Process Chemistry

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Drug Development
Outline

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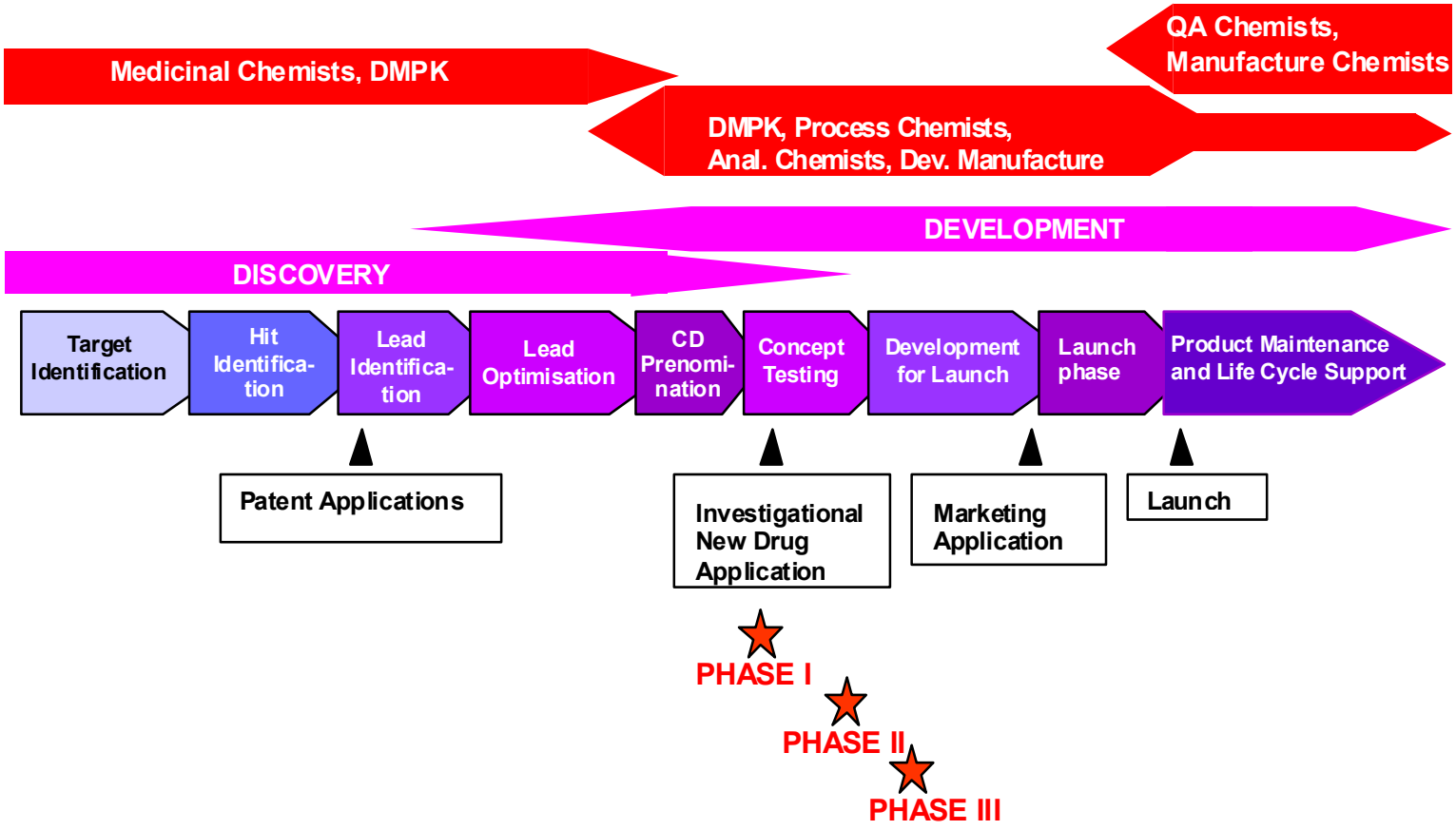
Drug Development
Process Chemistry in Context

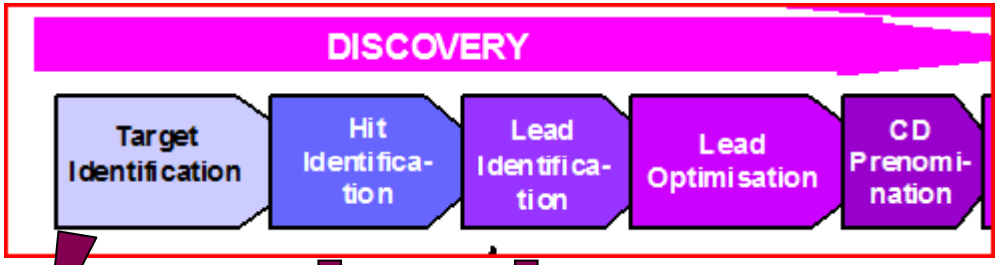
- The discovery of a new drug is somewhat like a relay race with different groups of scientists taking over as the project progresses
- The work is always multi-disciplinary – Groups of scientists with high level expertise in their own disciplines interact at all stages of R&D
- Different types of chemists are involved at each stage
- Each may have had a similar background in terms of training, but have to develop specialist skills tailored to each stage of development...

Drug Development



Drug Discovery

Drug Discovery



Recognise a potentially ‘druggable’ disease mechanism

Identify a way to measure the response of a biological test system to a potential drug molecule:
Hit to Lead...

Screening process allows Medicinal Chemists to synthesise compounds to identify new Leads

Rational design *vs* High Throughput Screening (HTS)

Lead Identification (LI) phase

Rational Design Vs HTS

Rational design *– the idealist's choice*

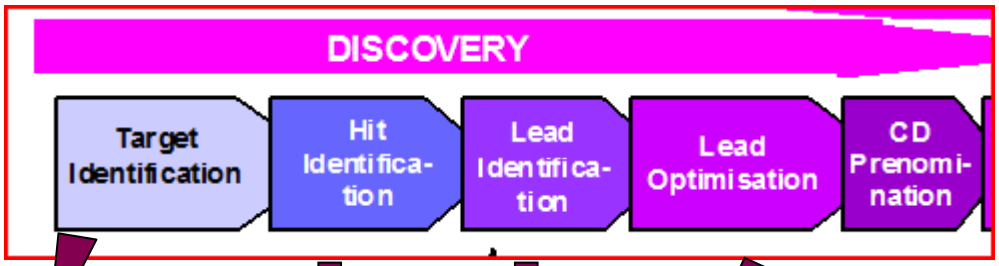
- Requires deep understanding of the biological target
- Aims to design a molecule to successfully interact with the target system
- Inspiration can be nature or prior art (existing drugs)
- Catch 22: Need to have a good idea of the key features of the Hit before we can synthesise a suitable Lead.

  ...The Hit needs to be already 'Lead like' if we are to succeed

High Throughput Screening *– the realist's choice*

- Automated, using tiny amounts of compounds (at random)
- Allows novel, unexpected types of Leads to be identified
- Gives better understanding of key structures which lead to activity - not intended to reach the final drug
- Gives better understanding of the biological target system

Drug Discovery



Recognise a potentially ‘druggable’ disease mechanism

Identify a way to measure the response of a biological test system to a potential drug molecule:
Hit to Lead...

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Synthesise and evaluate Lead compound(s)

Rational design *vs* High Throughput Screening (HTS)

Lead Optimisation (LO) phase

A key role for the Medicinal Chemist...
Synthetic chemistry is key to allow the following:

Identify structure-activity relationships (SARs) – positive *and negative*

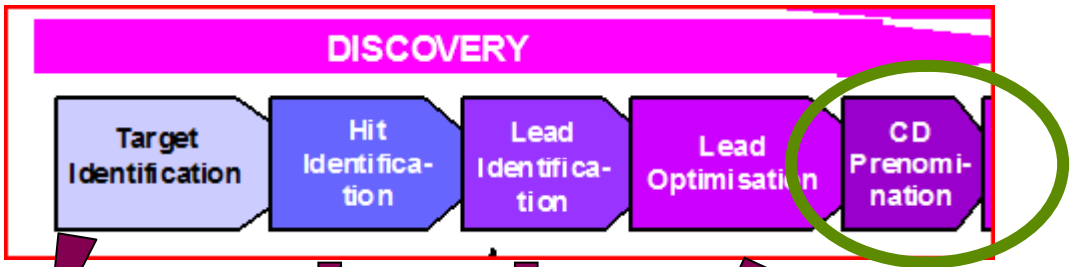
Improve potency against target

Reduce toxicity: 'off-target' effects

Improve physical properties: solubility, bioavailability

Improve metabolic properties: metabolism, pharmacokinetics, elimination

The Drug Development Milestone Model...



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Identify a way to measure the response of a biological test system to a potential drug molecule:
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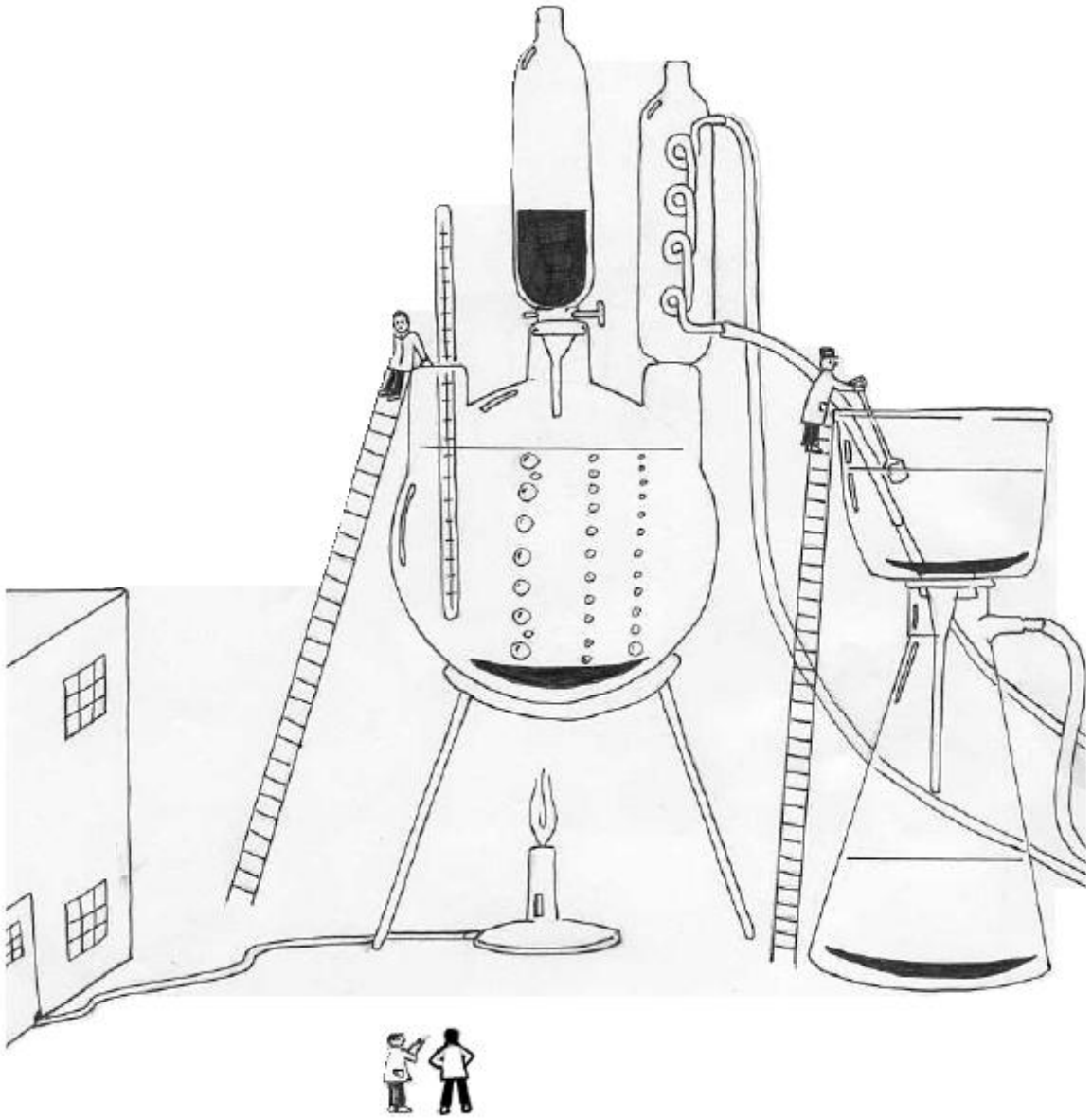
Rational design *vs* High Throughput Screening (HTS)

Drug Development

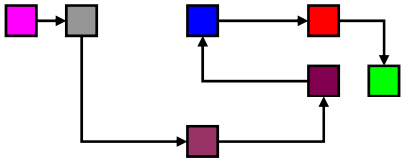
What do Process Chemists do?
Let's just scale up the reaction!



Medicinal Chemistry vs Process Chemistry

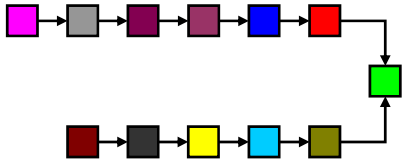
Is it Total Synthesis?

Medicinal Chemistry



Use of available methodology
to delivery target compound

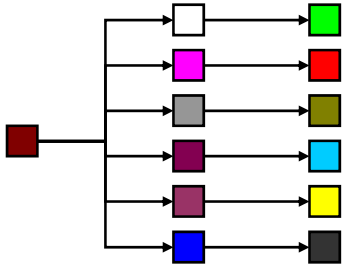
Process Chemistry



Identification of different routes
to the same target compound

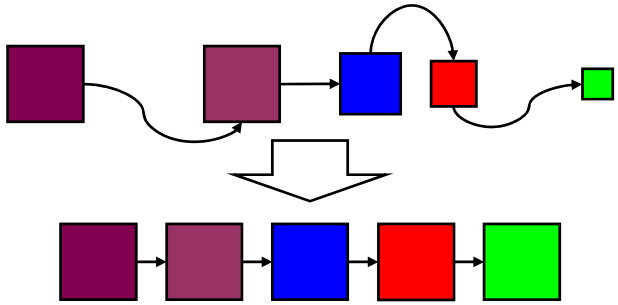
Is it Methodology Development?

Medicinal Chemistry



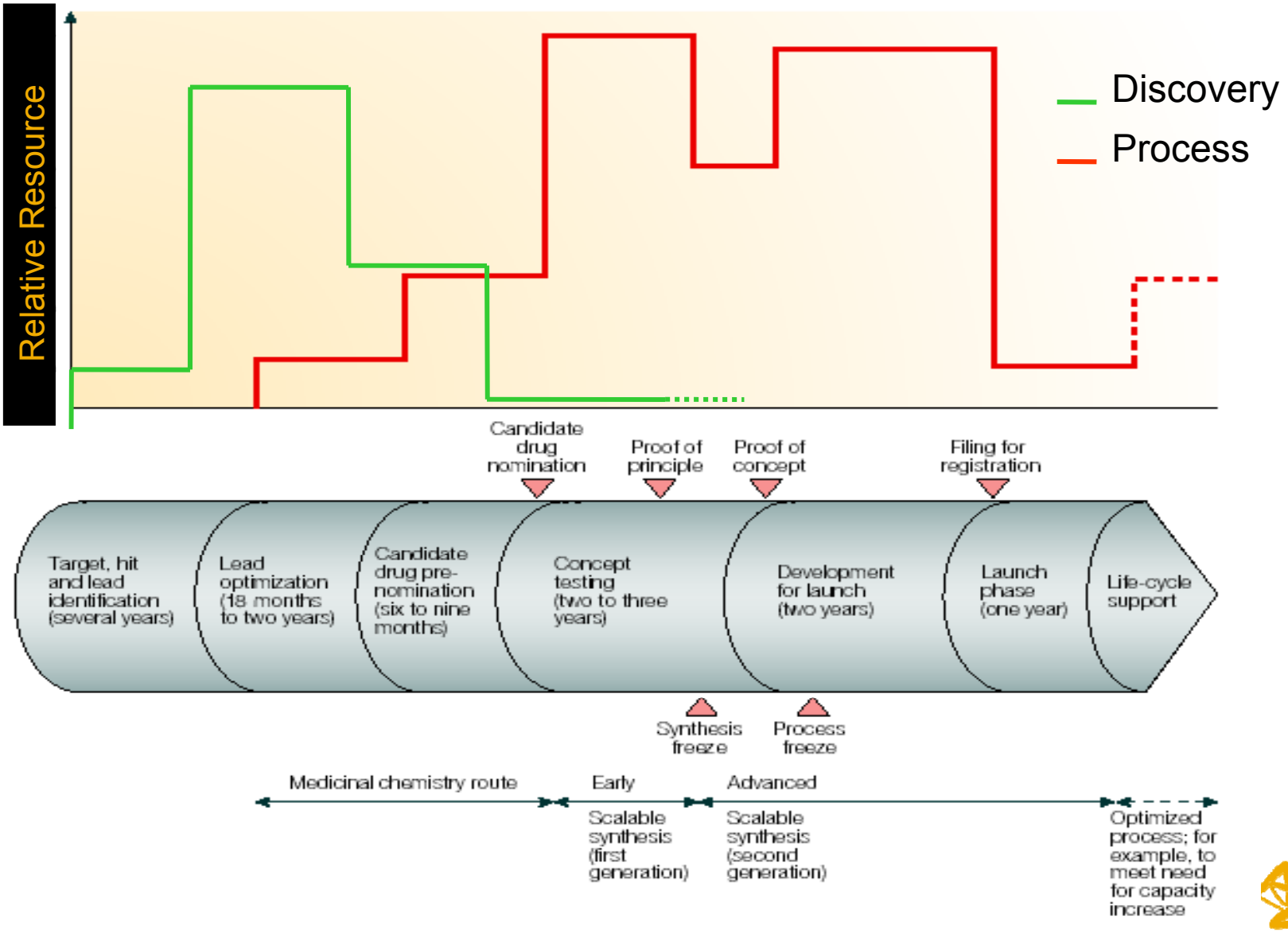
Development of methodology that
can deliver a variety of targets

