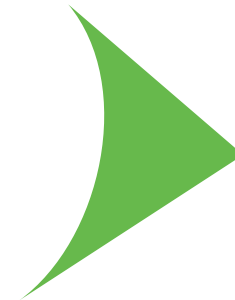


Rapid Pharma Development GmbH

**No API no Studies**  
**Accelerated CMC**  
**Development**

***RPD***

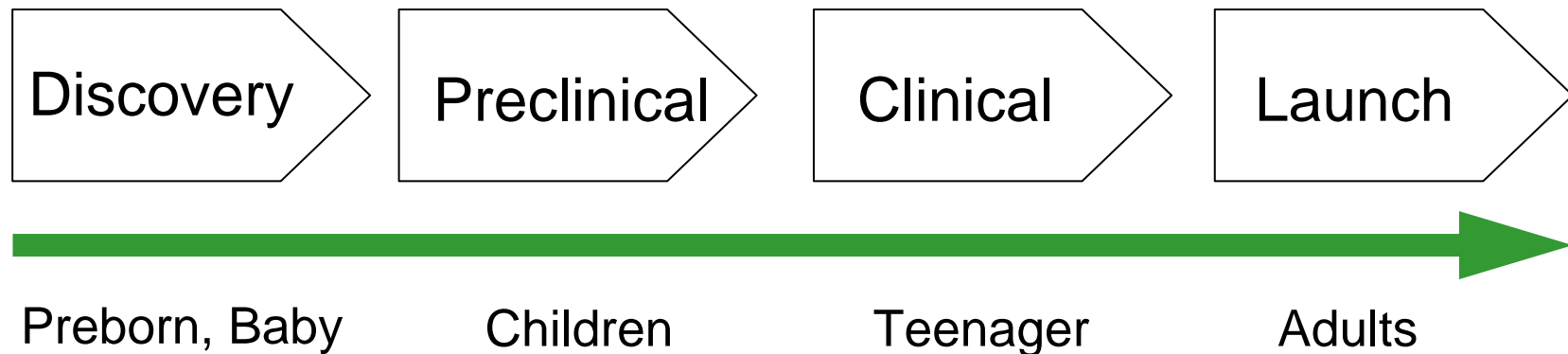


***Rapid Pharma Development***

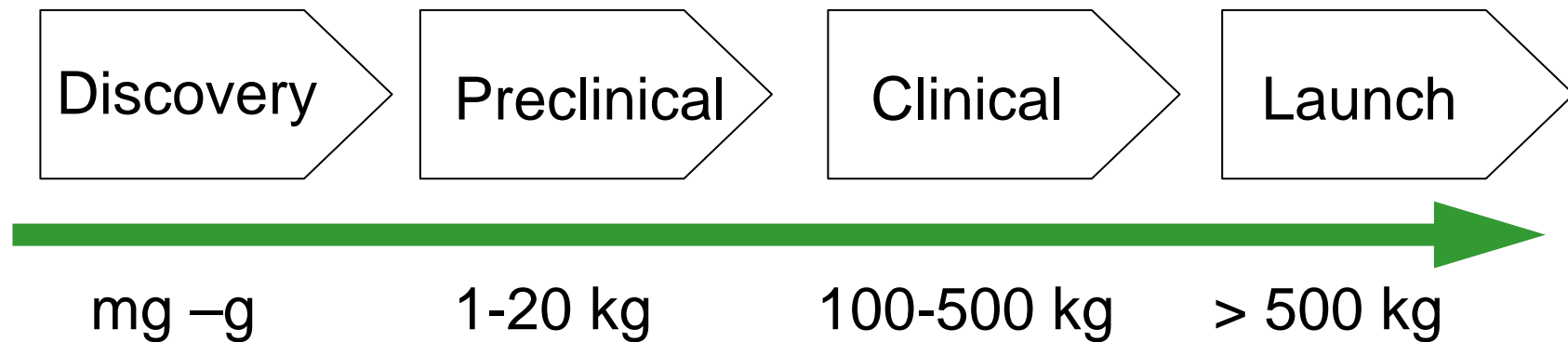
# Outline and Objective



- Objective: Requirements for Chemical Development during a drugs life, particularly in the Preclinical and Clinical Phase

