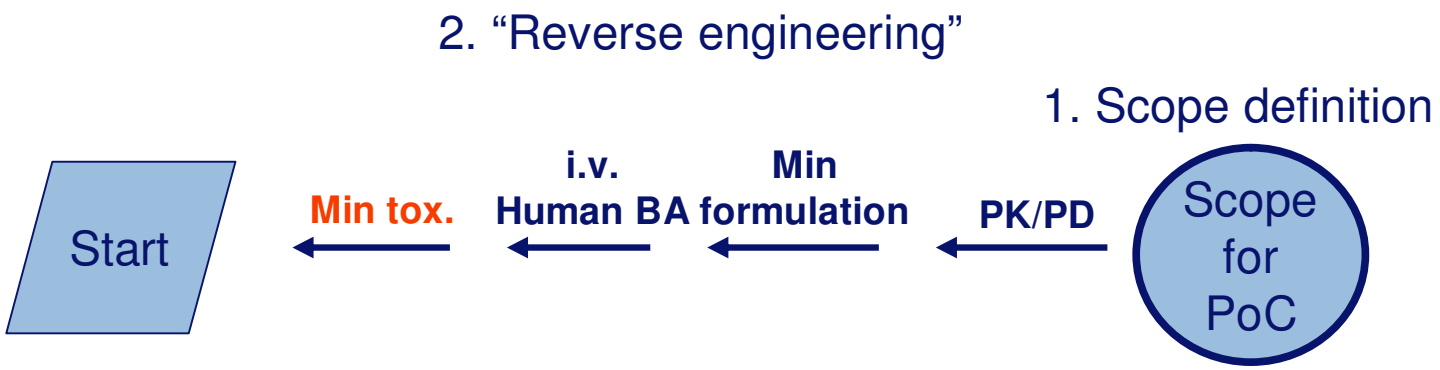

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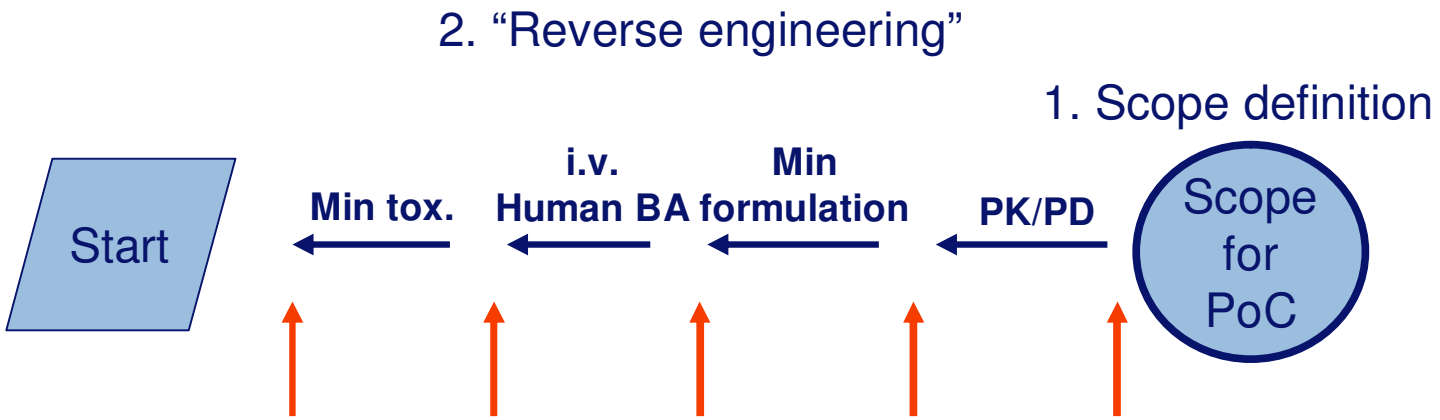