Process Chemistry

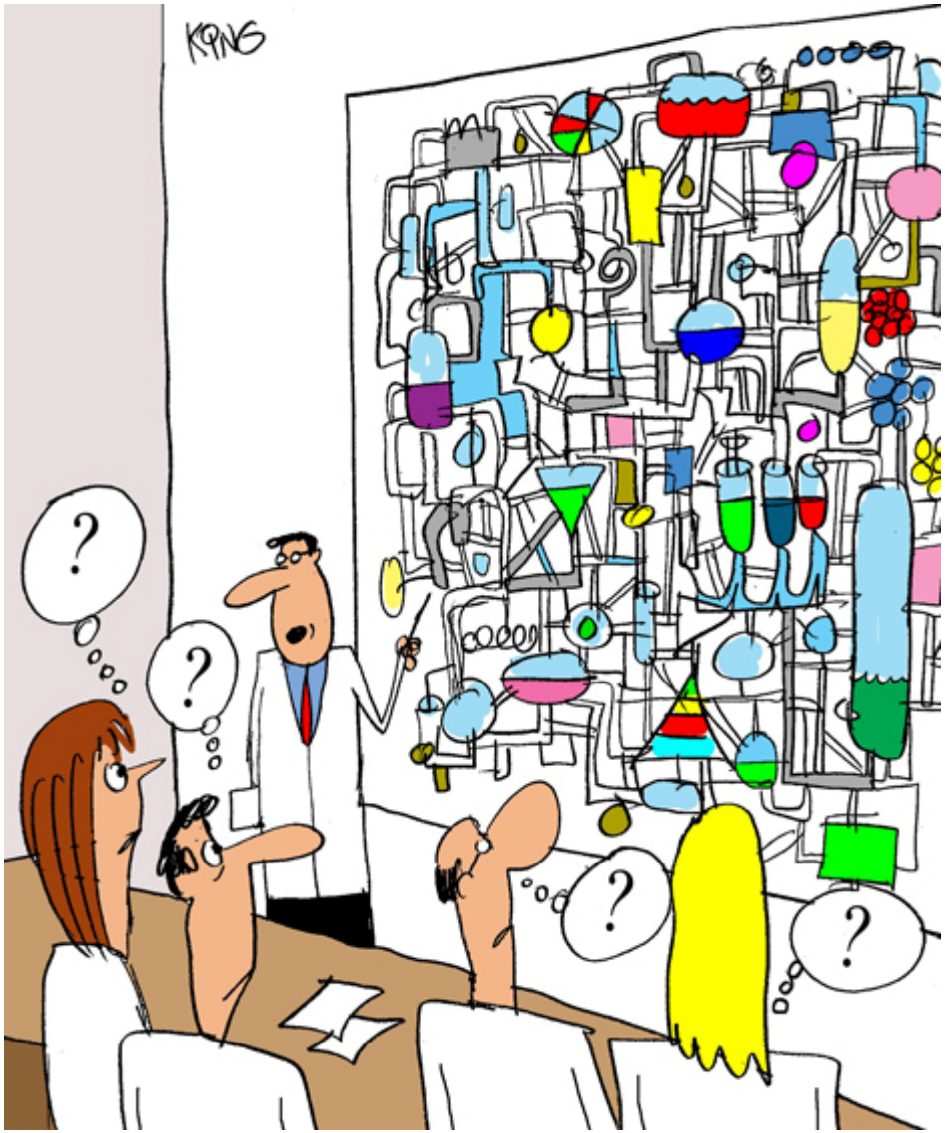


Development of high-quality,
robust processes

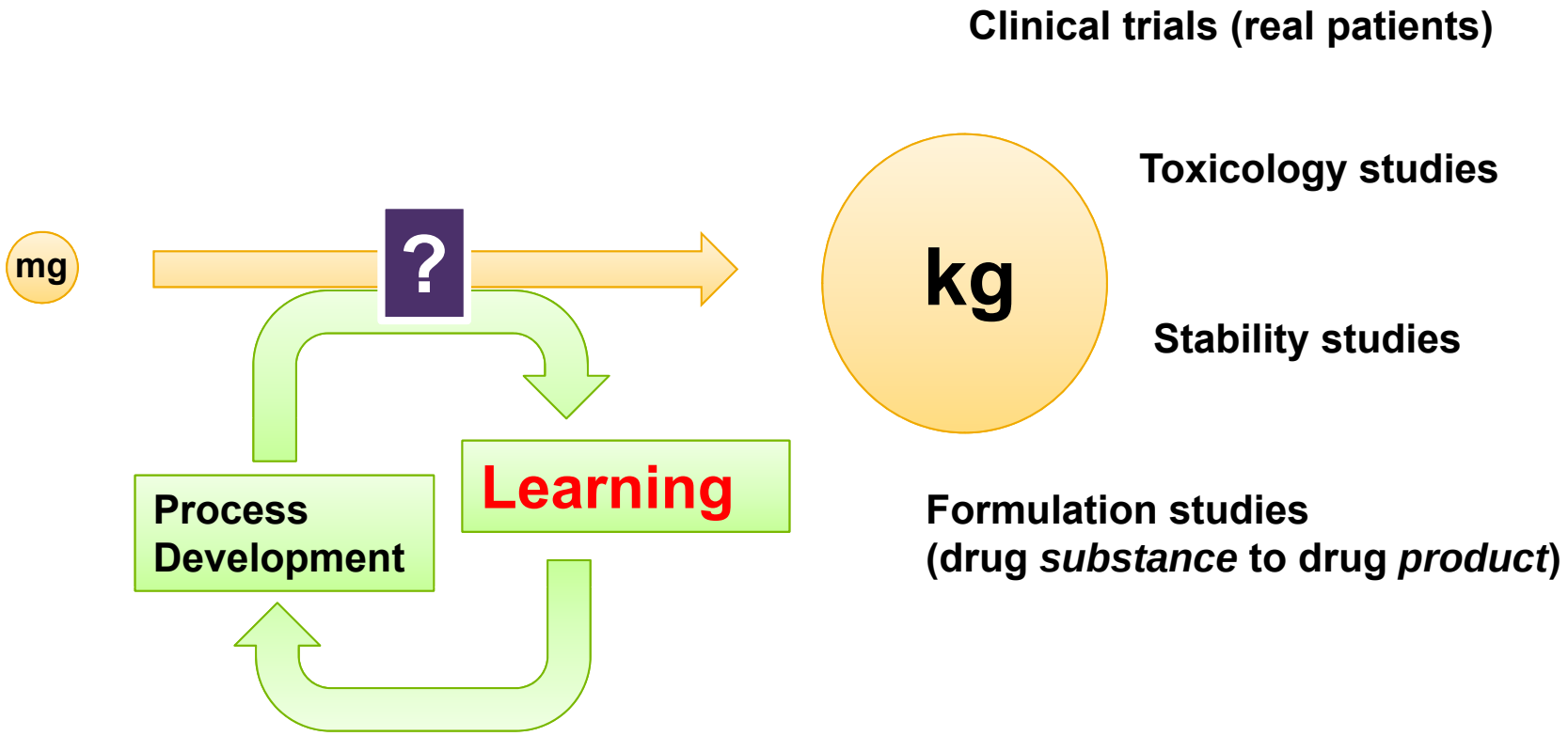
Chemist Involvement – Discovery vs Process



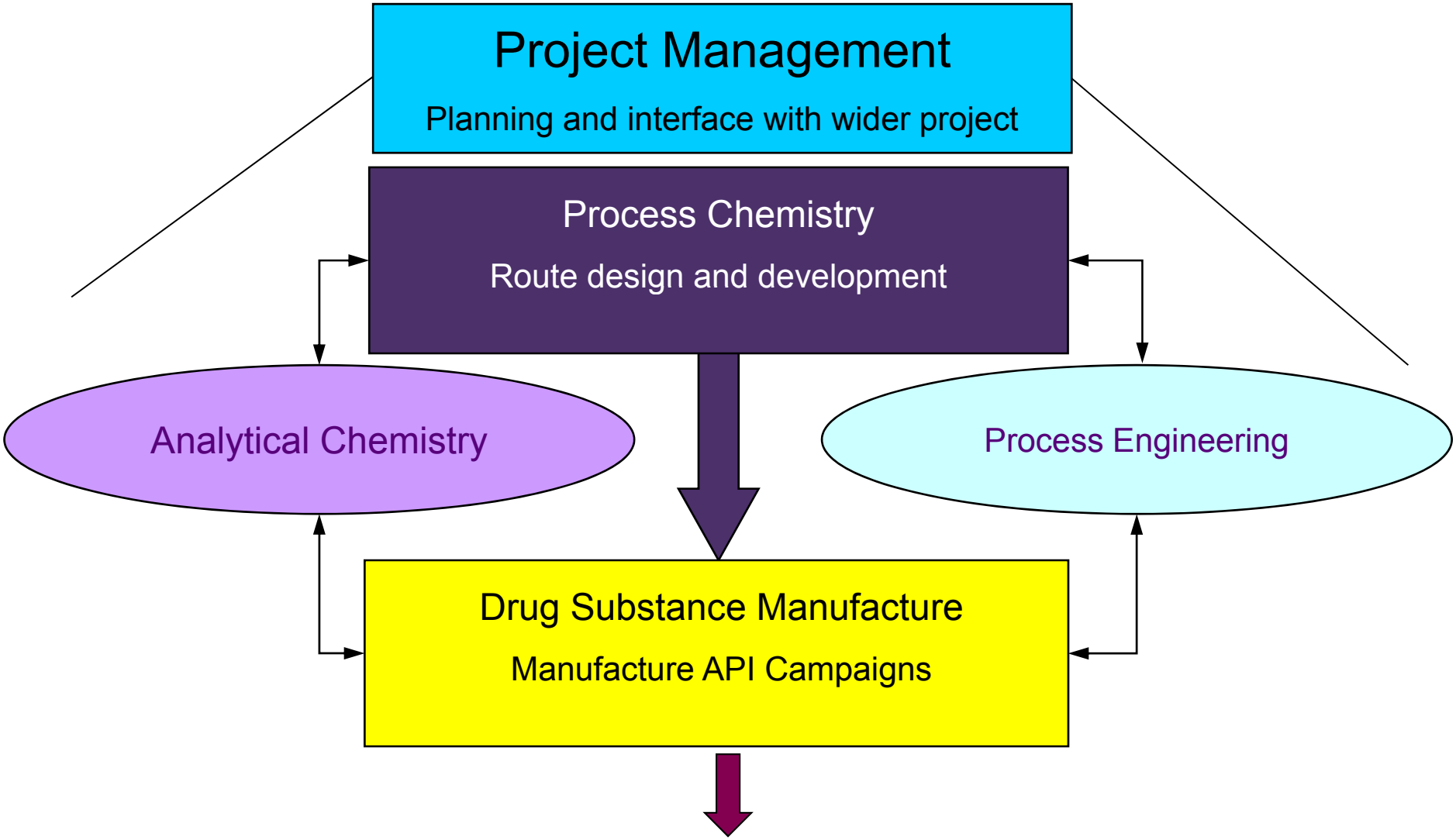
What do Process Chemists do?



Main Aims of Process Chemist



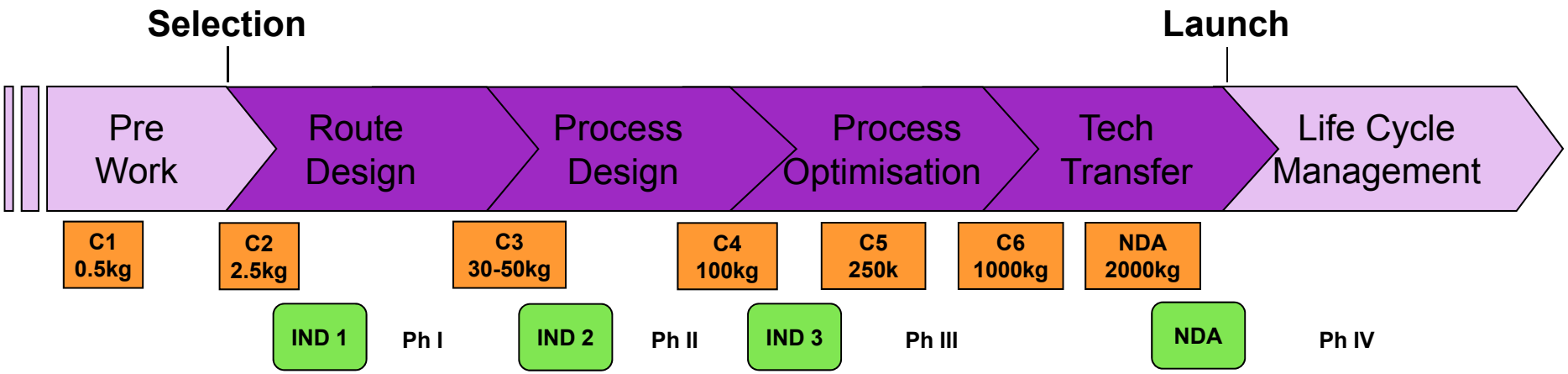
Thankfully, you're not alone...



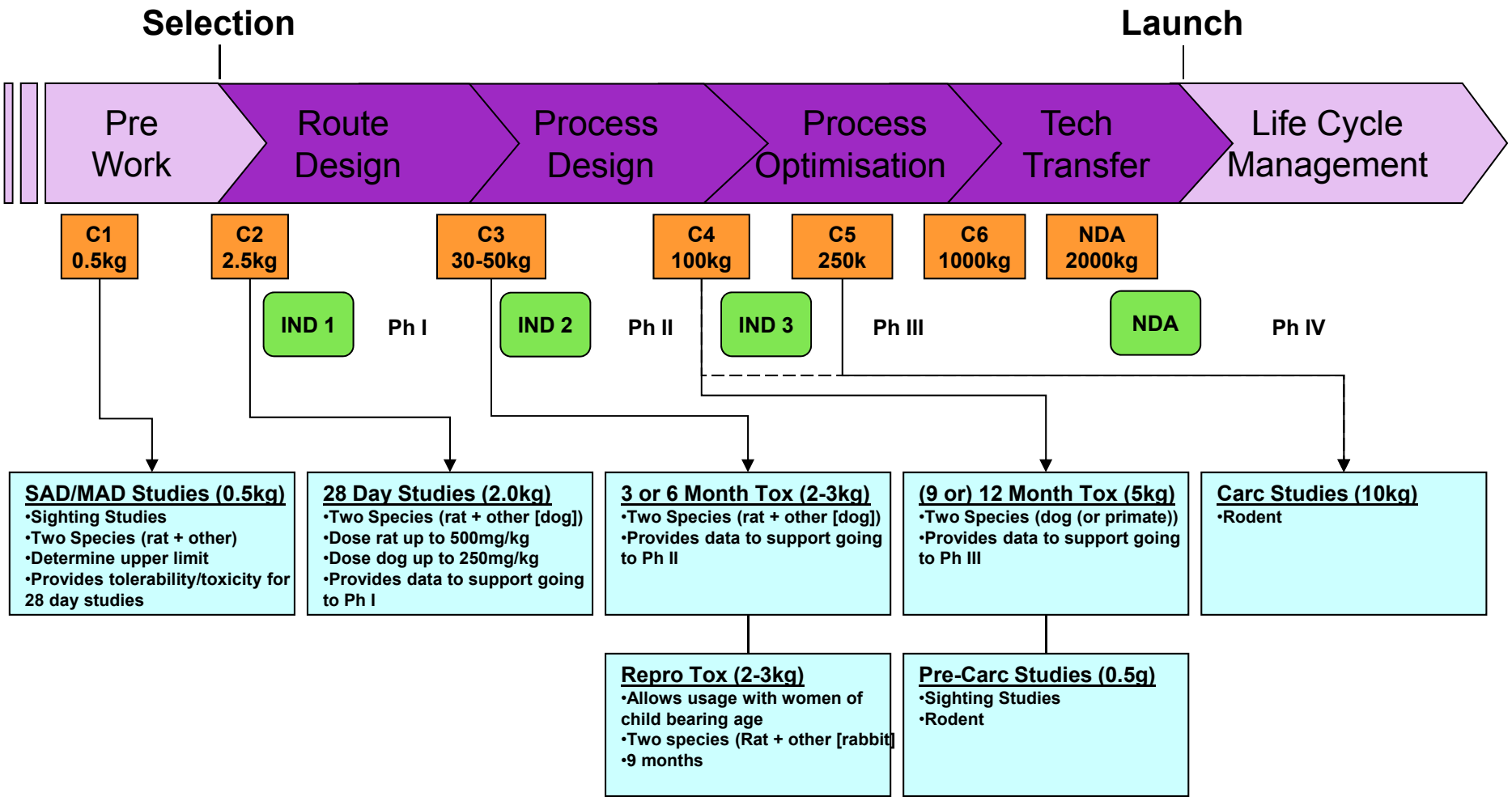
Supply chain (DS to DP to patients)

DS = Drug Substance; DP = Drug Product

Process Development Overview

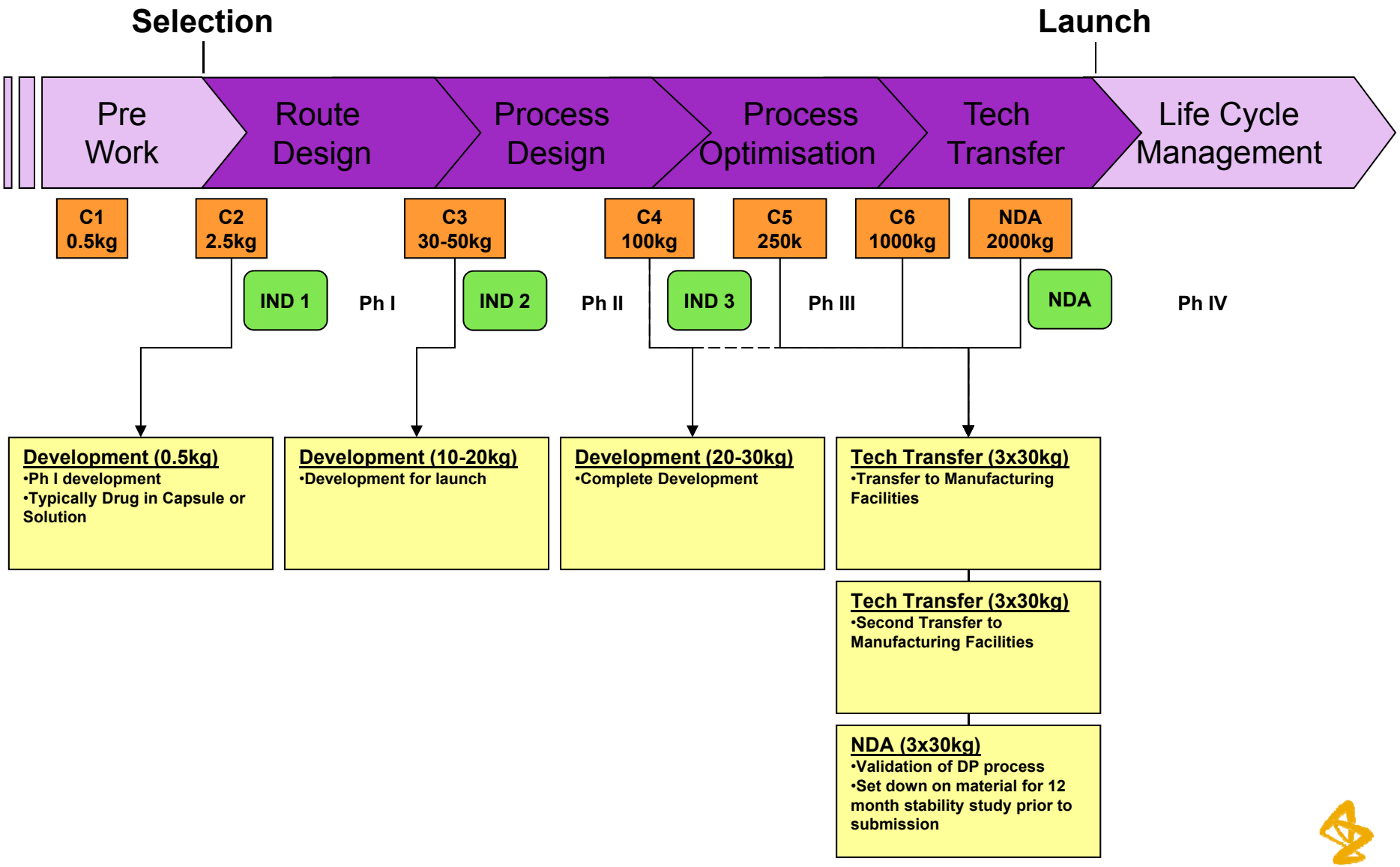


Where Does the Material Go? - Toxicology

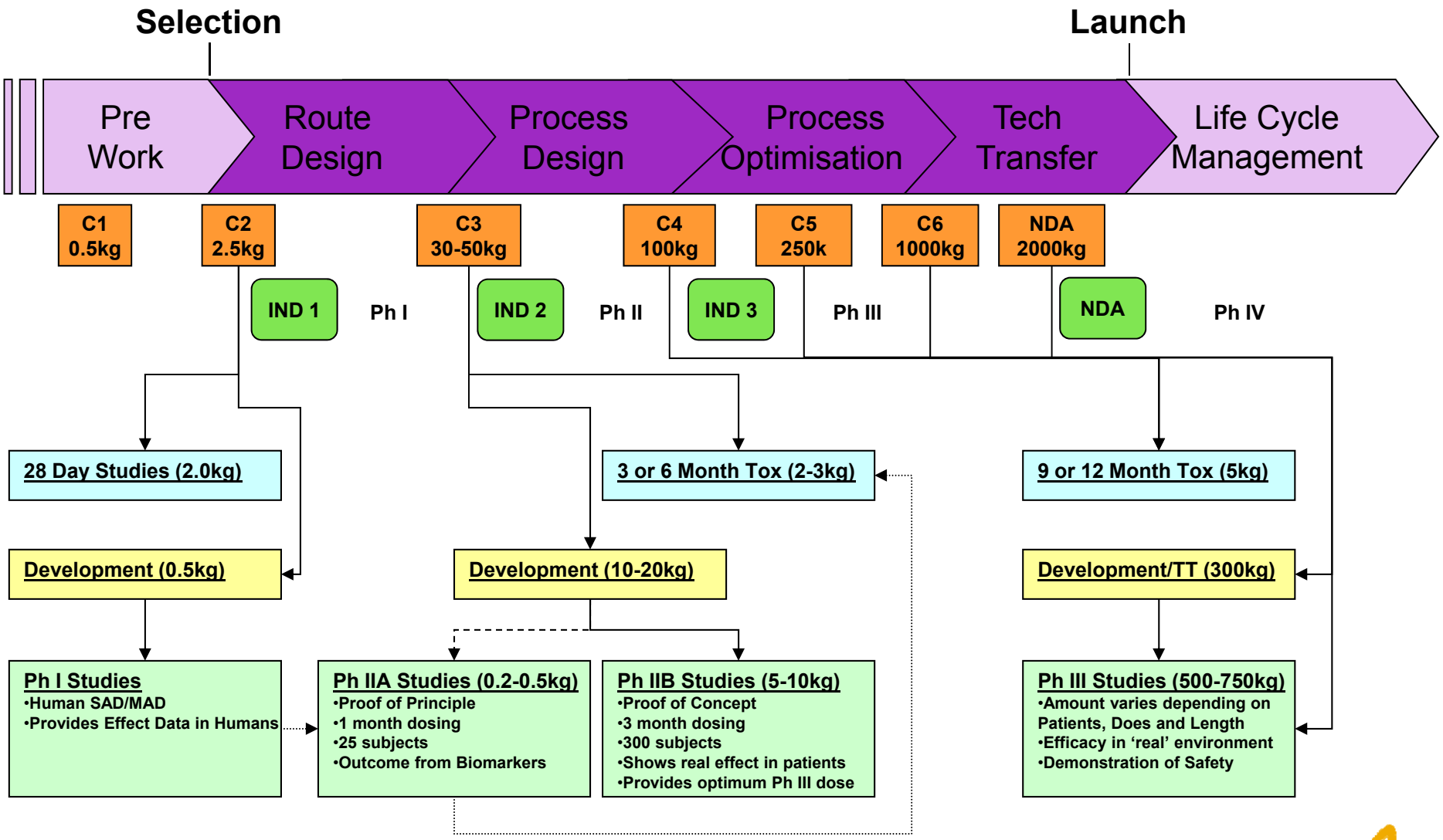


SAD – Single Ascending Dose
MAD – Multiple Ascending Dose

Where Does the Material Go? - Formulation



Where Does the Material Go? – Clinical Studies



Clinical Trials

Q) As a regulator, what *information* would you want to know before putting a compound into humans for the first time?...