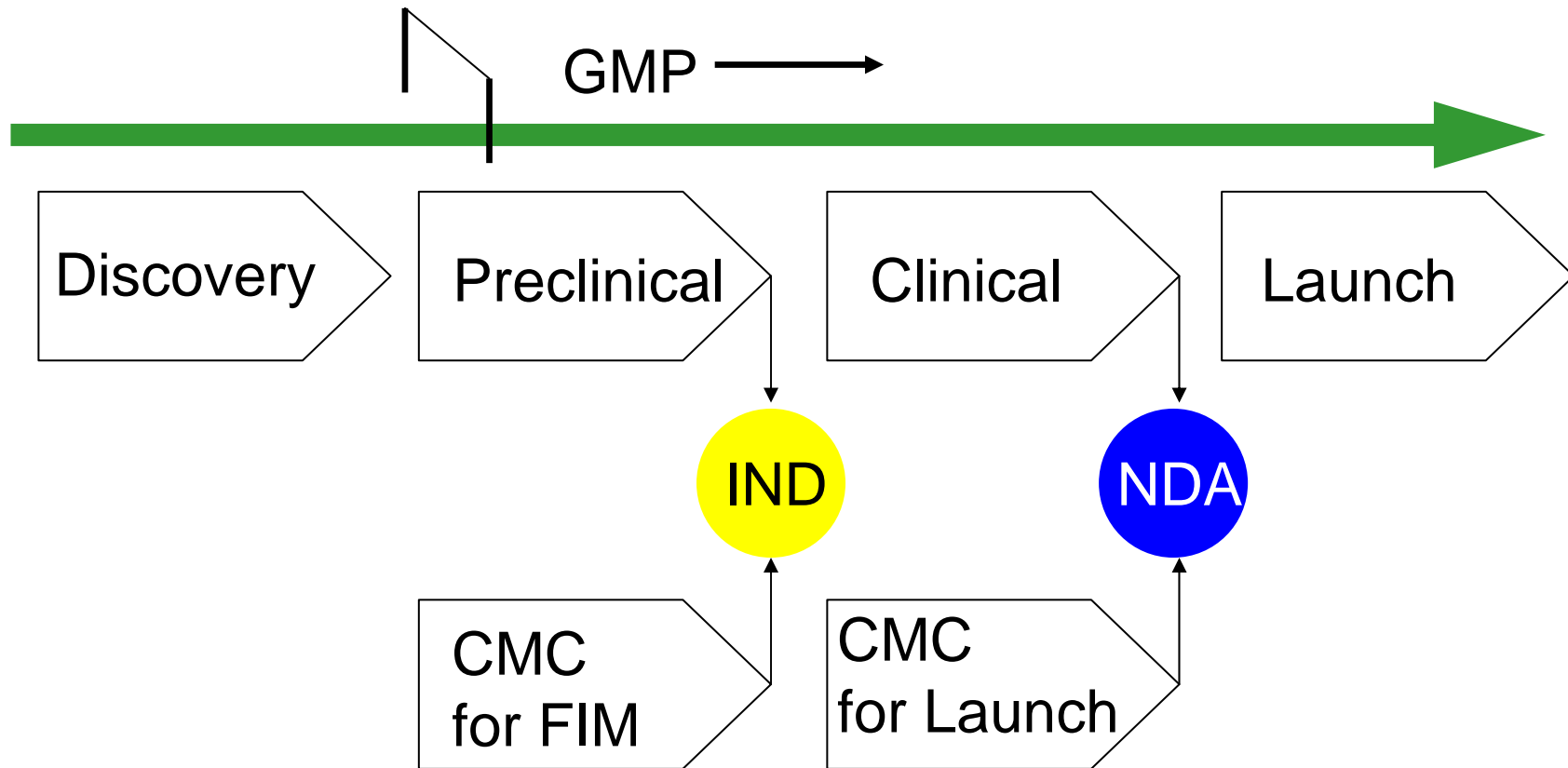


# API Supply: Quantities



API Supply is always on the critical path

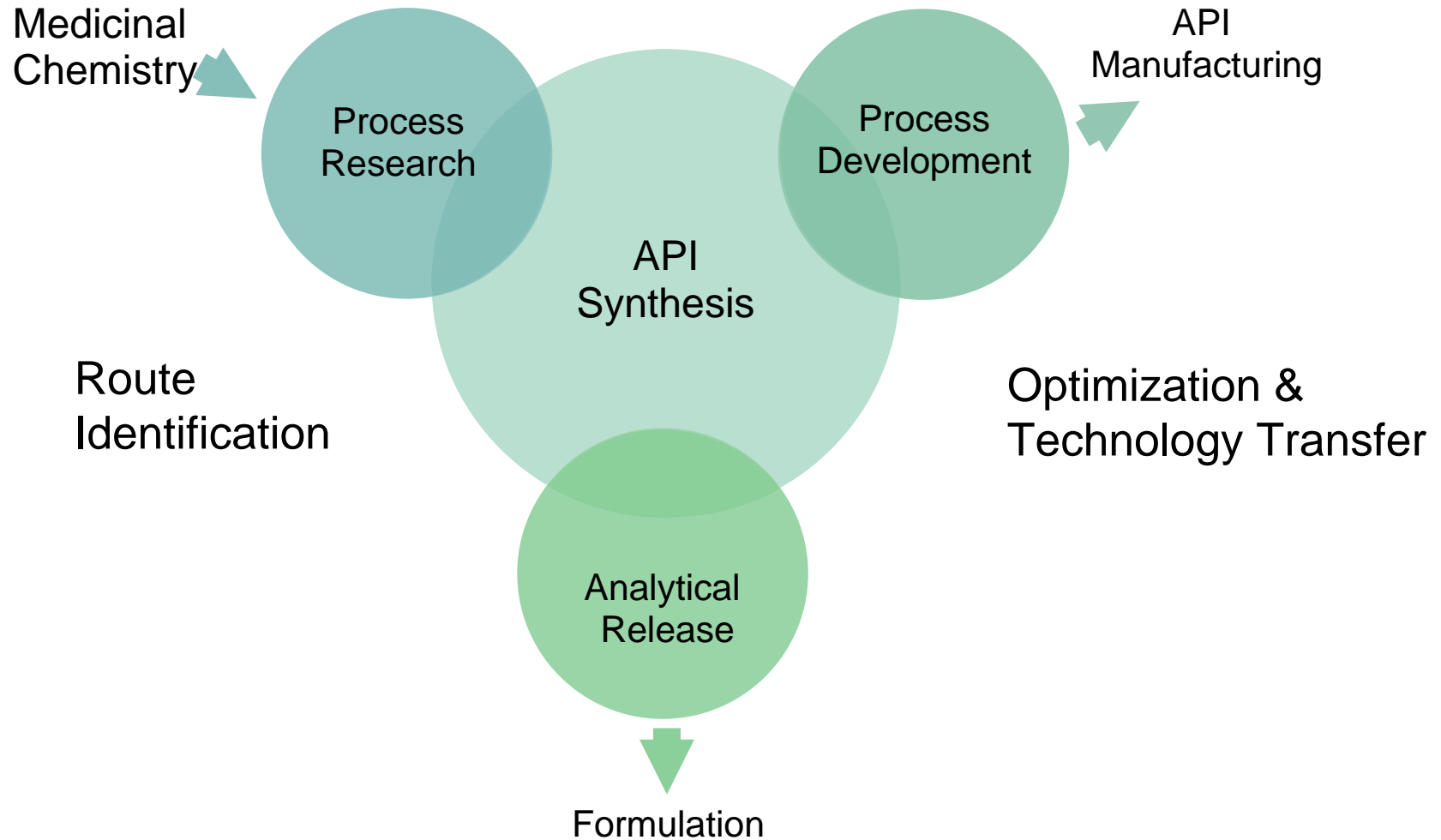
# API : Regulatory Requirement



Information Sources [www.ich.org](http://www.ich.org) [www.fda.gov/cder/handbook/](http://www.fda.gov/cder/handbook/)