3. Involvement of suppliers

Method: Reverse engineering for PoC

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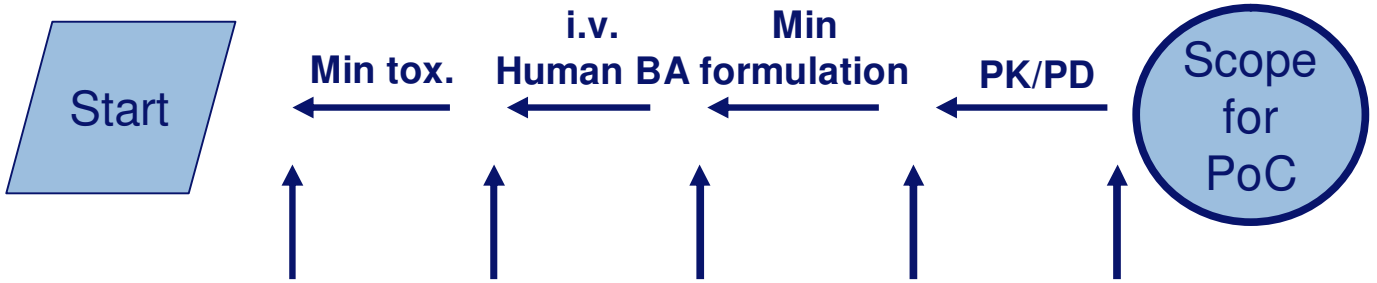
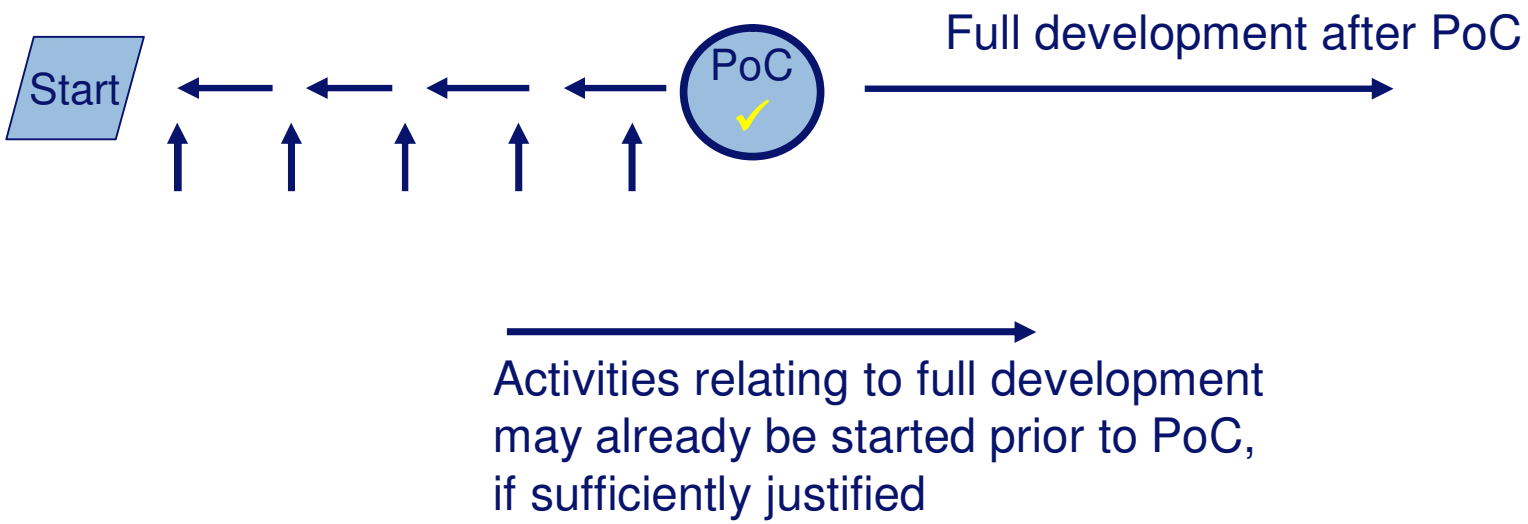