IND application covers three broad areas...

1) **Animal pharmacology and toxicology studies**
   ***Pre*clinical data to allow an assessment as to whether the product is reasonably safety for human trials.**

2) **Manufacturing information**
   Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the *drug product*. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

3) **Clinical protocols and investigator information**
   Detailed procedures for proposed trials- will these expose subjects to unnecessary risks? Information on the qualifications of clinical investigators. Finally, commitments to obtain informed consent from the subjects, and obtain review of the study by an institutional review board (IRB)

How do we get permission to do a clinical trial?

Submit all this information and then wait....

"Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk".

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

- **Patient safety is paramount;**

  We have an ethical obligation to get this right and do things properly

  ***What* we do and *how* we do it is crucial**

What does a regulator want to know?

Q) As a regulator, what *chemistry information* would you want to know?

How *have* you made it?

How *will* you make it?

Where will you make it?

How do you control the reactive chemistry?

How do you control quality?

Where will GMP controls begin?

How are you going to analyse your drug?

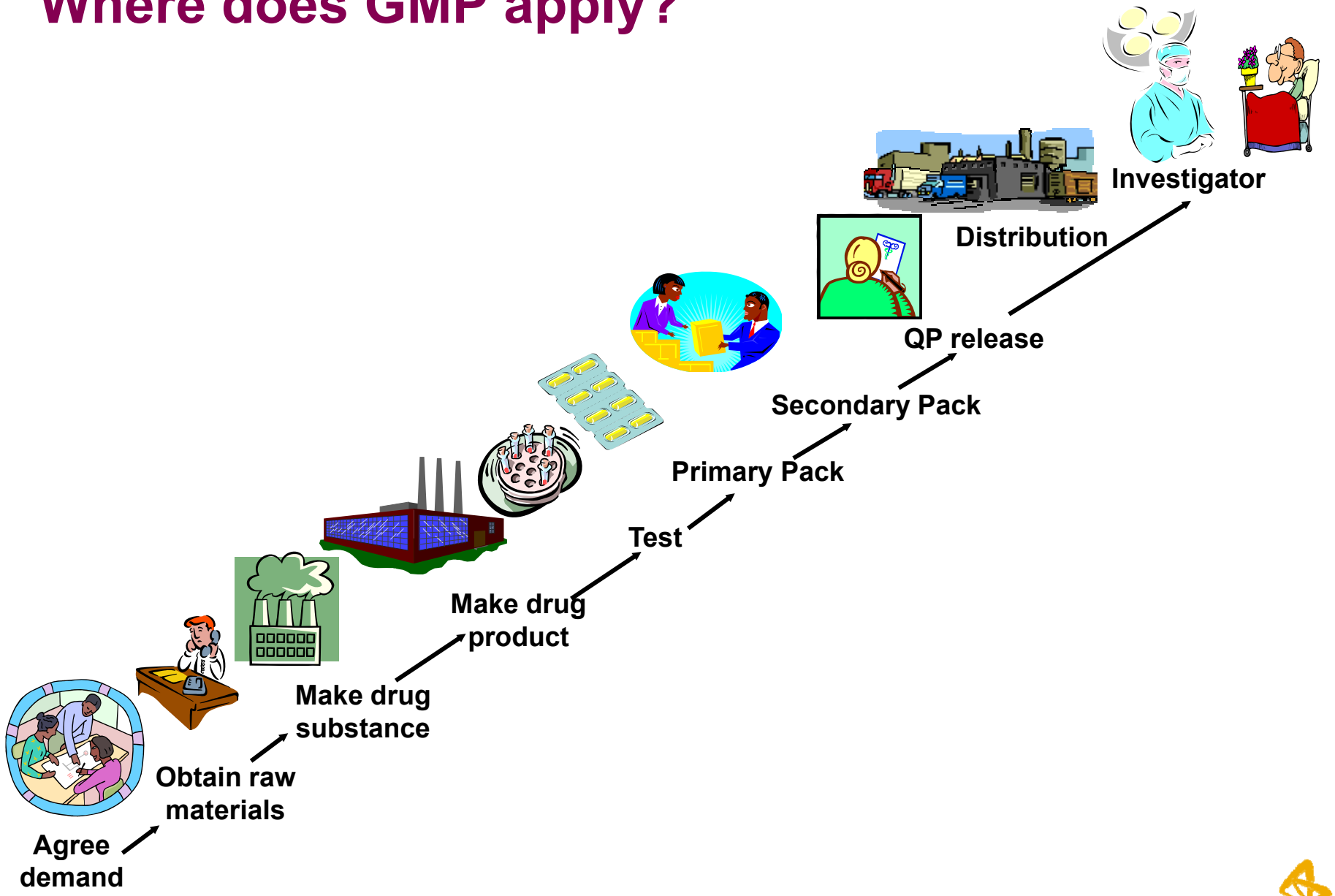
What quality are your input materials?

What impurities are present in your drug?

How stable is your drug?

GMP analogy...Have a Safe Flight!
You TRUST people working behind the scenes

Where does GMP apply?



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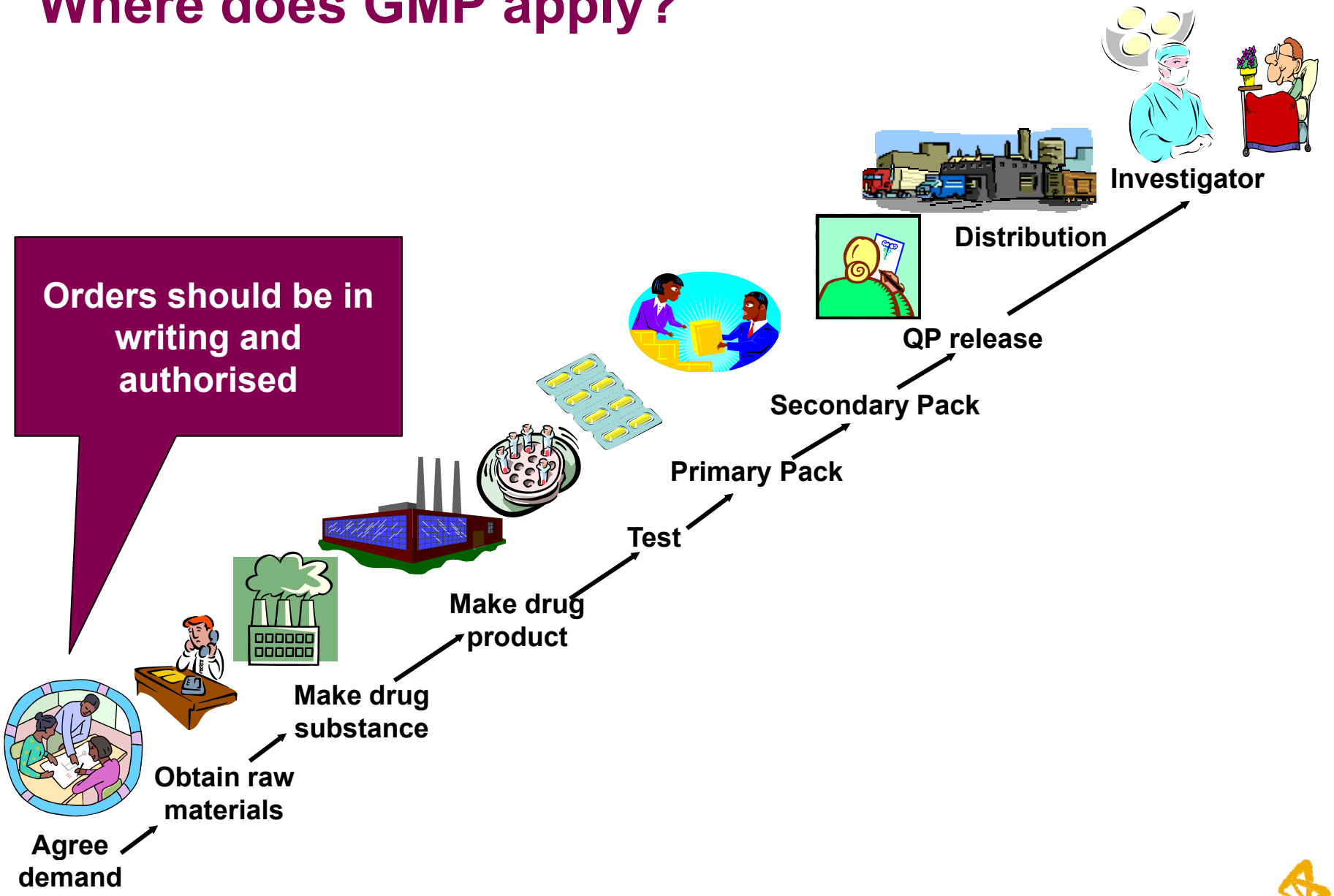

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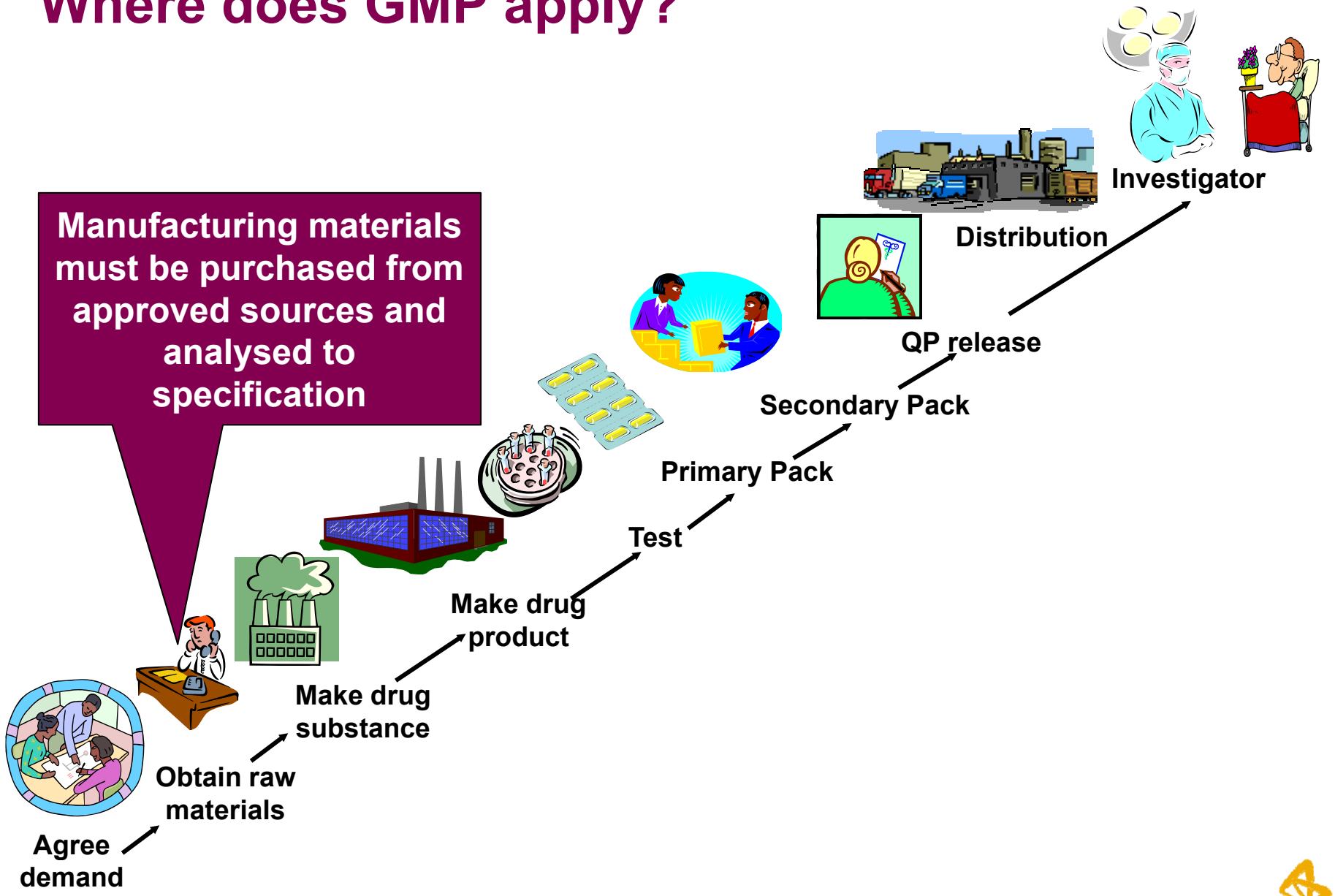

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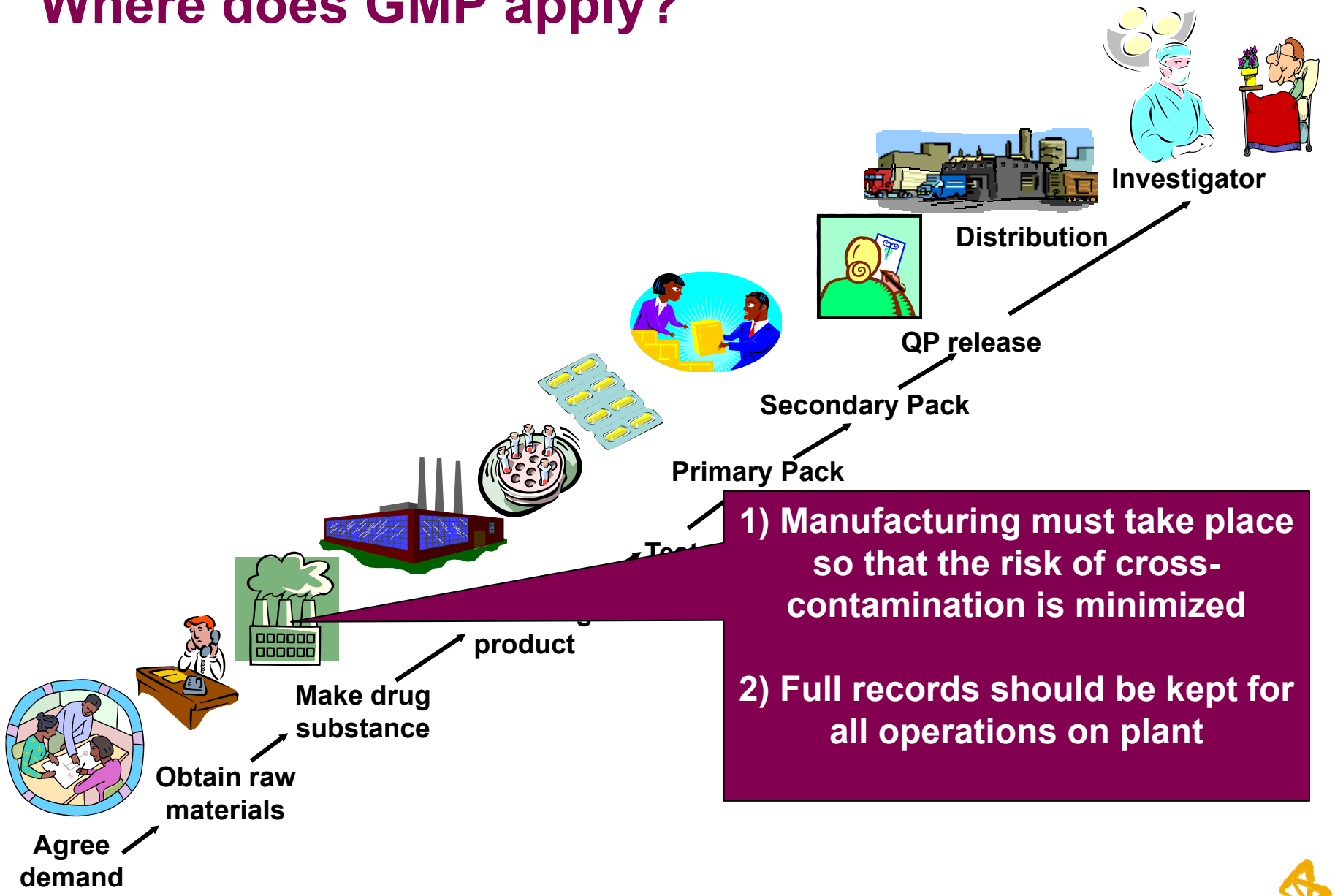


Marketing Submissions

- A marketing submission is a data package we submit to health authorities to ask for permission to sell our new drug to the patients that need it

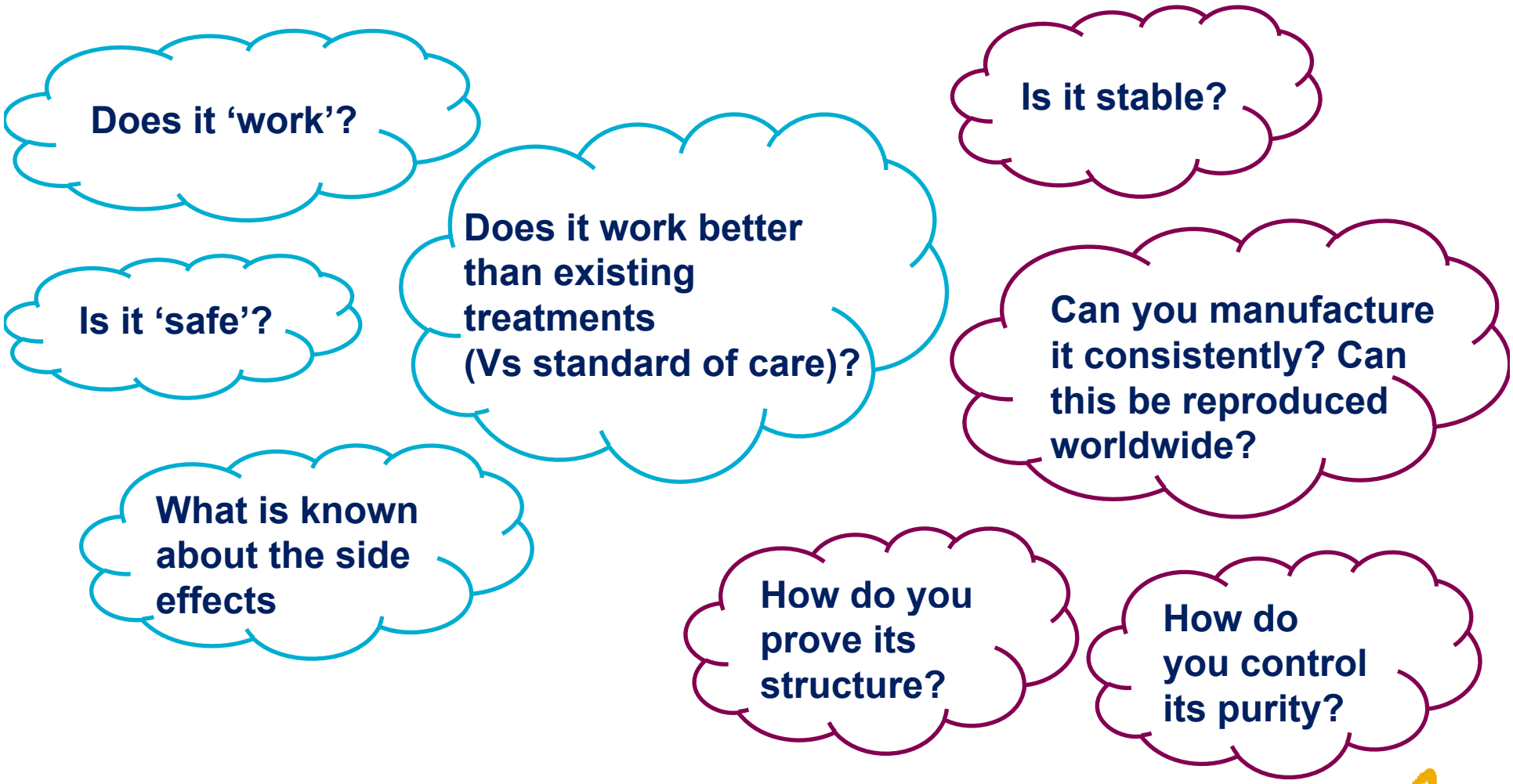
- Different health authorities have different procedures, expectations and names for their required applications.
  - In Europe it's a Marketing authorisation application (MAA)
  - In the US it's a New drug application (NDA)
  - In Canada it's a NDS, in Japan it's a JNDA etc.