<http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm>

# API Supply



# API : First Scale Up



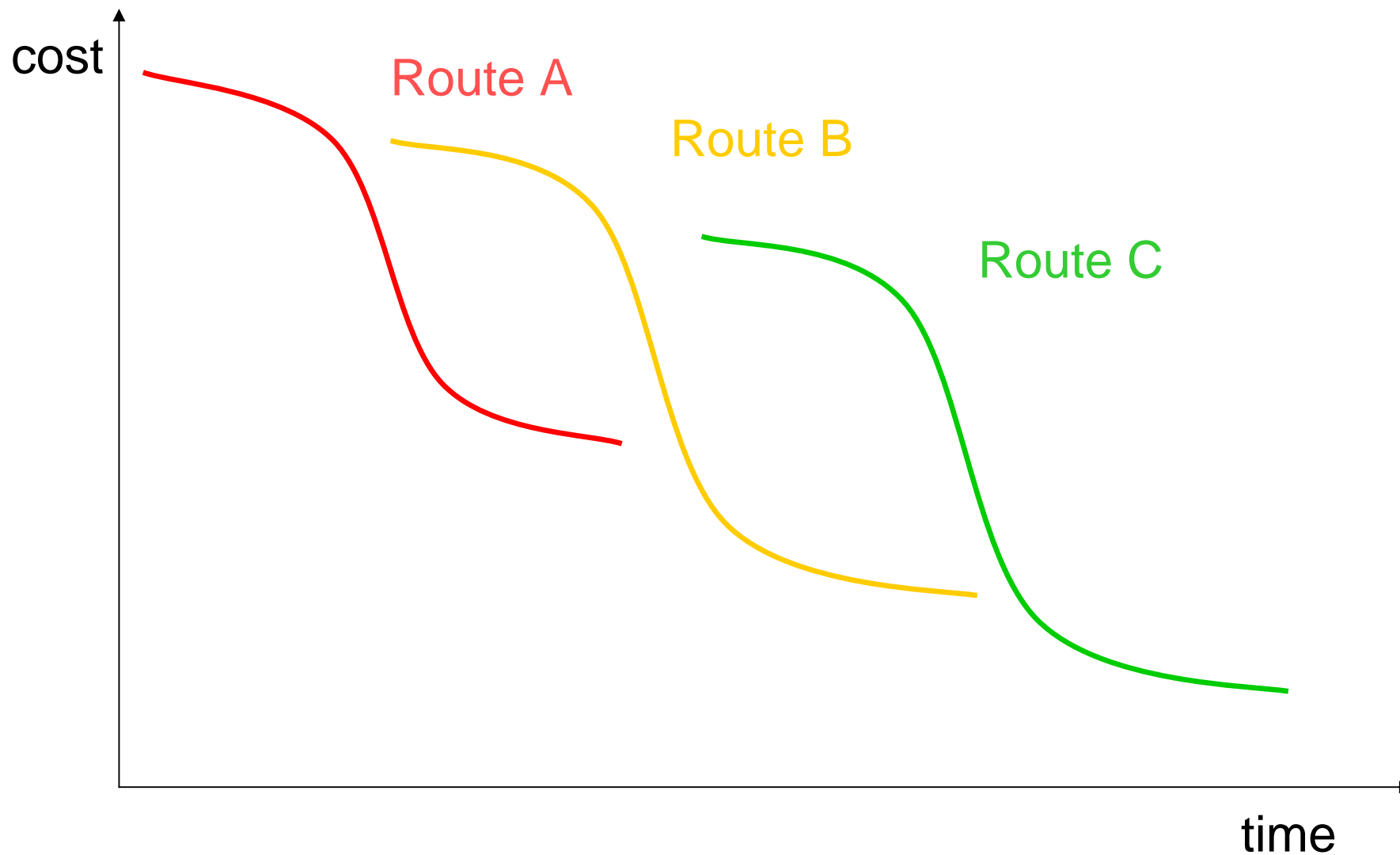
- Time is more important than cost
- Purity should be reasonable (not too high)
- Quantities
- 0.5 – 1 kg Toxicology, good documentation
- 5-10 kg FIM study, use GMP