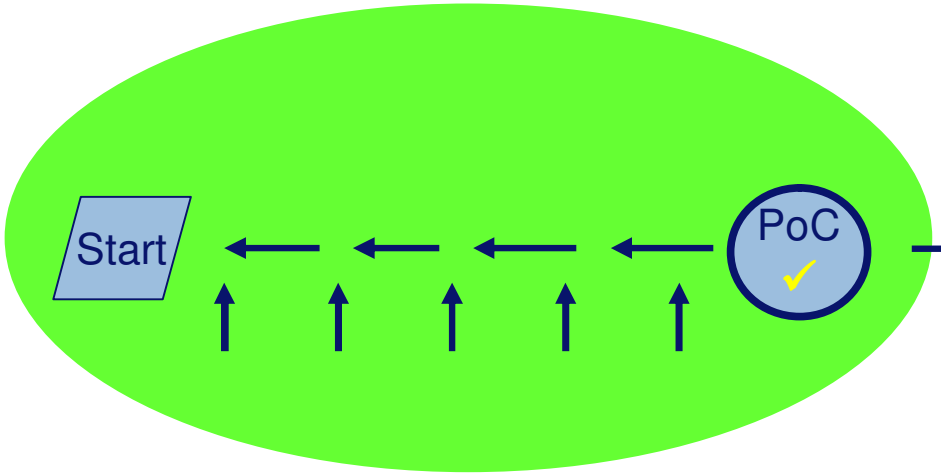
4. Planning and communication

3. Involvement of suppliers

Full development

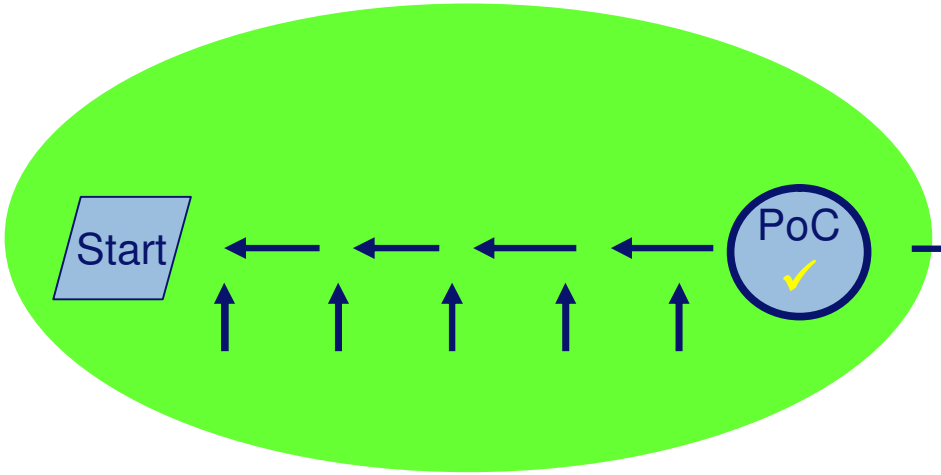


Expanded work area



Approach allows higher throughput in early stages and increase sustainability of pipeline

Expanded work area



Approach allows higher throughput in early stages and increase sustainability of pipeline

Early Development is the target work area of experts from “Phase I”

Summary

- Business aspects
  - ➔ Reduced output, increased cost and time
- Sustainability of the development pipeline
- Impact of cycle times for delivery of new products
- Process changes
  - ➔ From functional ownership to a process view
  - ➔ More power to the project management
  - ➔ Involvement of suppliers
- Development landscape with new opportunities
- Integration with a Proof of Concept environment and mindset
- Reverse engineering: Focused and “fit for purpose”

Is Phase I useful?

Yes and No.

There is a need for non-therapeutic trials in humans,
as targeted as possible,
but not as a "Phase",

rather as an integrated element in the
transition
from preclinical to clinical-therapeutic work