- While there are differences they are all broadly interested in the same things.

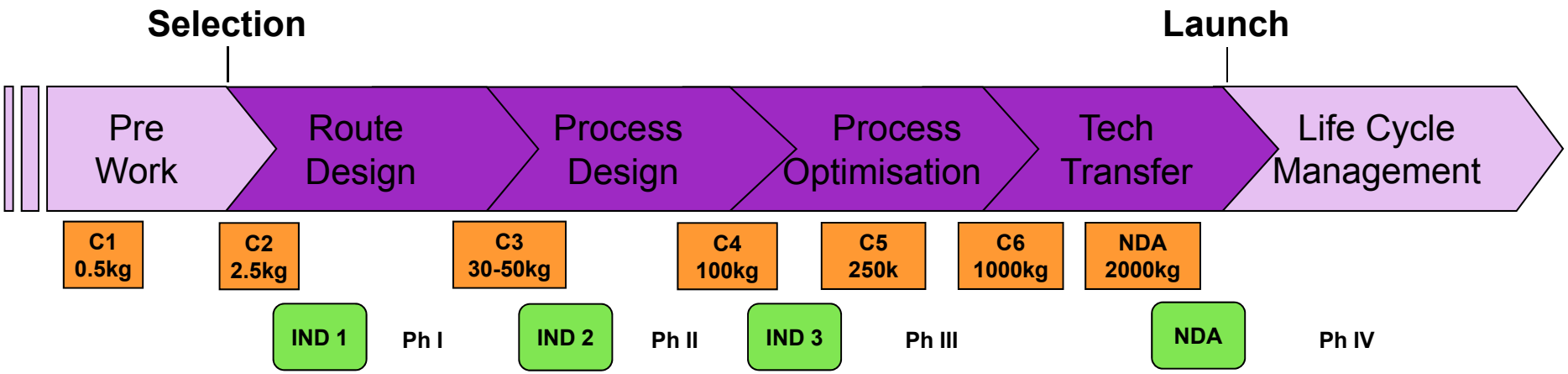
- All require a large package of scientific evidence regarding the drug....

What does a regulator want to know?

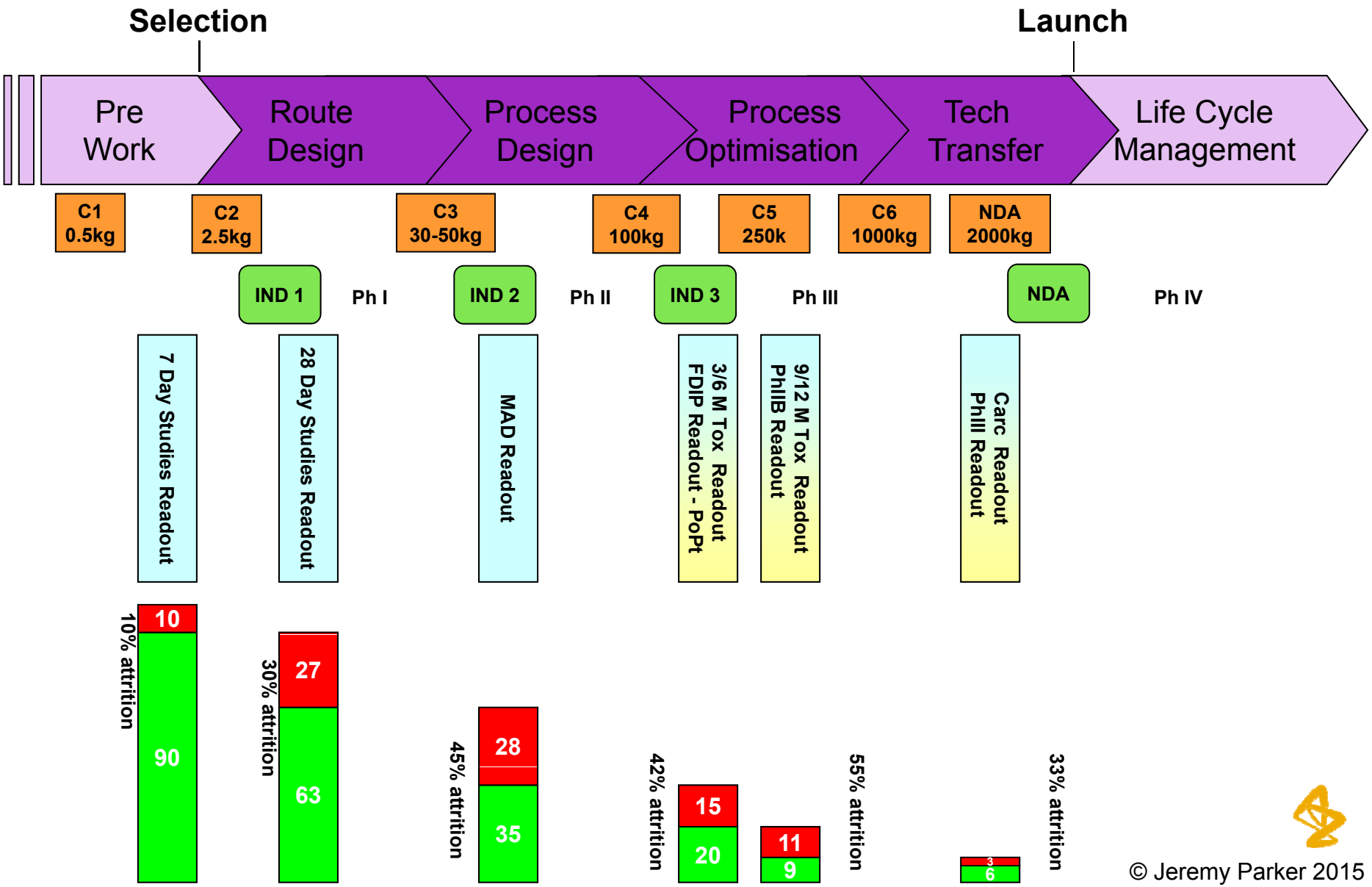
Q) As a regulator, what aspects of a new drug would you be interested in?



Process Development Overview



Attrition Through the Development Cycle



Process Chemistry
Route Design

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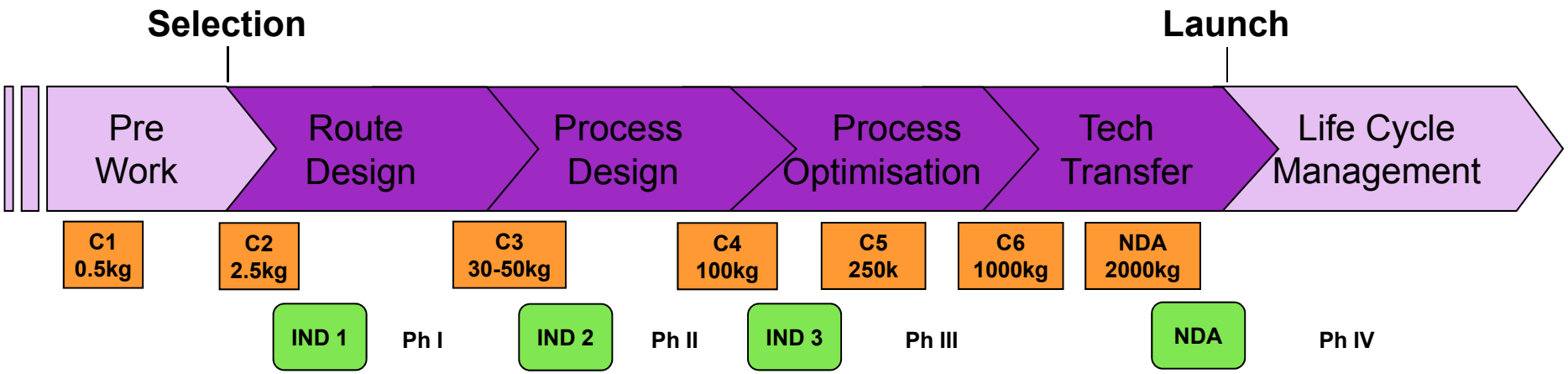
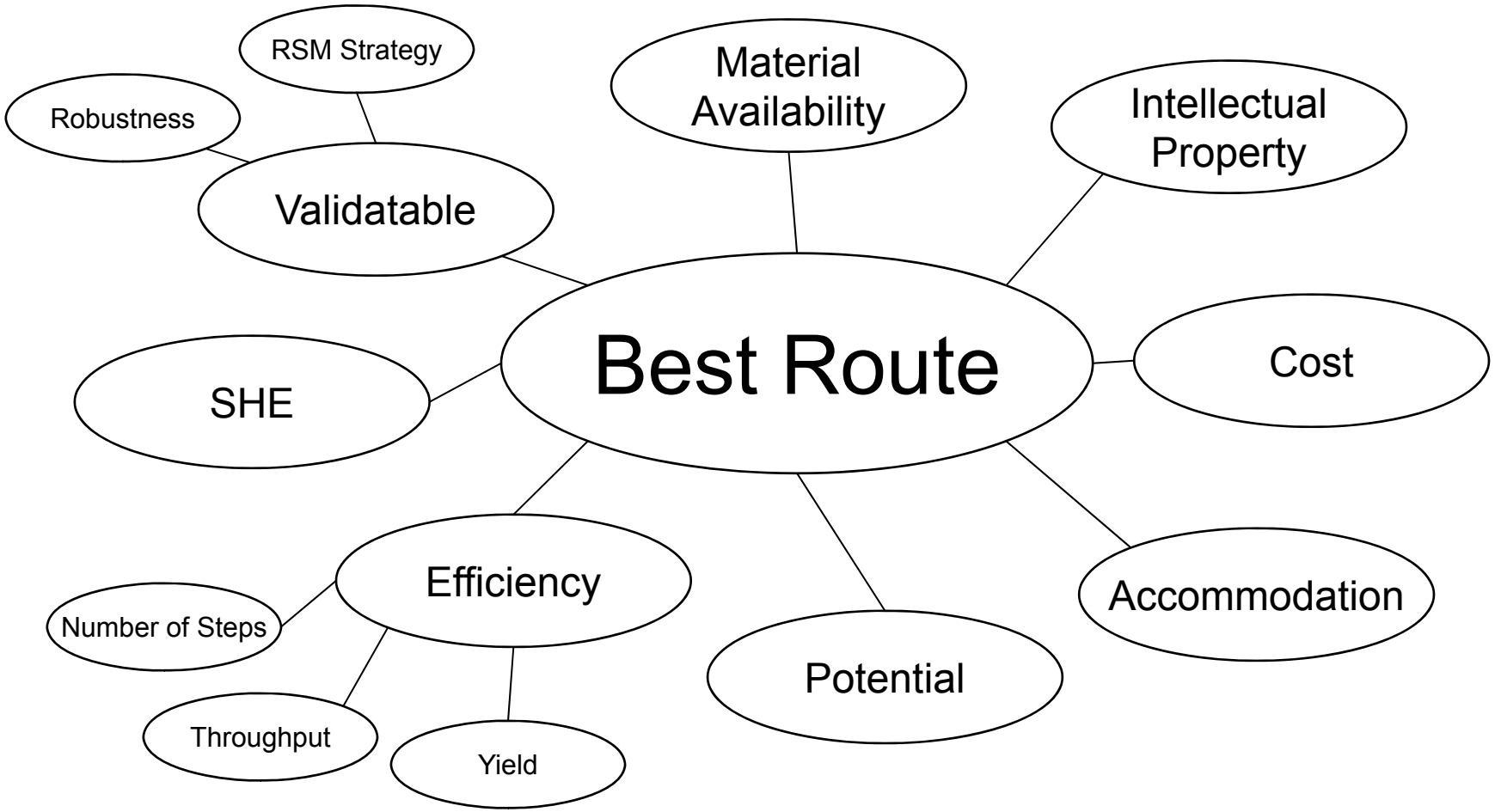
Process Development Overview



Why Change Route?

Route Selection



Best Route Criteria
Safety, Health and Environment (SHE)

•Any Safety, Health or Environmental issues need to be manageable

•Particular Health and Safety areas of concern:

- Explosivity
- Exothermic Events
- Gas evolution
- Highly Toxic Compounds

•Pharmaceutical Industry have a responsibility to develop processes which have minimal impact on the environment

- Use of Best Available Technology (BAT) to minimise waste of natural resources

Best Route Criteria
Safety, Health and Environment (SHE)

- Health Example:
  - Target levels for metals in APIs:
    - Pt, Pd, Ir, Rh, Ru, Os – 5ppm (Group)

- Environmental Examples:
  - Justification is required for use of all reagents and solvents, and alternatives must be explored
  - Dichloromethane can not be used in Sweden

Best Route Criteria
Validatable

- Robustness
  - All processes are robust
    - Laboratory work should translate well to larger scale
- Regulatory Starting Material Strategy
  - Route allows implementation of an effective RSM Strategy

Best Route Criteria
Material Availability

- Need to be able to source raw materials on scale
- Supply from catalogue companies
  - If large amounts are available from multiple suppliers then larger scale supply is unlikely to be an issue
  - If small amounts are available from only a limited number of suppliers then there are likely to be problems
- Demand drives supply
  - If a particular intermediate/raw material would be beneficial to deliver a compound then looking for a supplier is a good idea

Best Route Criteria
Intellectual Property

- Defensive Intellectual Property
  - Ensuring that we have patents in place for route and intermediates that we are using
  - Ensuring that we are not infringing anyone else's patents
  - Some discussion about how far you can go using chemistry covered in someone else's patent, but preferably not beyond C2
- Offensive Intellectual Property
  - A new route can offer additional patent protection for a product
  - Opportunity to claim novel intermediates, not just the final targets

Best Route Criteria
Cost of Goods

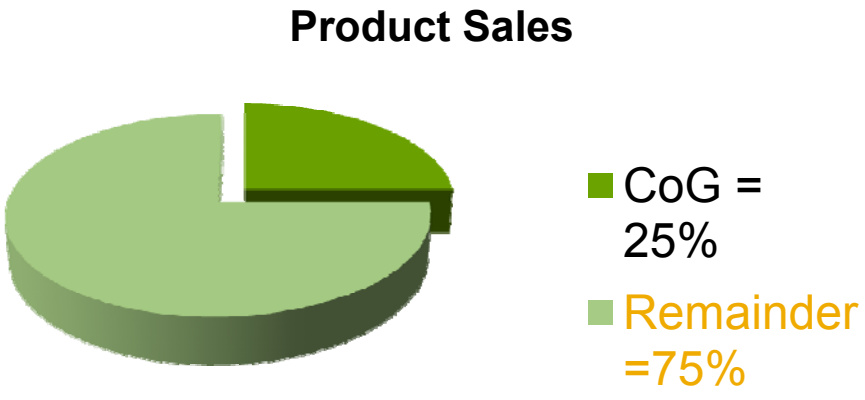
COG = Total costs involved in manufacture of a drug product

API manufacture *Formulation* *Packaging*

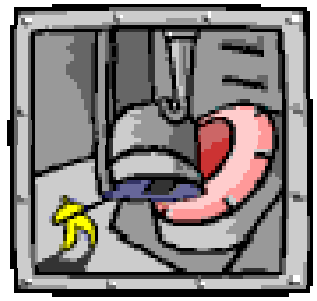
$$\%\ \text{Cost of goods} = \frac{100 \times (\text{API cost} \times \text{dose}) + \text{formulation cost}}{\text{selling price}}$$

£ / g g / day £ / day (•) £ / day

ie. Daily dose 0.15g / day; API cost £1.00 / g; formulation cost £0.10 / daily dose; selling price of £1 / day. COG = 25%



Best Route Criteria
Accommodation

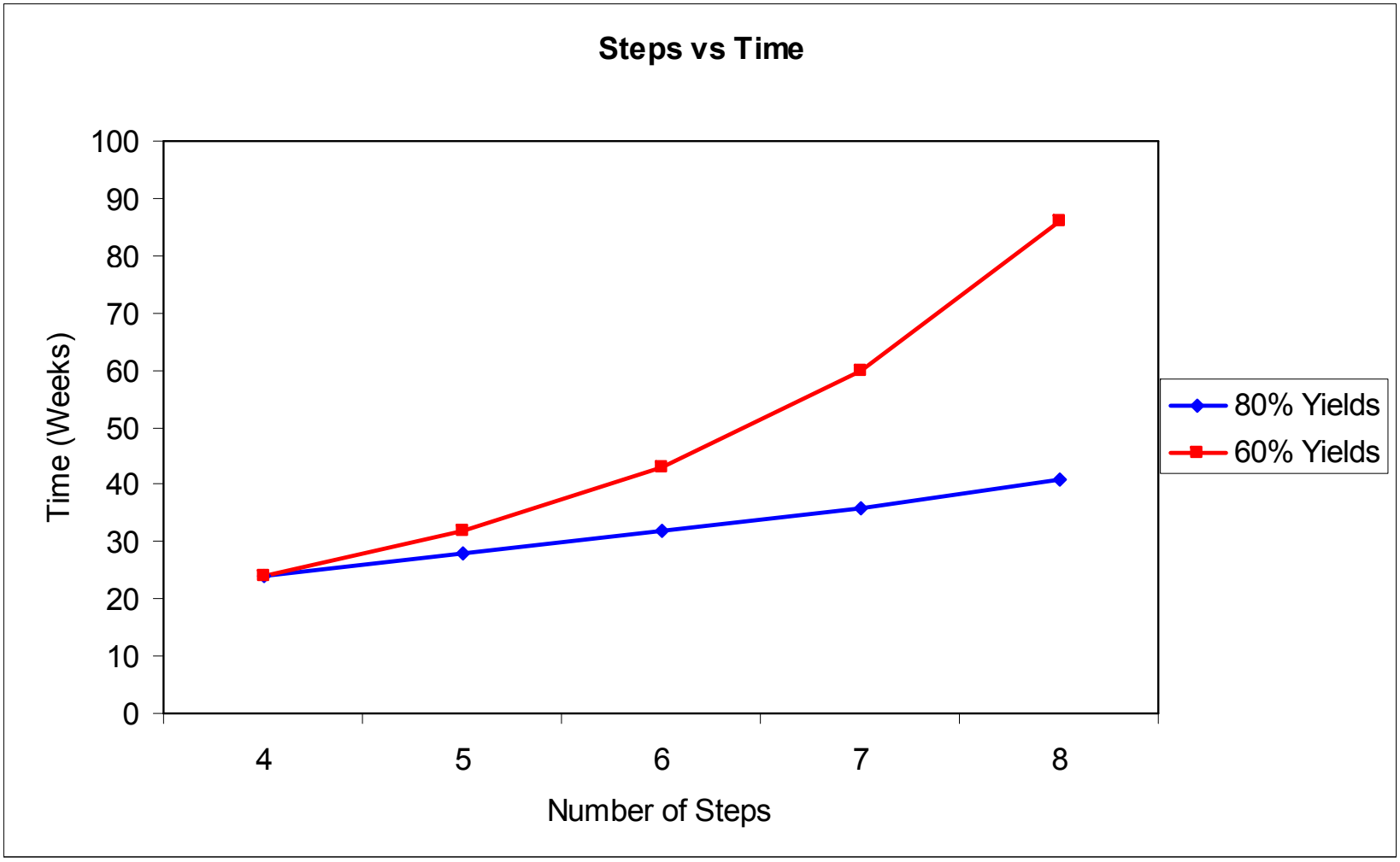


- Processes can easily be accommodated into existing manufacturing facilities
  - There is pretty much no chemistry that can't be run at a large scale but…
    - Operation outside normal plant operating ranges requires purchase of new equipment or the use of specialist contractors
      - Very low temperatures (-78ºC)
      - High pressures
      - Etc
    - Highly reactivity chemicals and intermediates can be used but often require specialist technologies
      - Use of Flow Chemistry with Azides