## How to get there



- Route ID versus Route Optimization
- Focus on throughput not on yield
- Qualify your impurities
- Cost of goods assesement

# Time vs Cost



## INPUTS

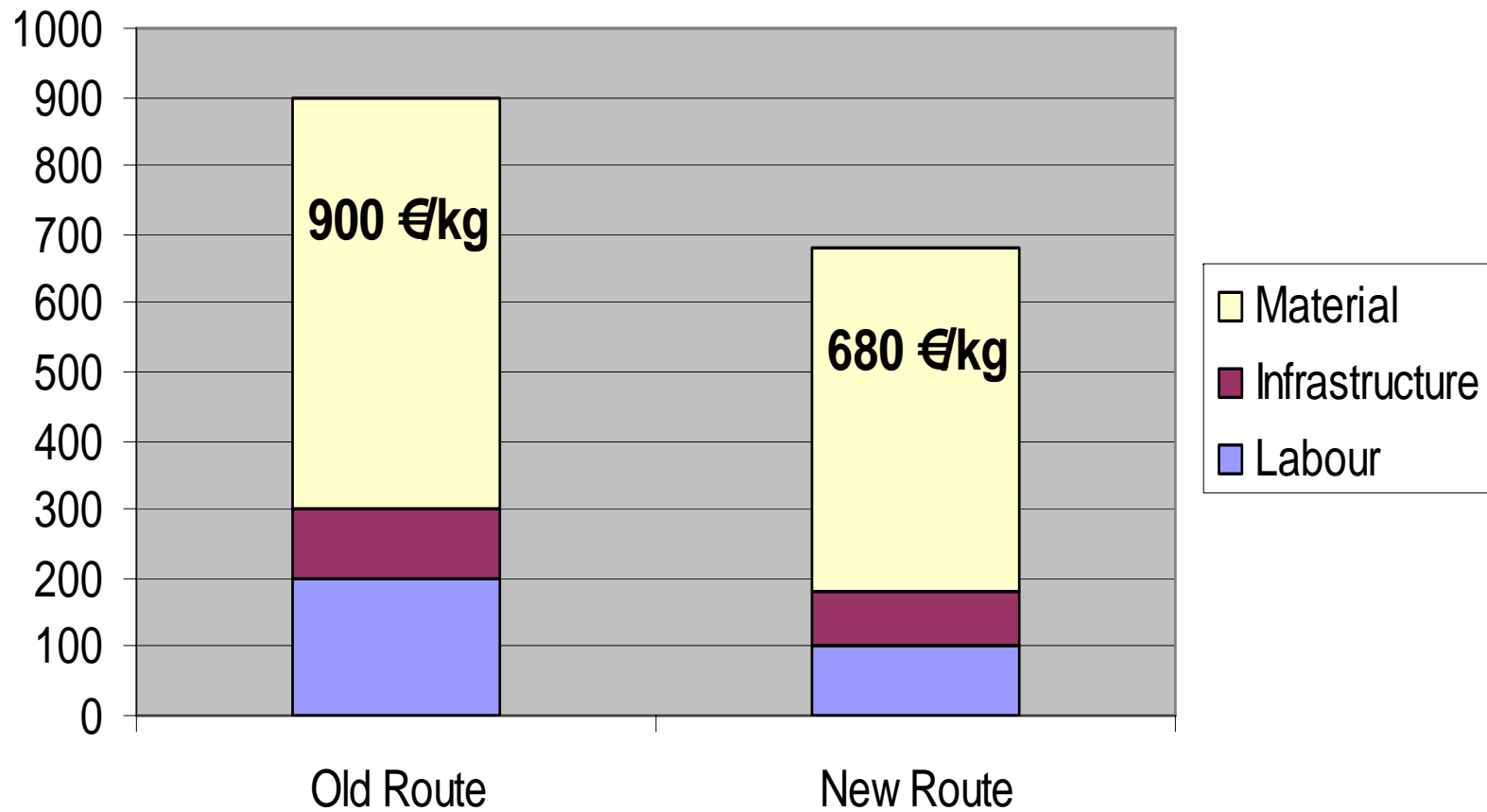
- Synthesis description
- Raw Material Prices
- Expected Annual Quantity
- Reactor and Labour costs
- Assumptions of Optimization