Best Route Criteria
Efficiency

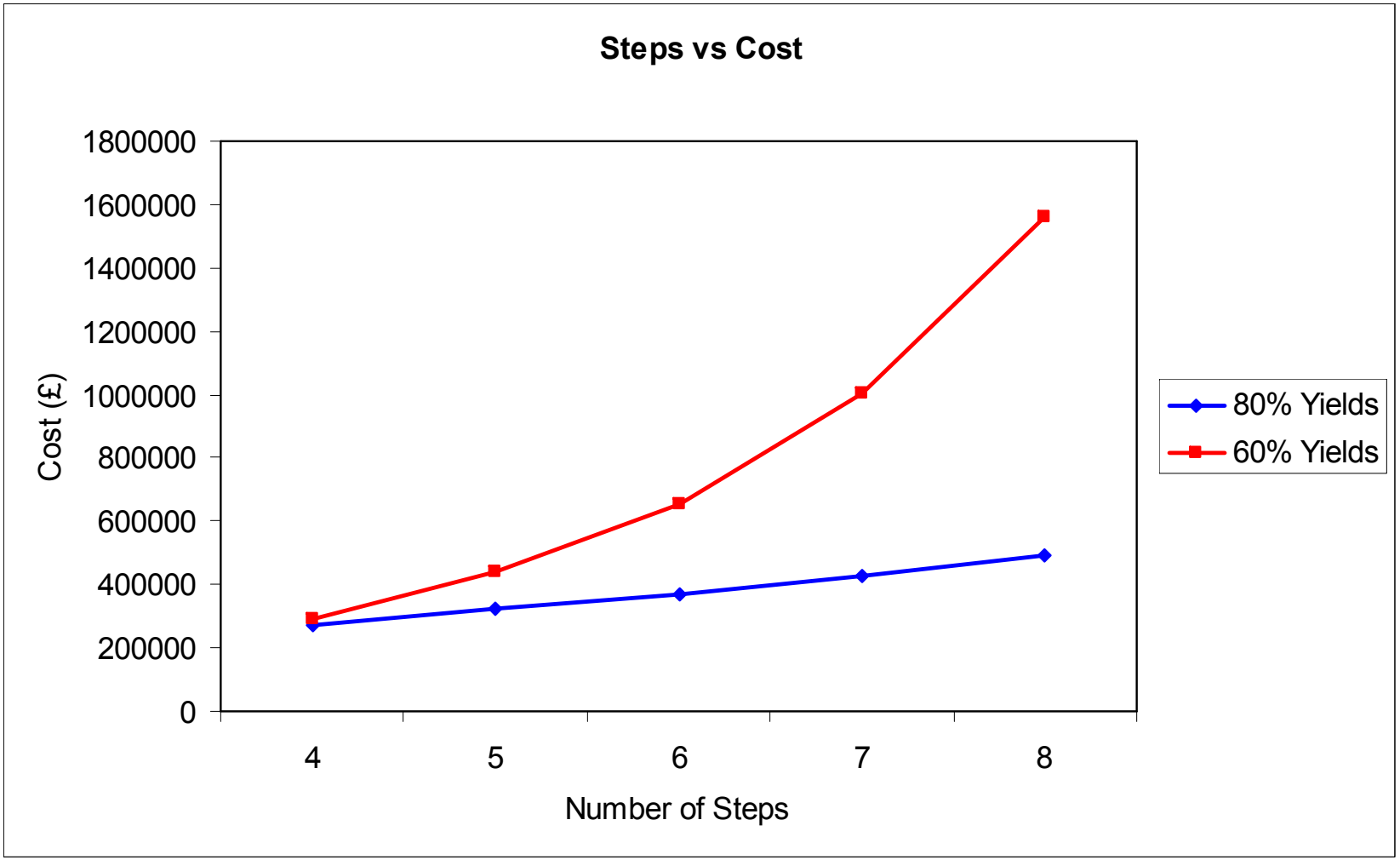
- *Number of Steps* – Route has minimum number of steps
- *Throughput* – Processes have high throughput
- *Yield* – Processes are high yielding

Steps *vs* Time



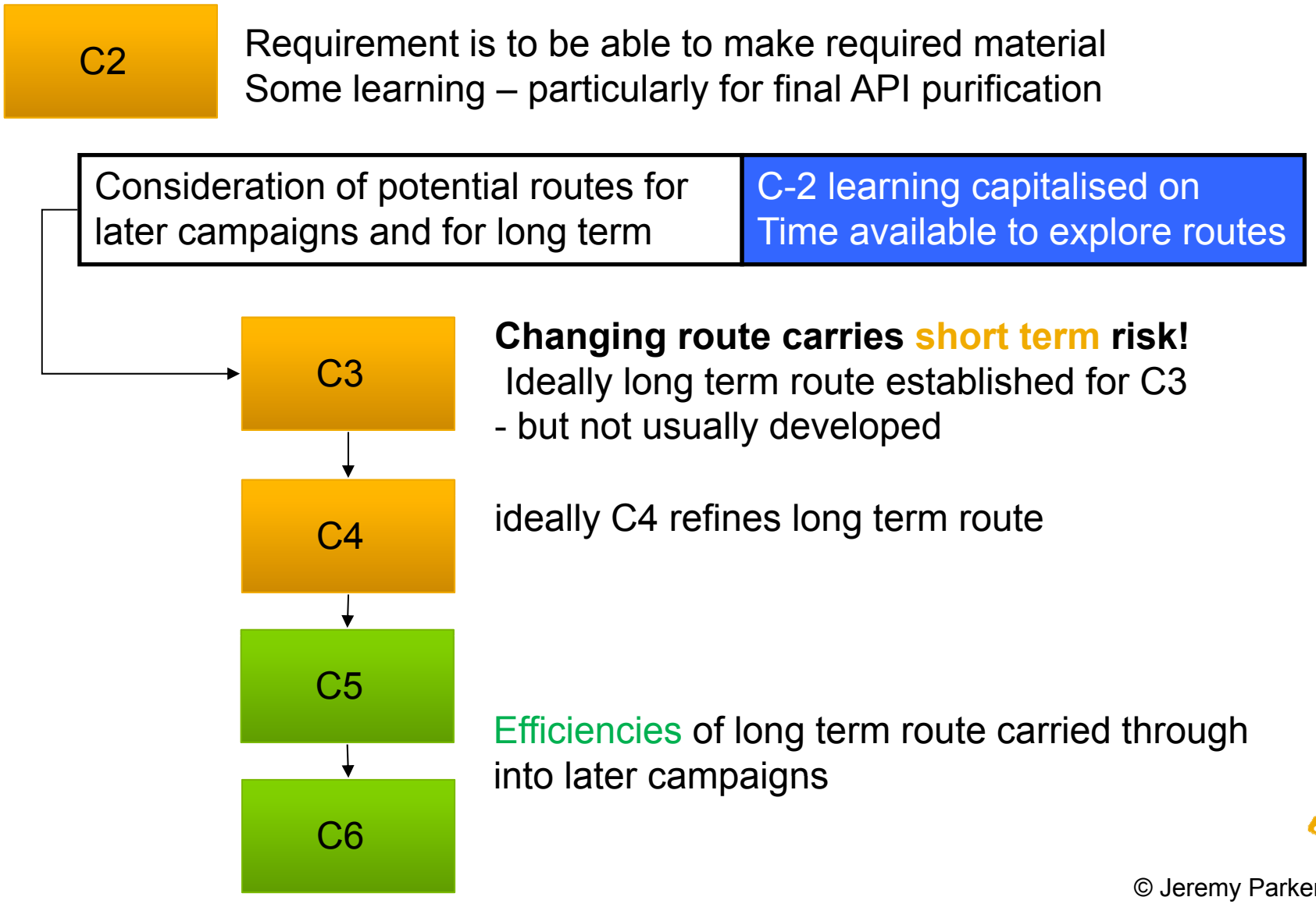
Theoretical Pilot Plant with 1000, 500 and 250L vessels
Production of 50kg of Drug Substance, running at one batch per week

Steps *vs* Cost

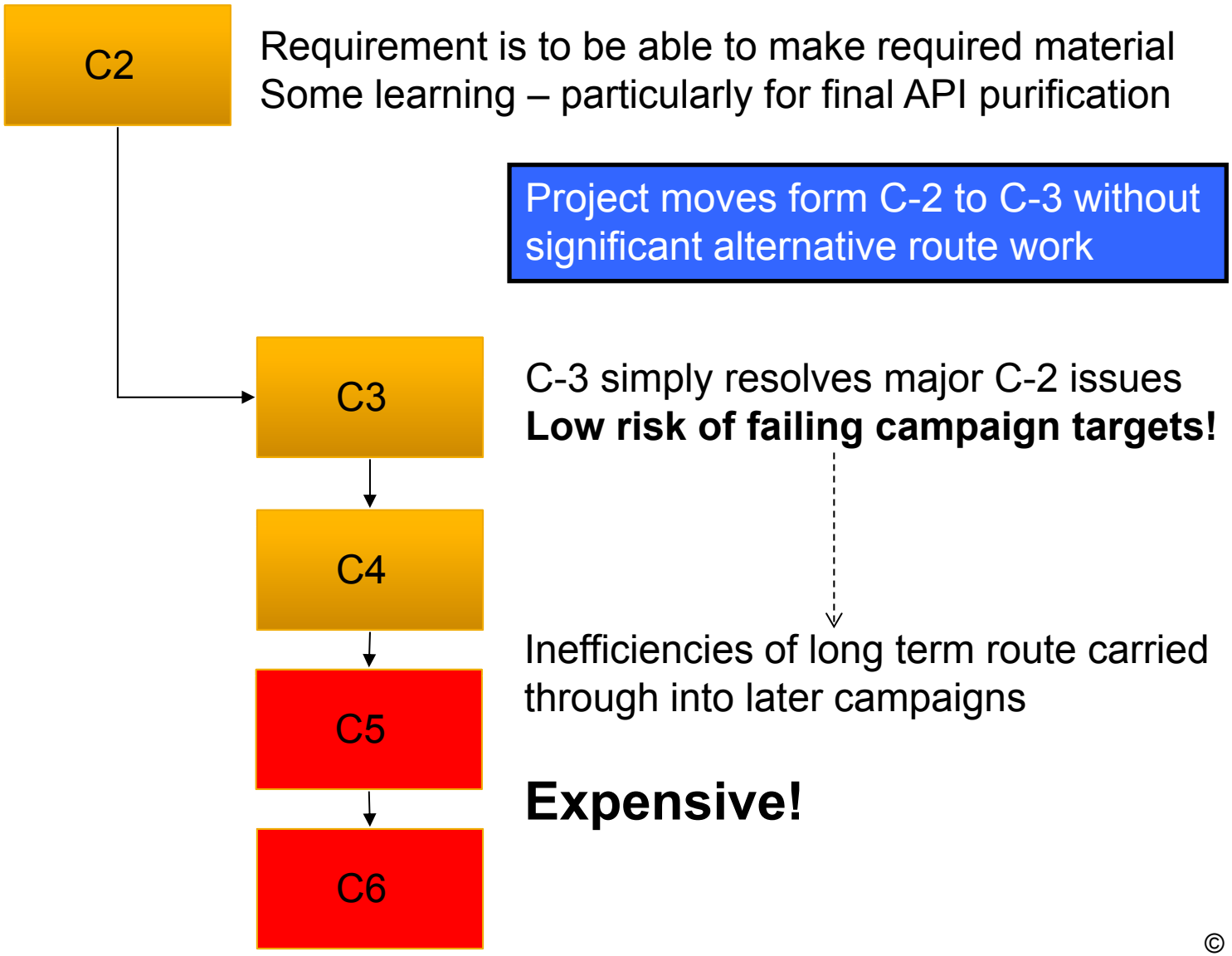


When should we do Route Design?

Routes, Learning and Campaigns
Ideal Model

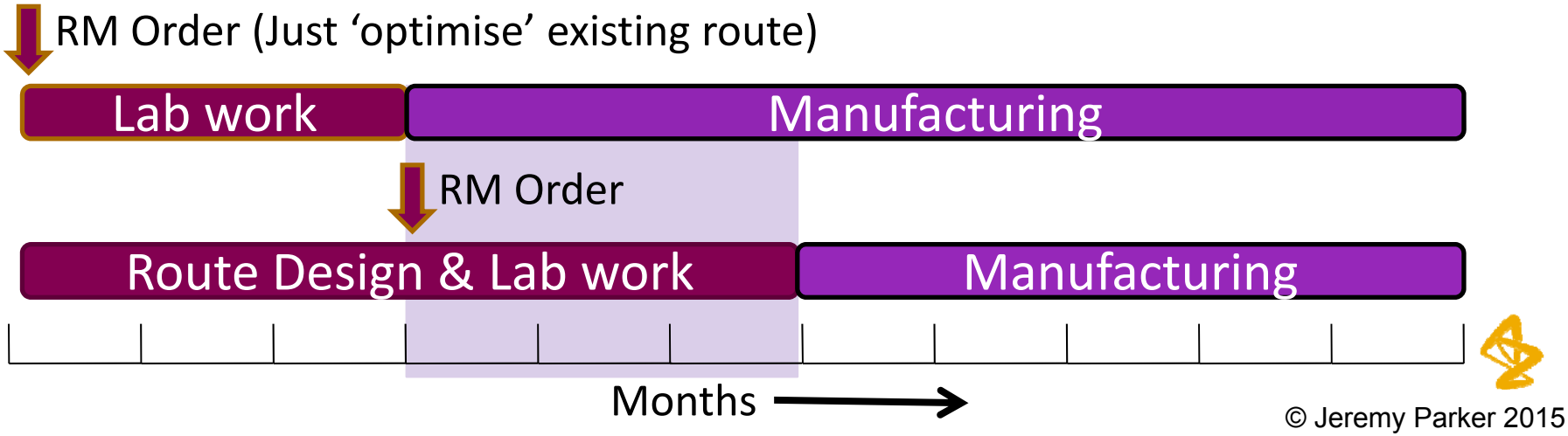


Routes, Learning and Campaigns
Do Nothing

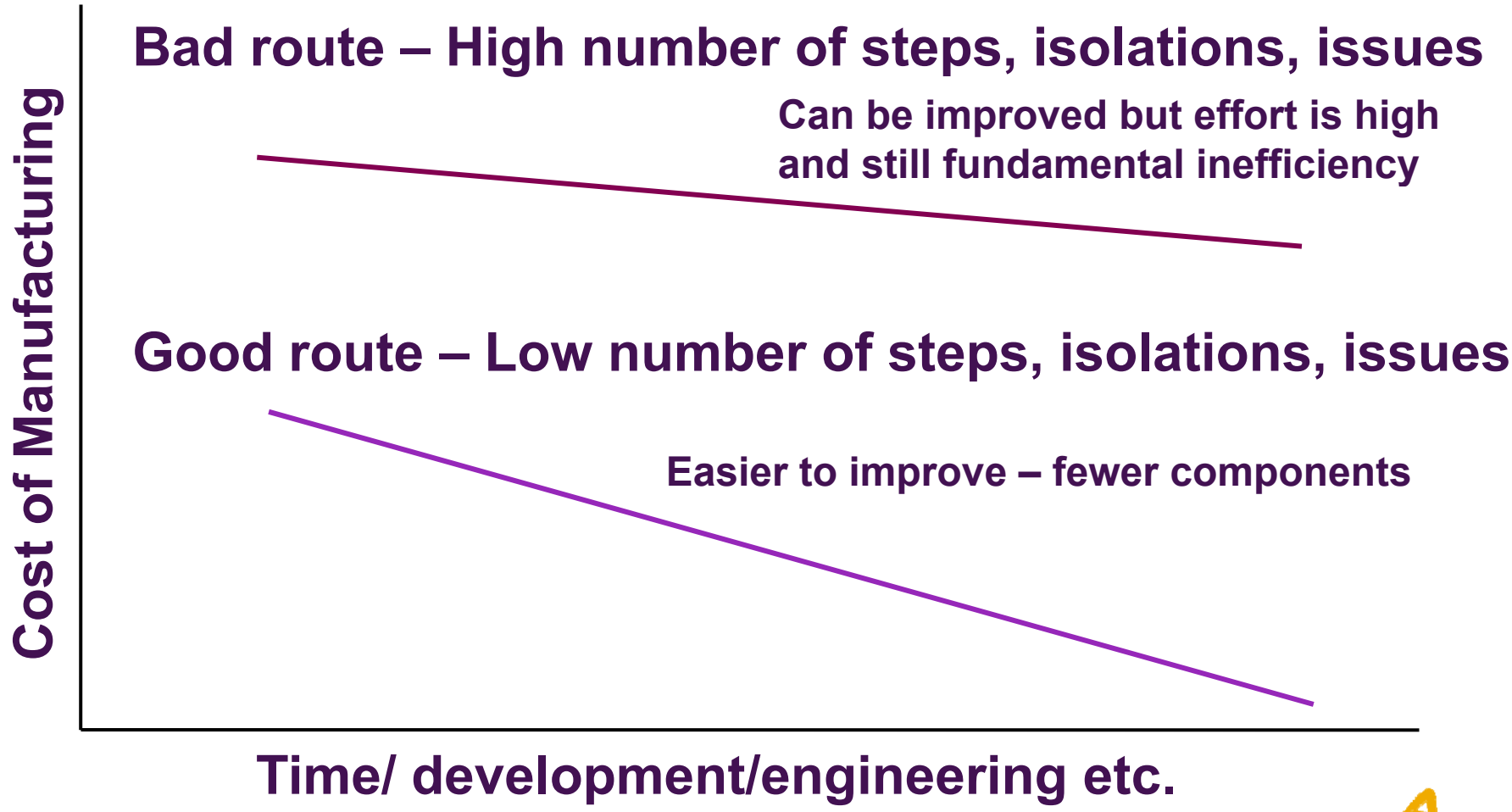


Why Change Route Early?

- An argument that has been used is:
  - 19/20 projects fail, so time/resource spent on route design is wasteful....
- Attrition is actually an added reason for route design
  - The largest proportion of the project budget is spent on materials and manufacturing – better routes use less materials & plant time
  - Manufacturing cost ≈ 10 x the cost of lab work per week
- Compare Lab and Manufacturing timings and costs:



Why Not Improve the Original Route?

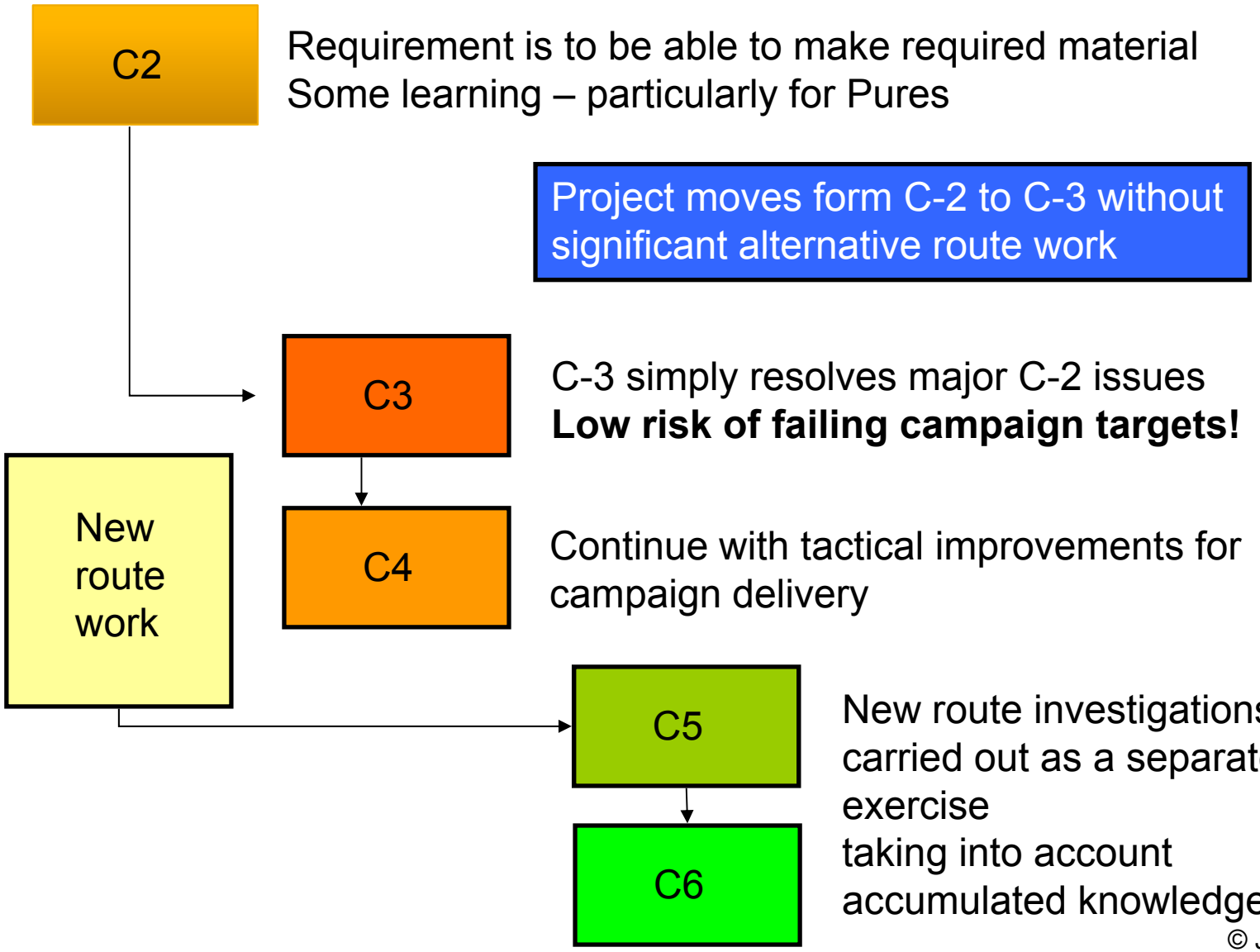


A Bad Route can be Improved...

You can spend a lot of time and money on it:

But it's performance will be based on the original design

Routes, Learning and Campaigns
Alternative Model that can be Effective



How do we do Route Design?

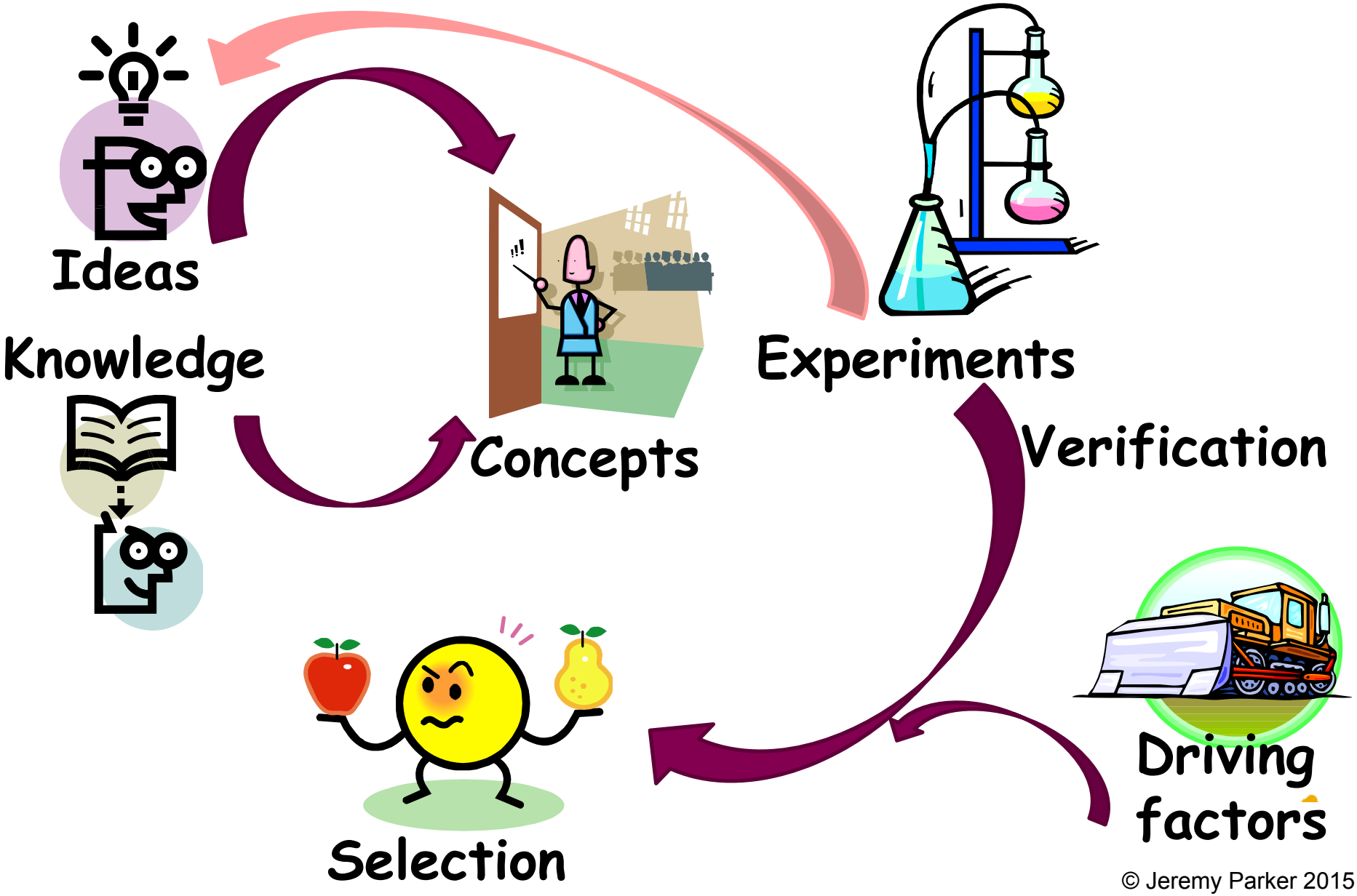
The Process Chemist's dilemma...

Q) What is the 'Best' Route?

A) The route which offers the best balance of key factors at the current state of knowledge

But how do we assess what this means in practice?...

Route Design – An Inventive Process



How to do you evaluate new routes against each other?

- SELECT
  - Safety, Environmental, Legal, Economics, Control, Throughput
    - Butters *et al*, *Chem. Rev.*, **2006**, *106*, 3002.

- Kepner-Tregoe Decision Analysis
  - Defining Must and Wants for optimum route
    - Parker and Moseley, *Org. Process. Res. Dev.*, **2008**, *12*, 1041.

SELECT

S AFETY

E_n NVIRONMENTAL

L EGAL

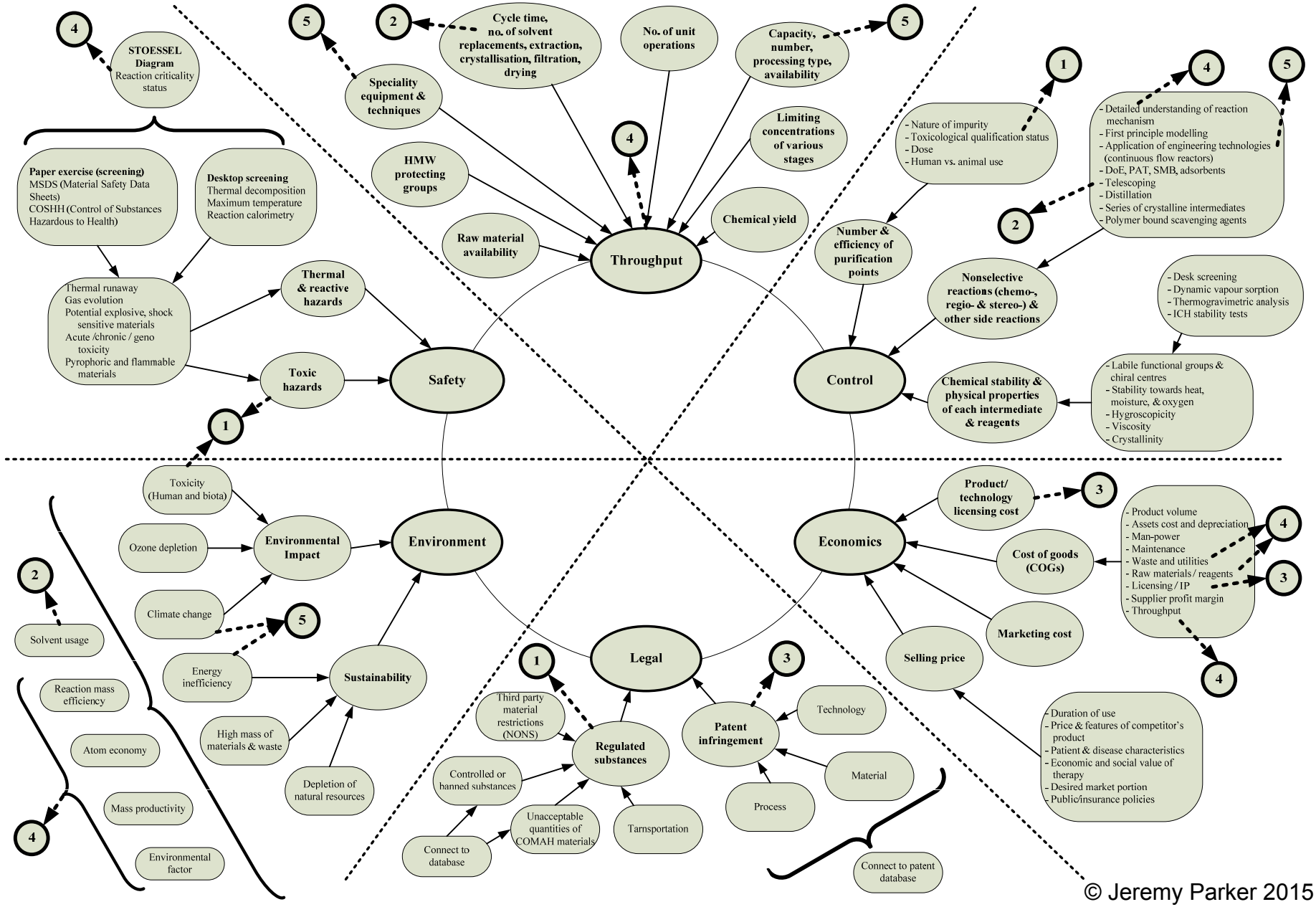
E_c CONOMICS

C ONTROL

T HROUGHPUT

- Exposes reasons for changing a synthetic route...
  .... and present criteria for choosing a long-term route

SELECT– It's not that simple!



Key Activities in Route Design

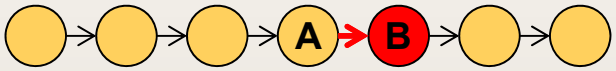
Route Design

Route Invention

Route brainstorm – summarise key transformations (paper exercise)

Rank potential routes based on **SELECT**

Define **routes** by rapidly **testing key transformations**



Narrow the routes; evaluate **Vs SELECT**

Demonstrate few (2-3) routes through to API

Route Selection

Evaluate:
Demonstrated
Routes against
SELECT
Criteria

Long term route

Route Brainstorm

6) RCM

11, 31, 45, 59) Pyridine reduction

12) Pyridine reduction – ambident diketone

18) Threonine-Wittig

18b, 32) McMurray

38) McMurray variant on C2 route

22) Intramolecular Wittig

25) Palladation-decarboxylation

34) Pre-formed Pip carboxylic acid

40, 43) Ramberg-Backlund

49, 69) Condensation

53) Malonate condensation

48) Exo-endo double bond migration

72, 72a) Alkyne cyclisation

64) Intermolecular Wittig

73) Inter. Wittig (II)

15) Condensation

8,9) Alkyne/Overman cyclisation

10) Ketene cycloaddition

20) Diester Diels-Alder

24) Multicomponent coupling

28) Nitrene insertion

39) *Aza silyl prins* – asymmetric Petasis

47) Conia-ene reaction

65) Exomethylene formation

71) Vinyl-metal addition

69, 12) Polonovski

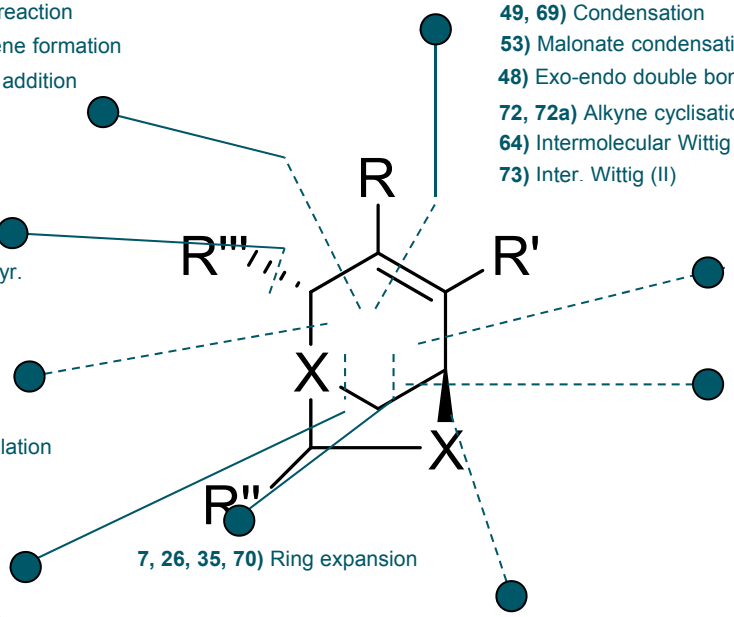
14) Nitrile addition

19) Sulfamidate S_N2'

45) Epoxide S_N2'

46) Palladation from reduced pyr.

51) Formaldehyde trapping



23) Pyrazinone Diels-Alder

39) *Asymmetric Petasis* – aza silyl prins

60) Ene-reaction

5) Furan Diels-Alder

17) Glucuronolactone manipulation

30) N-Acetyl D-Glucosamine manipulation

42) Penicillin ring-expansion

44) S_N2 with pantolactone aux.

50) Epoxide opening (and Wittig)

64) Reduction/displacement

1,2) Iodolactamisation

3) Nitroso-ene

4) Overman rearrangement

16) Aza-Michael addition

18b) Threonine-ascorbic acid

27) Serine-Threonine

45) Shi epoxidation of reduced Pyridine

57) Nitroso Diels-Alder

58) Pyrone Diels-Alder

61) Asymmetric allylation

66) Chiral epoxide opening

67, 68) Intramolecular Mitsunobu

7, 26, 35, 70) Ring expansion

13) Epoxide opening

21) Diester condensation

29) Kojic acid elaboration

33) Mitsunobu from amnino alcohol

36) Chloride displacement with threonol

41) Aziridine opening

55) Valine approach

63) Aziridinium ring-expansion

62) Oxidation

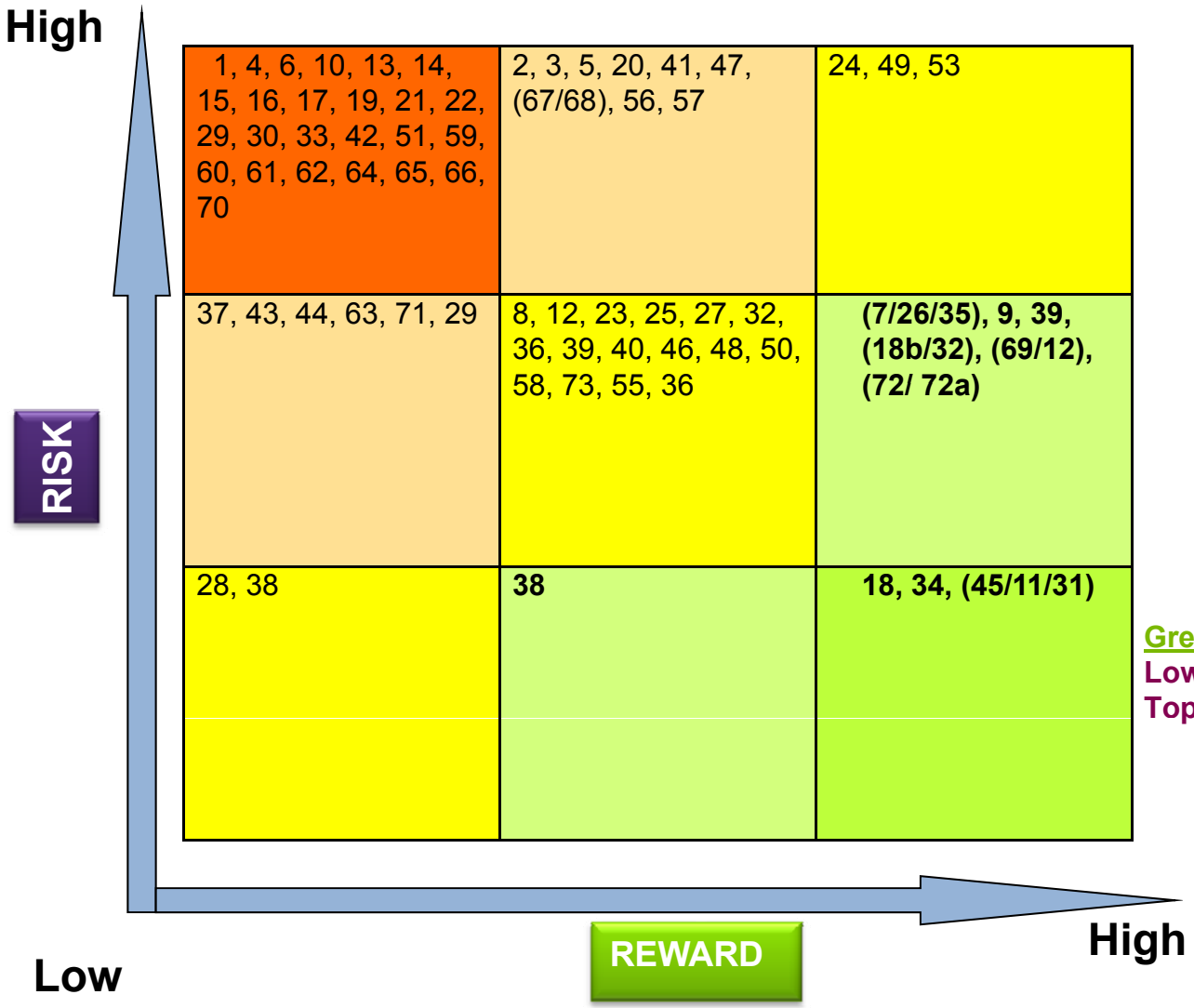
Route Prioritisation
Example of Prioritisation Criteria

- **S/En/L**: Consider **obvious showstoppers only** at this stage of development
- Consider **Ec/C** as key elements for this project
- Consider **T = projected longest linear step count**.

	Risk (C)	Reward (T/Ec)
Low	•Strong literature on similar compounds •High chance of regio / stereocontrol at 5-posn (2-) •Good protecting group strategy – not likely to add steps •Easy access to key step (1FTE <1 month) **High likelihood of success**	•Predicted ≥14 steps •No benefit to atom economy Vs C2 •Expensive, non-commercial RMs •Difficult manufacturability •Little or no projected cost benefits over C2
Med	•Some literature to support key steps •Some chance of regio / stereocontrol / resolution at 5-posn (2-) •Plausible protecting group strategy •Moderate access to key step (1FTE <2 months) **Reasonable likelihood of success**	•Predicted 12-13 steps •Improved atom economy Vs C2 •RMs reasonable cost & availability *or* accessed in a few steps •Reasonable manufacturability •Some projected cost benefits Vs C2
High	•Minimal literature / lit contradicts idea •Little chance of regio / stereocontrol at 5-posn (& 2-posn) •Complex protecting group strategy •Predict slow progress to key step (1FTE >2 months) **Low likelihood of success**	•Predicted ≤11 steps •Markedly better atom economy than C2 •Cheap, readily available RMs •No major manufacturability issues •Obvious projected cost benefits Vs C2

Example Output: Risk-Reward matrix

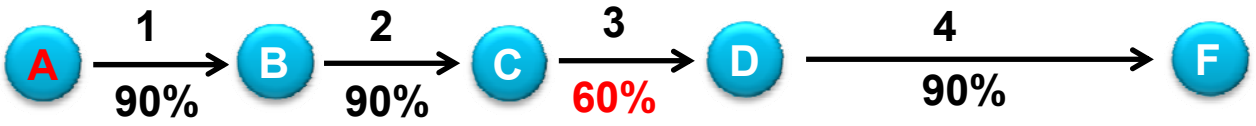
- **Each number represents a discrete route idea...**



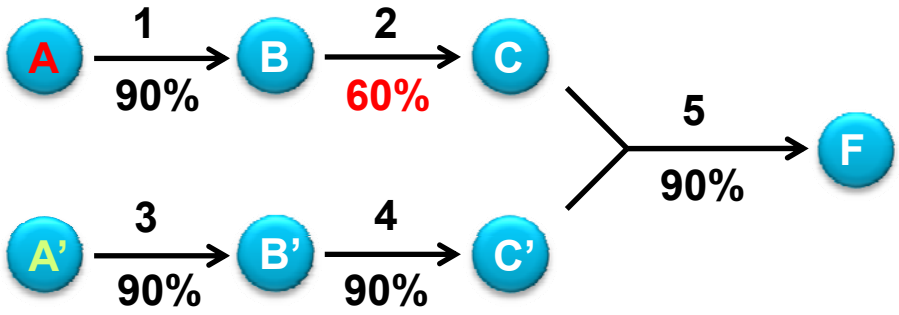
Green =
Lowest risk, highest reward;
Top 10 work packages