## OUTPUTS

- Cost of Goods per kg
- Cost distribution
  - Materials (raw and waste)
  - Labour (operators, cleaning, set-up)
  - Infrastructure (reactors, centrifuges)
- Cost drivers (Yield!)

# Cost Evaluation System

## Cost Analysis based on 5 ton/a



## Tips for early Scale-Up



- Safety: Run DSC; RC-1 involve experts
- Robustness: Avoid inhomogeneity
- Only replace reagents/solvents that you absolutely cannot use
- Chromatography yes but not for API
- Crystall forms: use n+1 Strategy

# Solid State Issues



- API may occur in different forms: hydrates, polymorphs, amorphous, with different counterions
- The solid state form influences the bioavailability and needs to be controlled
- Do a crystallization study and if applicable a salt screening study as early as possible

# Polymorphism: Ostwalds Rule



- When leaving a given state and in transforming to another state, the state which is sought out is not the thermodynamically stable one, but the state nearest in stability to the original state.

Wilhelm Ostwald, Z. Phys. Chem. 1897

Solution → Amorphous → Crystal form I → form II

## Examples: Ritonavir

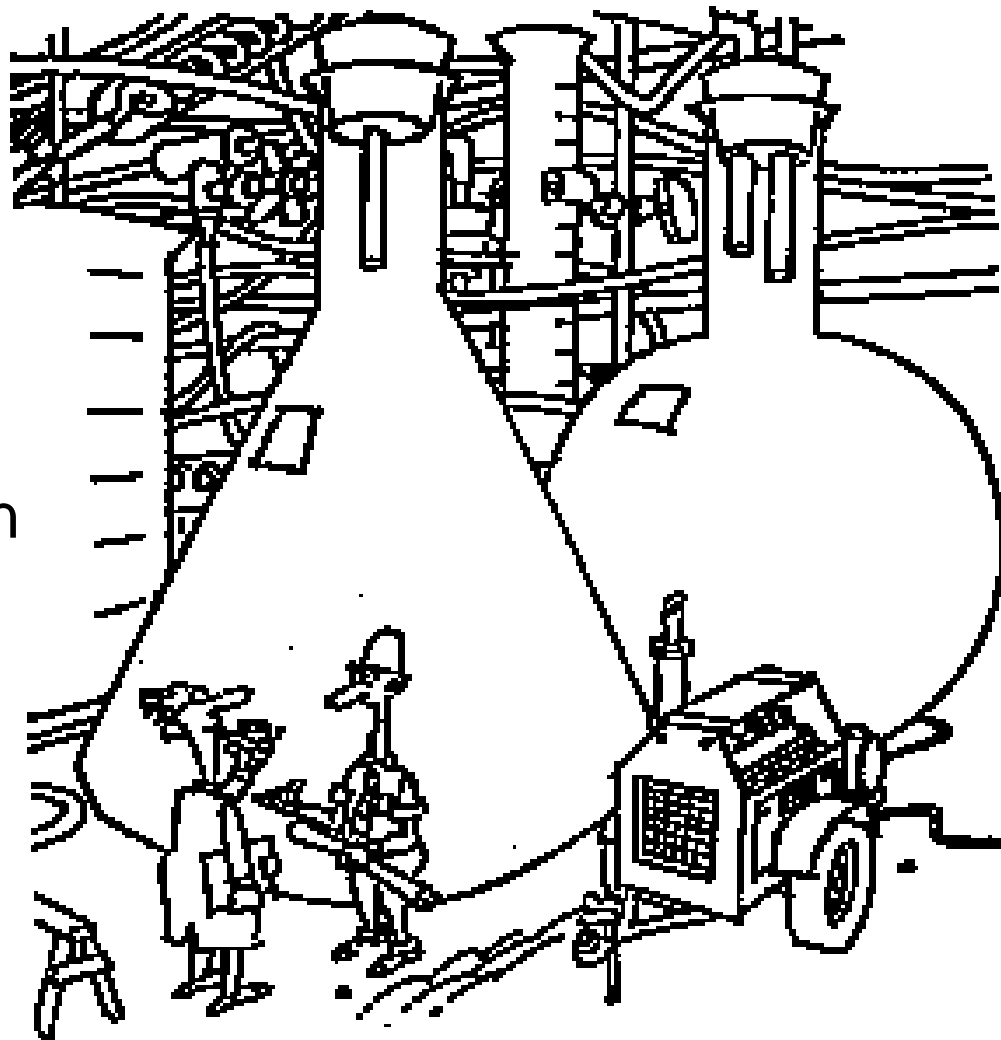


- In 1996 Ritonavir was approved and launched as Norvir. In 1998 a form II appeared which failed dissolution testing.
- Abbott was quickly in a market crisis because the supply was depleting and API process no longer delivered form I
- Finally Abbott could prove that they have control over manufacturing of form I

Lit. Org. Proc. Res. & Dev. 2000, 413

# Commercial Process for API

From kg quantities  
to  
commercial production



## Phase II/III/Launch:



- Impurity profile fixed (freeze process)
- Quantities several hundreds of kg, c-GMP
- Cost of goods competitive but not generic

# API for phase III and launch



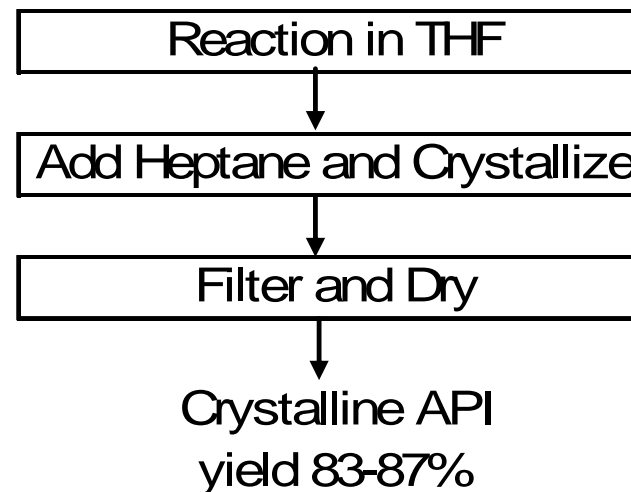
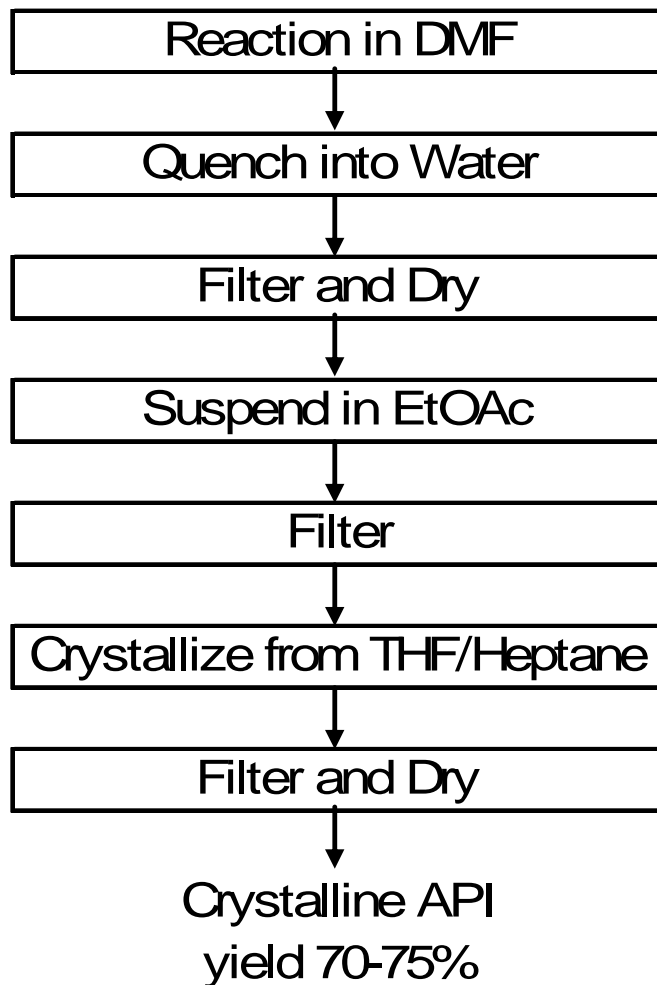
- Investigative Optimization first with a focus on cost drivers
- Replace chromatography
- Use automation for
  - Reaction screening
  - Crystallization i.e solvent screening
- Select your suppliers (at least two)
  - For raw materials intermediate
  - CMO partners
- Identify critical parameters