Linear Vs Convergent Synthesis

Linear 1
5 steps (all linear)
39% yield from A



Linear 2
4 steps (all linear)
44% yield from A



Convergent
5 steps (3 linear)
49% yield from A

Process Chemistry
Process Safety

Jeremy Parker, Principal Scientist
Chemical Development, Pharmaceutical Development
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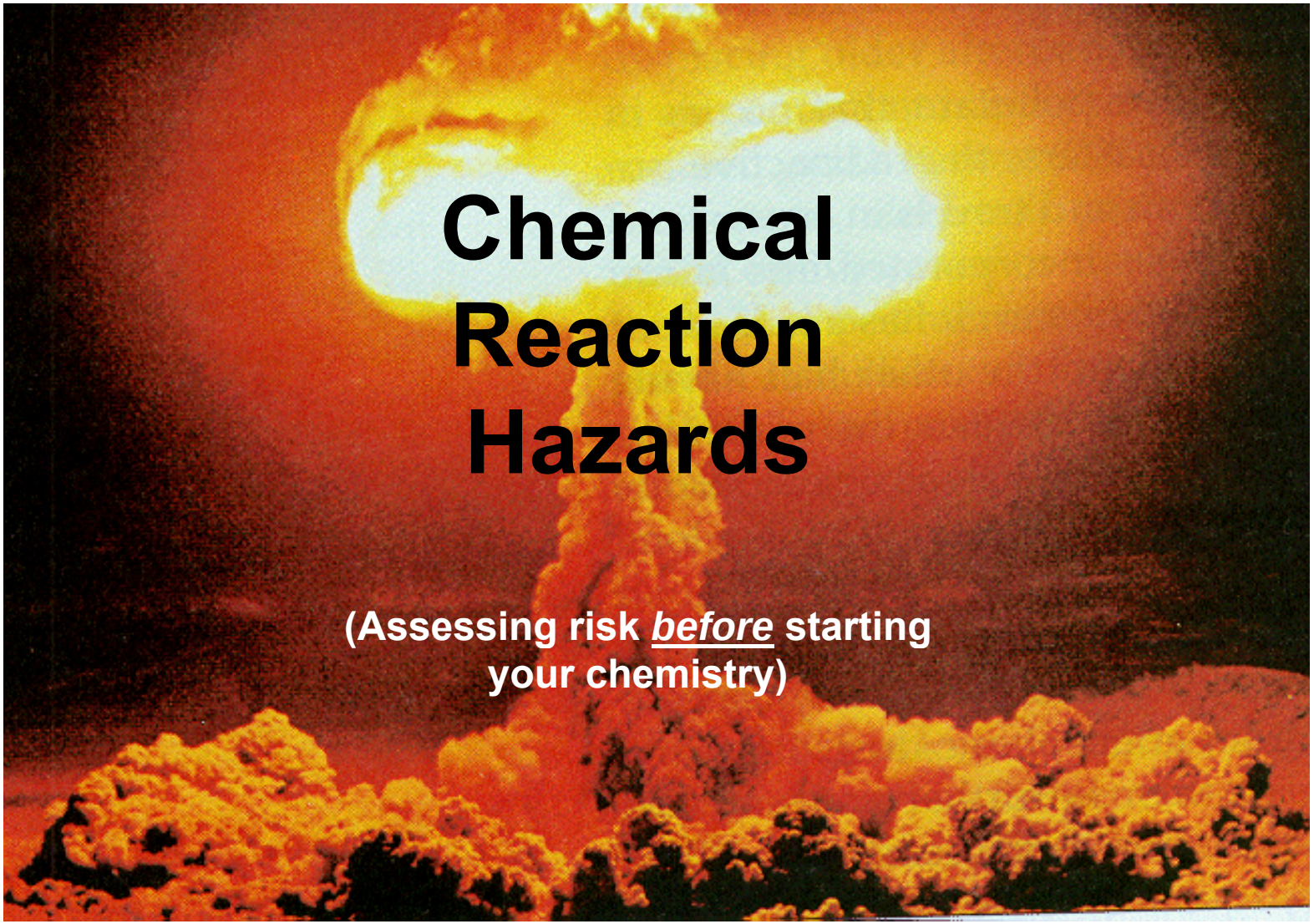


Incident

Chemical Reaction Runaway (Thermal Decomposition)

- Bayer Crop Science (West Virginia, USA) – 2008
- 2 fatalities, 8 treated for possible toxic chemical exposure

Incident
Runaway Reaction in ‘Treater’ Vessel

- High conc of methomyl passed to ‘Treater’ with low solvent volume and heated
- Decomposition of this overwhelmed the cooling capacity of the ‘Treater’ and the associated gas evolution could not be adequately vented
- Vessel pressurised and subsequently ruptured

What Makes Chemical Reactions ‘Dangerous’?

Three main areas:

1) Biological Hazards
Toxic, carcinogenic...
Covered by COSHH

2) Operational Hazards
Static discharges,
flammable atmospheres

3) Chemical Reaction Hazards
Result from ***uncontrolled*** *chemical reactions*

SELECT

What Makes Chemical Reactions 'Dangerous'?

3) Chemical Reaction Hazards
Result from ***uncontrolled*** *chemical reactions*

Heat generated > Dissipation rate
(heat lost to surroundings)

Temperature increase

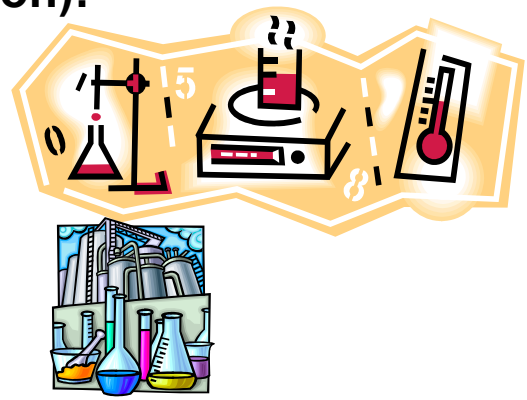
Increase in reaction rate

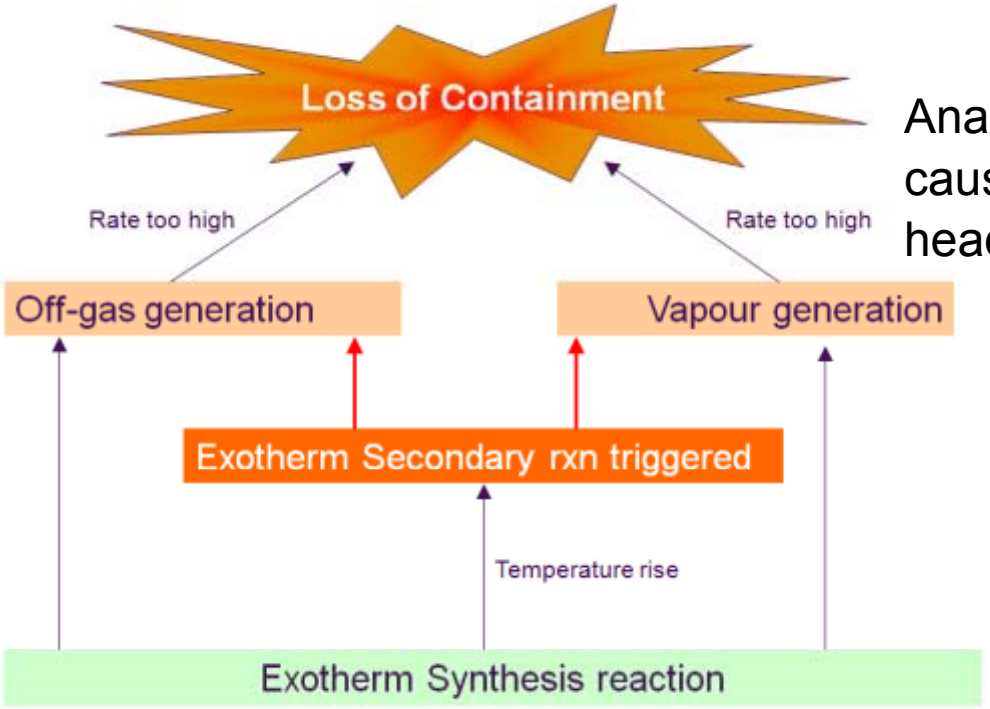
E_a = activation energy
T = temperature

$$k = Ae^{-E_a / RT}$$

Chemical Reaction Hazards

- **Arise from :-**
  - **Thermal instability (undesired reactions/decomposition):**
  - **Rapid exothermic reactions - raising the reaction temperature to decomposition or violent boiling**
  - **Rapid gas evolution**





Analysis of incidents revealed that the causes can be classified under two main headings.

– Lack of chemical understanding

or

– Experimental design / operation

[Video Clip]

Runaway Reactions

- Occur when exotherm is large
  ...and cooling capacity is inadequate
- Increasing the scale of a reaction increases the rate of heat output and requires greater heat dissipation
- Rate of energy release is more important than the *quantity* of energy release
- Can be remedied by providing adequate cooling

1 L flask → **1000 L reactor !!??**

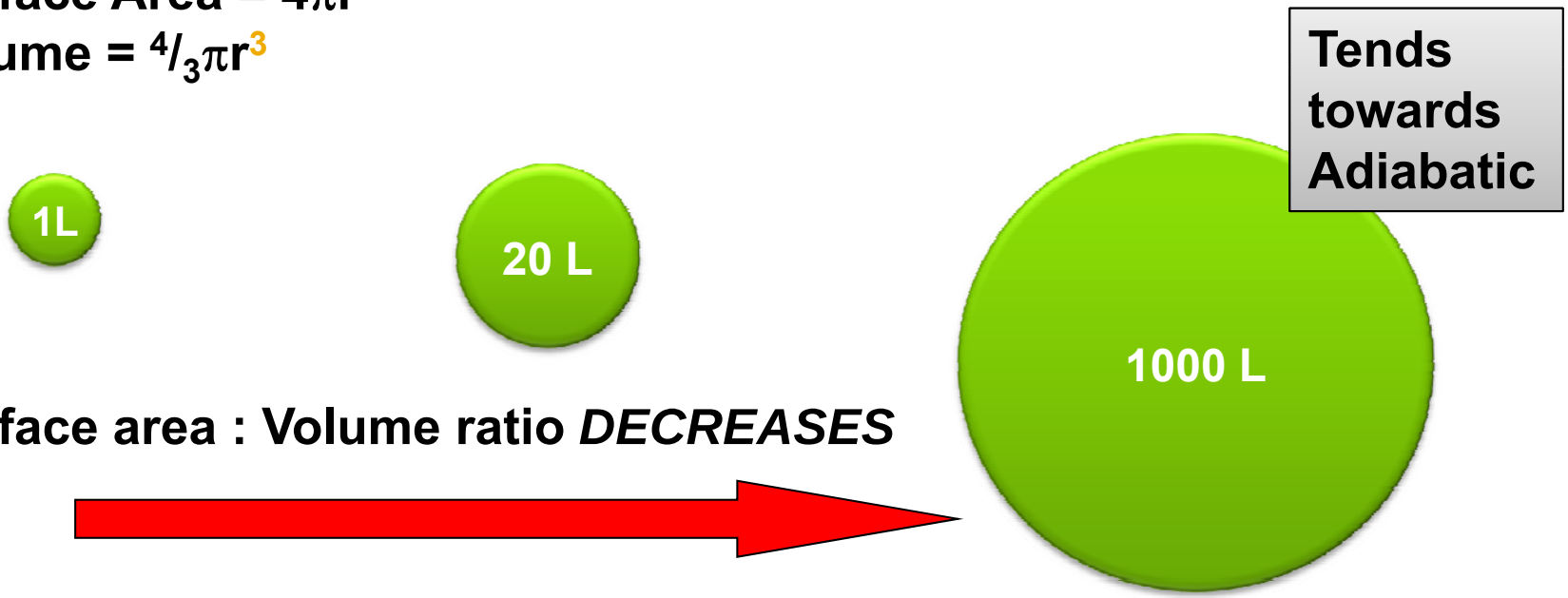
Fire or explosion may result from accelerating reaction rate

Reaction scale should never be increased without also increasing cooling capacity (appropriately)!!

Scale-up Vs Heat Loss

- Model the reaction vessel as a perfect sphere....
- Surface area is the key to heat 'loss' (dissipation)

Surface Area = $4\pi r^2$
Volume = $^4/_3\pi r^3$

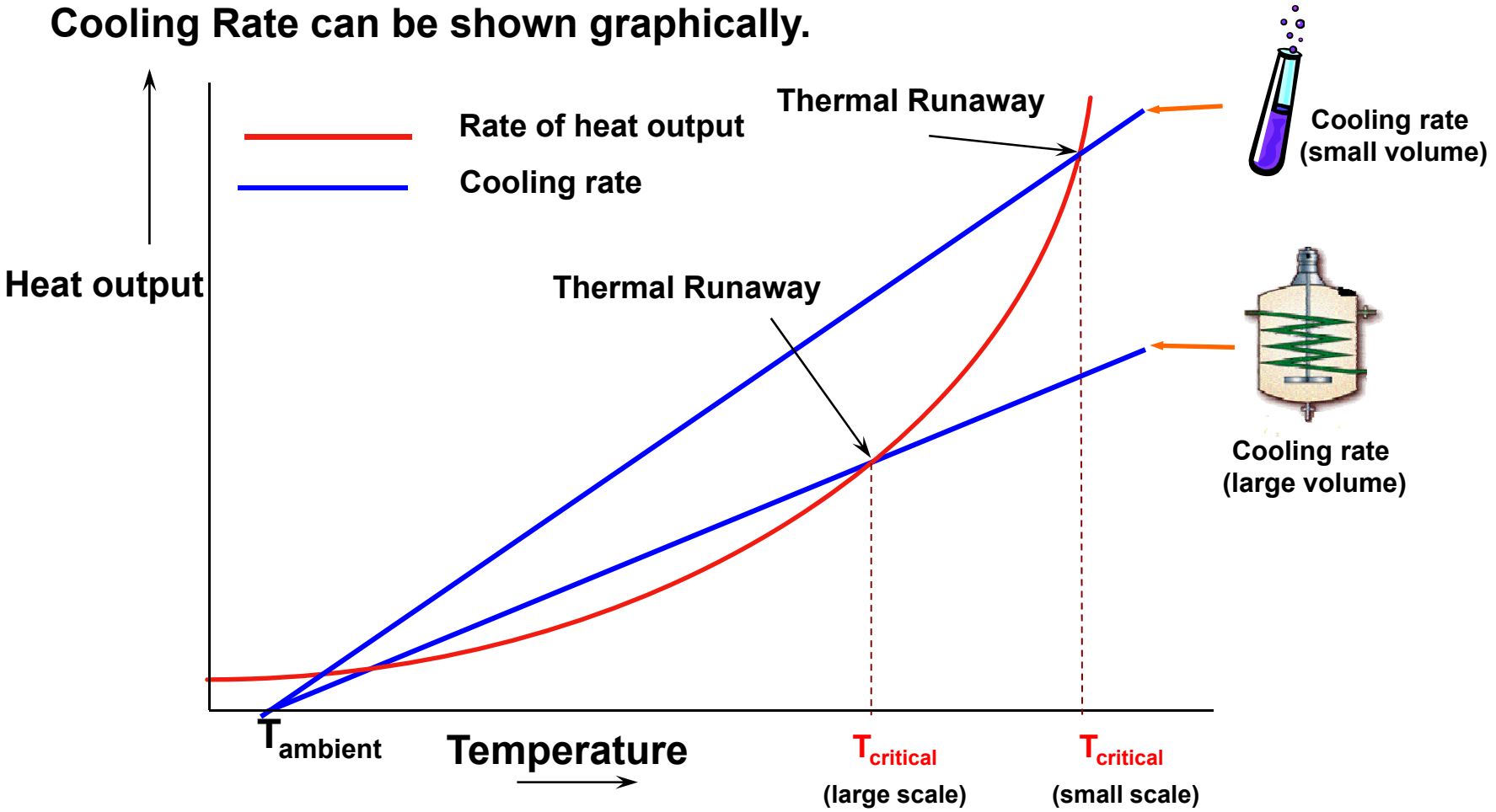


Surface area : Volume ratio *DECREASES*

- Also....plant vessels are often lagged
- What about loss of power? (ie cooling)...

Heat Loss with Respect to Scale

The relationship between Temperature, Rate of heating and Natural Cooling Rate can be shown graphically.



'self-heating' will occur from T_{crit}

Some Definitions...

Adiabatic temperature rise (ΔT_{ad})
= the rise in temperature assuming no heat is lost to the surroundings

1000 L+?!

$$\Delta T_{ad} = \frac{\Delta H}{\sum m.C_p}$$

where **ΔH = heat of reaction (J)**
m = mass of reactants (g)
C_p = heat capacity of reactants (J K^{-1} g^{-1})

Heat Capacity(C_p)
= the quantity of heat required to raise a unit mass of a substance by one unit in temperature*

**(assumes constant phase, pressure & volume)*

Adiabatic Temperature Rise – Example

- Exothermic reaction: **A + B -> C**
  A is dissolved in solvent at 50°C and then **B** is added...

- We have a choice of **toluene** or **water**...

- C_p water = 4.184 J/g/K
  C_p toluene = 1.7 J/g/K

- Let's assume:
  a typical heat of reaction, 100 mL water, A and B = 10g each.

ΔH = -120 KJ mol^{-1} A, MW A = 100
C_p [A+B] = 1.3 J/g/K

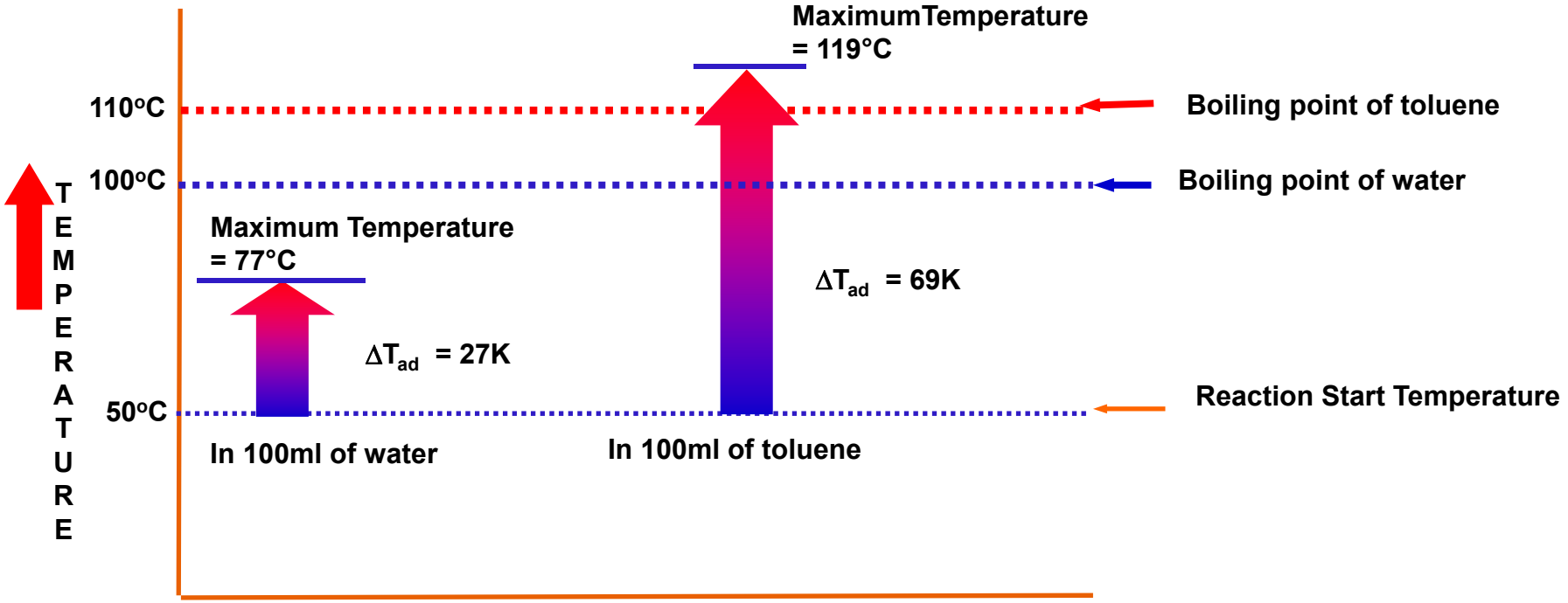
$$\Delta T_{ad} = \frac{\Delta H}{\sum m.C_p}$$

= 12,000 / [(100 x 4.184) + (1.3 x 20)]
= 27 K

...A reaction carried out in toluene will result in a larger temperature rise (69 K) than one carried out in the *same volume* of water.