# The Perfect Process



- Heat the reactants, cool down and filter off the crystals
- How to get there?
- Start at the end: What is my  $n+1$  step

# The bottom up approach



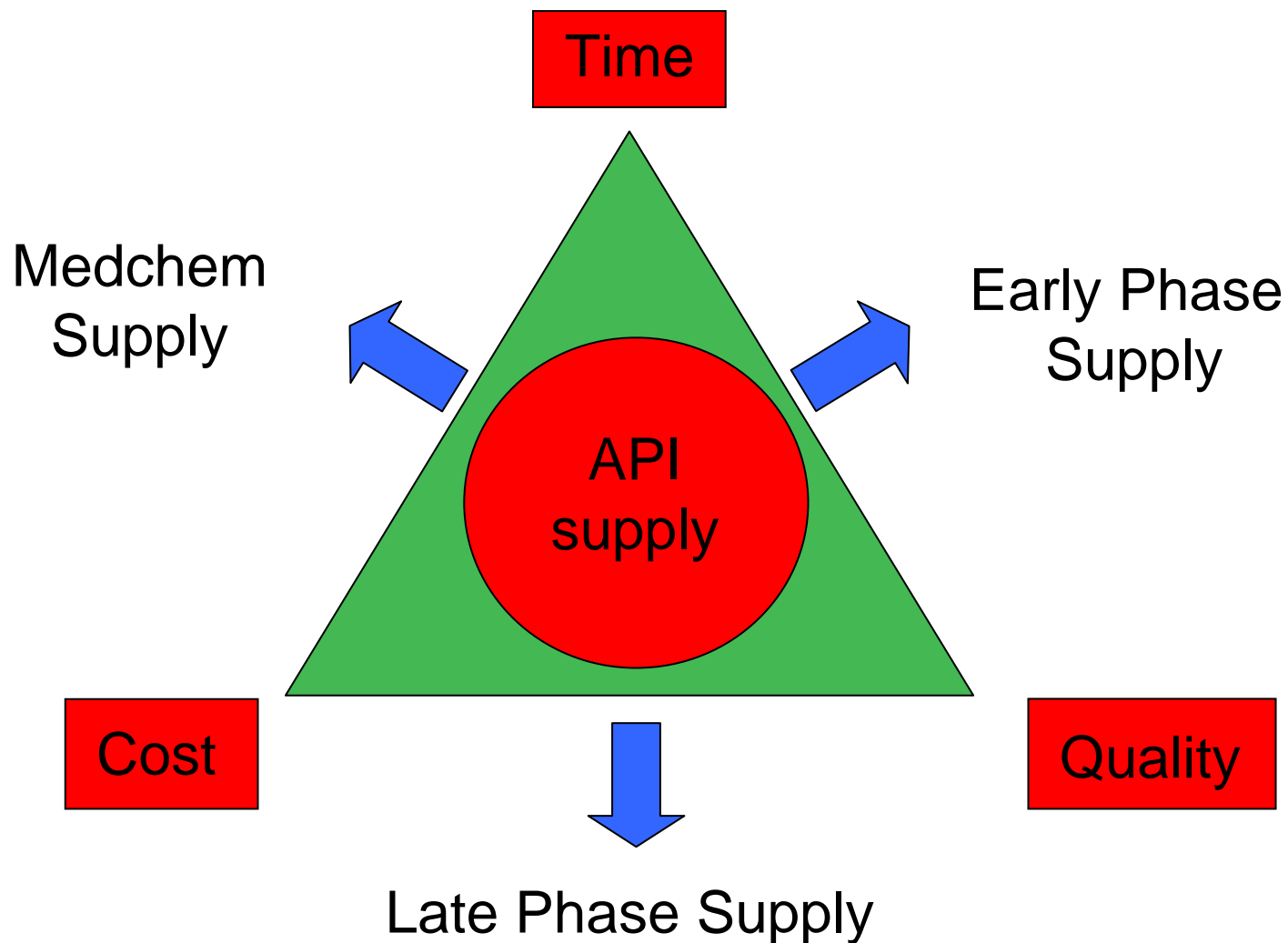
Lit.: Org Proc Res & Dev 2001, 508

## Further questions



- What is my best GMP strategy wrt starting material?
- When do I do my Process Validation?
- How do I release my API and drug product?
- Which is the right batch to be used for real time stability data?
- How do I deliver my API, what is my drug product?
- What is my cost of goods at launch?

# The QCT (Bermuda) Triangle

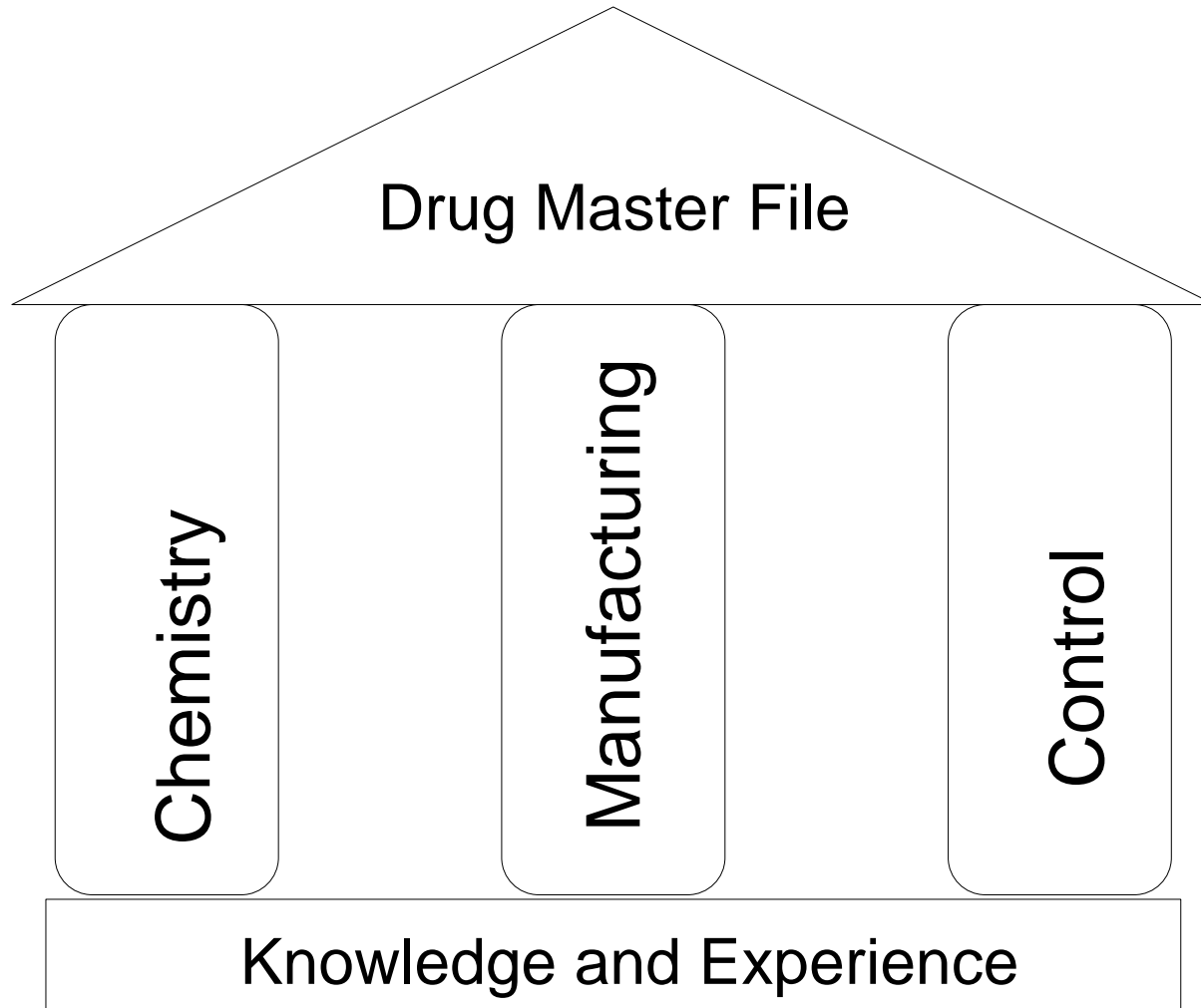


# Conclusions



- API Process different in early phase and late phase
- Cost of Goods Analysis
- Solid State Issues

# Conclusion



**Don't build your house without an architect**



# The architects



**Dr. Dieter Krimmer**  
Managing Partner at RPD  
Project Manager at Roche

Track Record: Tamiflu, Saquinavir, Tenovovir,  
Nelfinavir, Viread...



**Dr. Robert Hett**  
Managing Partner at RPD  
Site Manager at Carbogen  
Senior Scientist at Sepracor, USA

Track Record: Bortezomib, Arformoterol...

Need help? Contact us



Dr. Robert Hett  
rh@rpd-ch.com  
Tel. +41 41 5441822  
Rainstrasse 33  
CH-6314 Unterägeri  
Switzerland

[www.rpd-ch.com](http://www.rpd-ch.com)