Effect of Heat Capacity

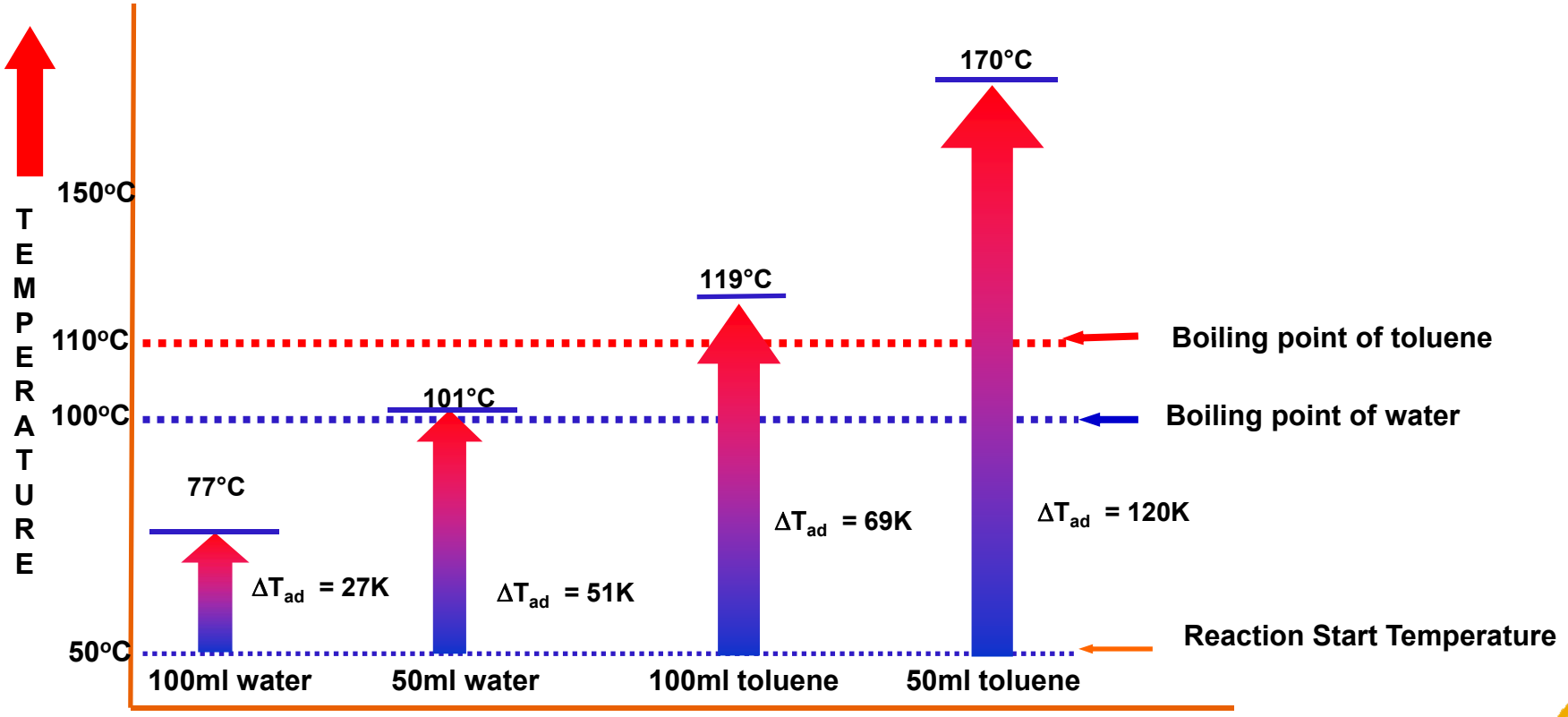
- Calculation using 100ml of water as the solvent indicates that an adiabatic temperature rise of 27K is possible.
- Calculation using 100ml of toluene as the solvent indicates that an adiabatic temperature rise of 69K is possible.
- So what does this mean in terms of potential hazard ?



Effect of Concentration

- The *concentration* of the reaction will also effect the overall temperature rise.
  The concept of a heat sink...

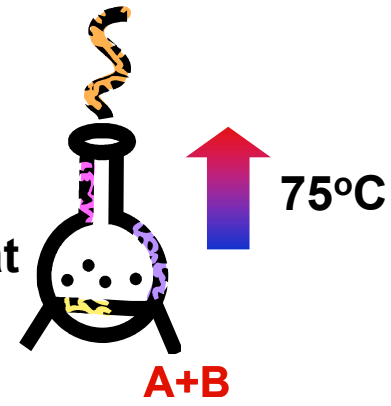
- Assume Water and toluene are the solvents but in half the volume as before;
  ie. double the concentration
- Hence, the maximum rise in 50 ml of water will be 51K (compared to 27 K in 100ml) and 120K in 50 ml of toluene (compared with 69K in 100 ml)



Mode of Operation

Again considering a general reaction:

$$A + B \longrightarrow C$$

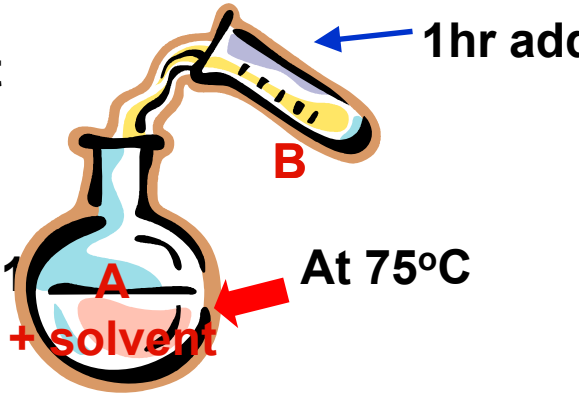


Method 1

- **1 eq of A and 5 eq of B are charged to the reactor at 25°C ('All-in' batch reaction).**
- **Heat mixture to 75°C to complete reaction (1h)**

Method 2

- **1 eq of A and solvent are charged to the reactor at 25°C.**
- **The mixture is heated to 75°C.**
- **1.1 eq of B are added in a controlled manner over 1 h. Reaction complete at end of addition.**



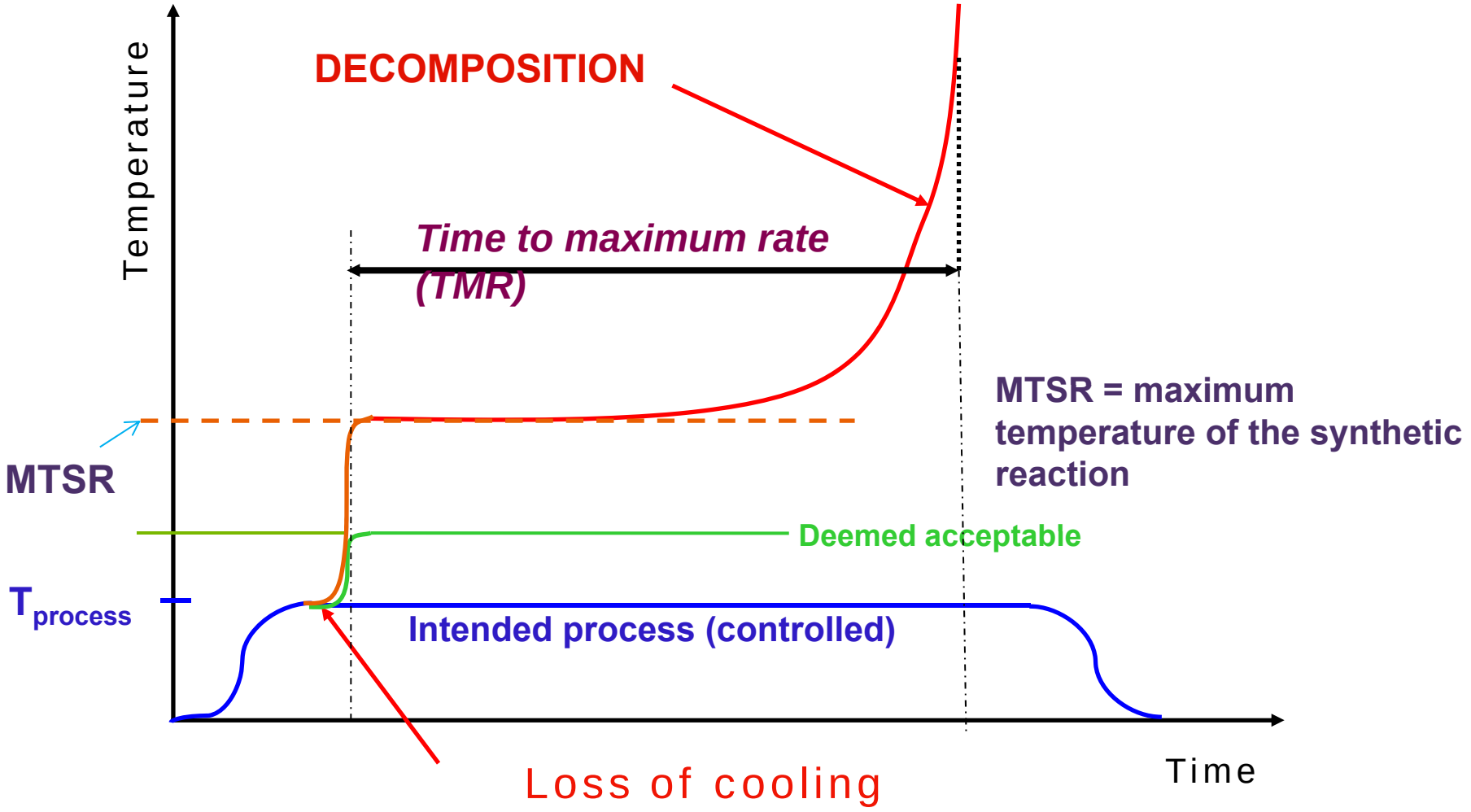
Mode of Operation - Consequences

- Method 1 uses no solvent – neat reaction.
  Highly concentrated: little or no real heat capacity
- ...temperature rise associated with Method 1 will be much higher
  More likely to access boiling point / decomposition events
- Large excess of reagent in Method 1 could favour secondary reactions
  Reduce thermal stability further – remember vicious circle!
- 'All-in' reactions are very difficult to control
  No hold over the rate of heat generation
- ..Slow addition allows degree of control over rate of heat generation
  Stop the addition –> stop the heat generation

Conclusion: Use method 2
It is often the *way* a reaction is *carried out* that is potentially unsafe, rather than it being inherently hazardous.

...but not always!!!

Normal Mode of Operation vs MTSR



Thermal Hazards –Five Classes of Reactions

1) MTSR < *boiling point* < decomposition temp
   (including a 90^{o}C safety factor) = Inherently thermally safe process

2) MTSR < decomposition temp < *boiling point*
   Latent heat of vaporisation cannot act as a safety barrier in this case
   - Install measures to prevent overheating

3) (MTSR > boiling point) < decomposition temp
   Possibile overpressurisation – need to control reaction *and* assess capability of vessel to relieve pressure

4) (MTSR > boiling point) ~ decomposition temp
   Will initiate decomposition if uncontrolled. Reaction control and/or protection must be applied.

5) (MTSR > decomposition onset) < boiling point
   Loss of reaction control (ie cooling) **will** initiate decomposition.

   Preventative or protective measures **must** be put in place.

MTSR = maximum temperature of the synthetic reaction

Thermal stability screening of reaction mixtures

1. **Thermal screening calorimeters**

Only require **small quantities of material** (mg - g) but are **relatively insensitive**

- Differential Scanning Calorimetry (DSC)
  - Sample heated at 5K /minute, between 0 and 500^{o}C
  - Exotherms and endotherms are observed as a deviation from the baseline
  - Gives onset temperatures of 'thermal events' and heat output measurement
  - Gas evolution can **not** be measured
  - *CARE! Insensitive test*

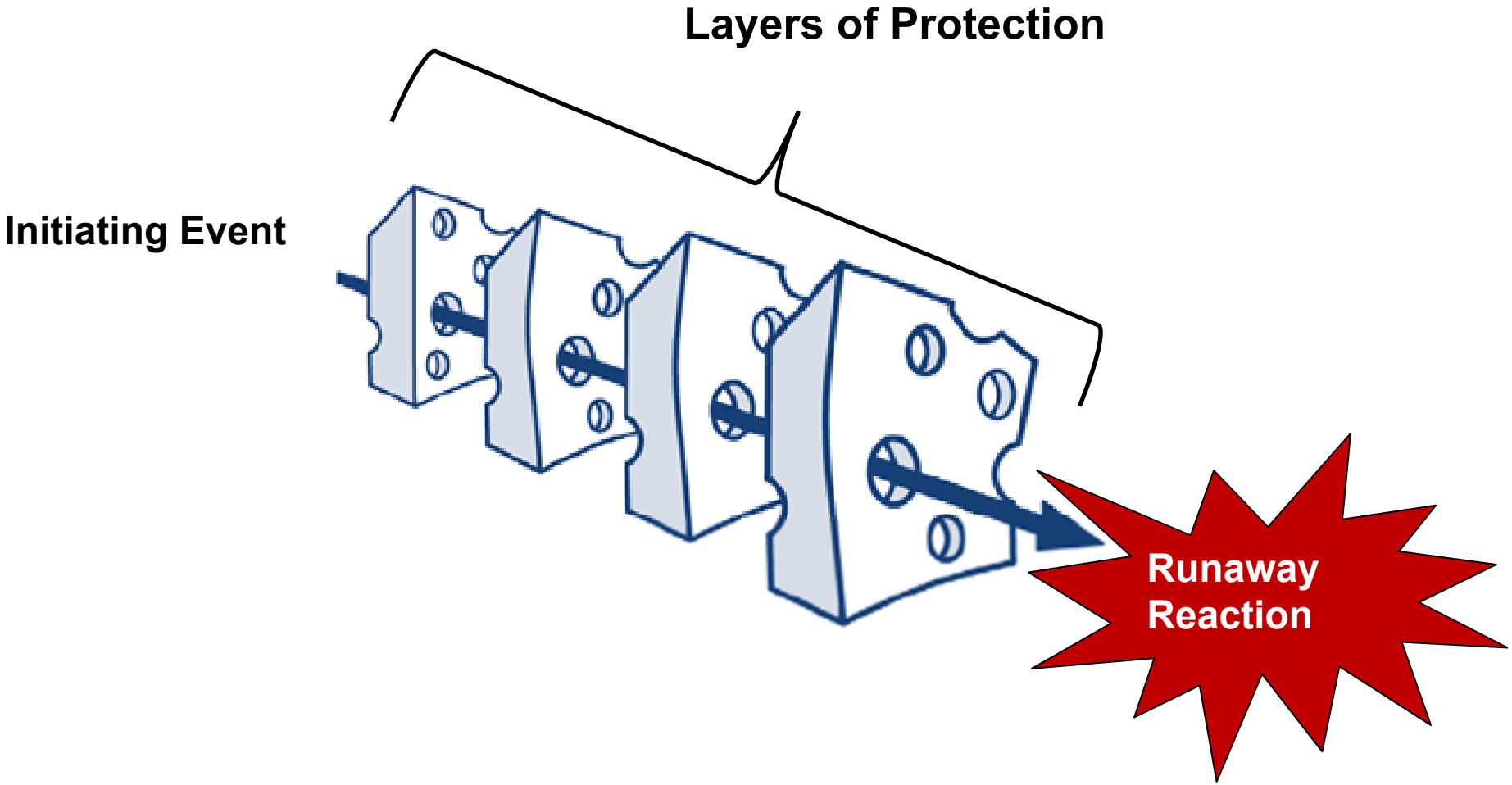
- Carius tube test
  - Pressure detection allows gas evolution to be measured
  - Still relatively insensitive

2. **Adiabatic calorimiters**

Require **larger quantities** (10g+), but designed to minimise heat loss; measure the heat generated from a chemical reaction or decomposition, 'without' losing heat to the surroundings. **Greater sensitivity**

- Accelerating Rate Calorimetry (ARC)
  - uses heaters to generate an 'adiabatic shield'
  - don't need to apply large safety margins – directly applicable to scale up
  - adiabatic temperature rise data, self-heat rate data against time or temperature and pressure *rate* data can be obtianed.

Risk Assessment and Mitigation
The 'Swiss Cheese' Model

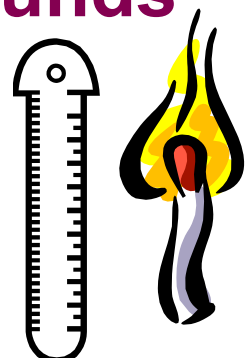


Prevent the initiating event from becoming a runaway reaction:

1. **Reduce the area of the holes (= likelihood)**
2. **Increase the number of layers**

Working safely in the labs...

Identifying Potentially Unstable Compounds



- Relative heat of formation – can be useful for judging the energy release which would accompany a compound's decomposition
- Examine chemical structure: Nitrogen content; *violent release of N_2*
  - Azides
  - Diazonium Salts
  - Nitro compounds
  - Tetrazoles
  - Triazines
  - Diazo compounds
  - Hydrazinium salts
  - N-nitroso compounds
  - Tetrazenes
  - Dinitrophenylhydrazine
- Explosive properties can be related to specific functional groups (see Bretherick's Handbook of Reactive Chemical Hazards)

Aliphatic azo compounds	(-C-N=N-C-)	Organic azides	(-C-N_3)
Diazonium salts	(-$CN_2^+Z^-$)	N-nitroso compounds	(>N-N=O)
Aromatic sulphohydrazides	(-SO_2-$NHNH_2$)	Peroxides	(-O-O-)
Nitro compounds	(-NO_2)	Hydrazides	(R-NH-NHR)

Potentially Explosive Groups

- Key Groups:
  - Aliphatic azo compounds (-C-N=N-C-)
  - Organic azides (-C-N_3)
  - Diazonium salts (-$CN_2^+Z^-$)
  - N-nitroso compounds (>N-N=O)
  - Aromatic sulphohydrazides (-SO_2-$NHNH_2$)
  - Peroxides (-O-O-)
  - Nitro compounds (-NO_2)
  - Hydrazides (R-NH-NHR)

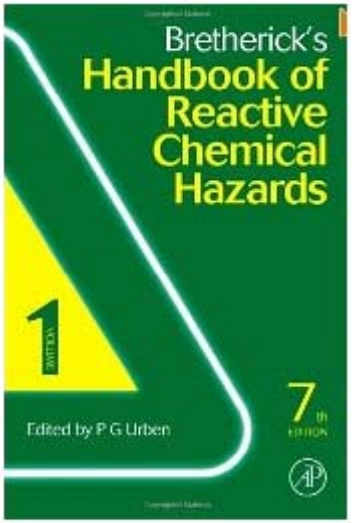
Oxygen Balance

- Oxygen Balance is a guide to the propensity of an organic compound to decompose or explode using only the oxygen contained in the molecule
- For $C_XH_YO_Z$
  - OB = [-1600 x (2x + y/2 - z)]/molecular mass

Oxygen-Balance	Hazard Ranking
More positive than +160	Low
+160 to +80	Medium
+80 to -120	High
-120 to -240	Medium
More negative than -240	Low

Sources for Identifying Hazards

1. Chemical literature/peers
2. Bretherick's Handbook of Reactive Chemical Hazards.
3. Sax's Dangerous Properties of Industrial Materials.
4. Material Safety Data Sheets (MSDS).
5. UK Chemical Reaction Hazards Forum (www.crhf.org.uk)



Remember :Even if experimental / literature citations do not mention a hazard, it does not necessarily mean there is no hazard.

Process Chemistry
Process Design

Jeremy Parker, Principal Scientist
Chemical Development, Pharmaceutical Development
AstraZeneca
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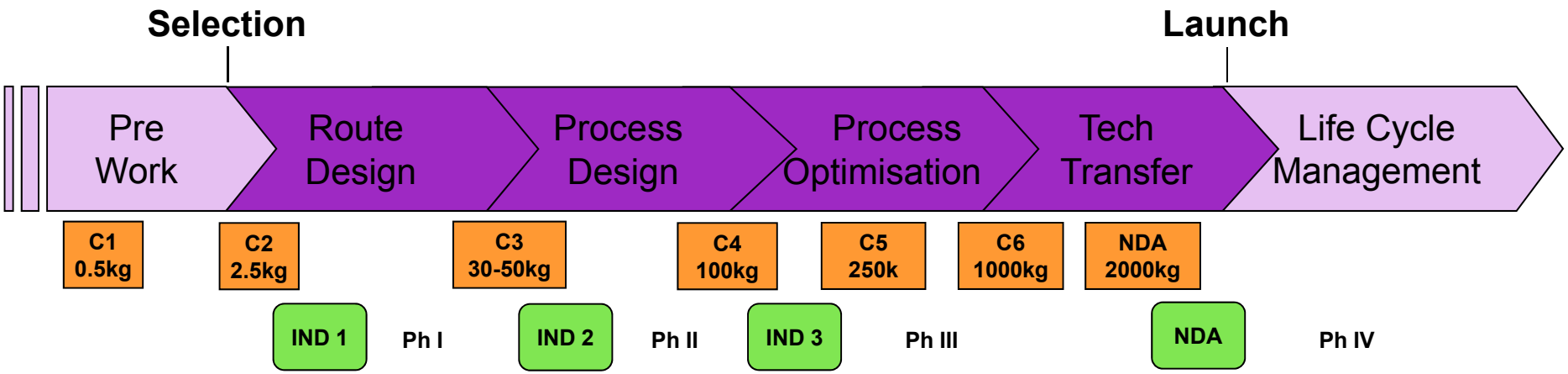
Process Development Overview



Process Design...

"It is no good offering an elegant, difficult and expensive process to an industrial chemist, whose ideal is something to be carried out in a bath tub by a one-armed man who cannot read, the product being collected continuously through the drain hole in 100% purity and yield."

Sir John Cornforth, *Nachr. Chem. Techn.* 1976, **24**, 35.

What sort of Chemistries?

What Sort of Chemistries?

There is no sort of chemistry that cannot be scaled up – the challenge is to find the most efficient and cost effective solution...

What Sort of Chemistries?

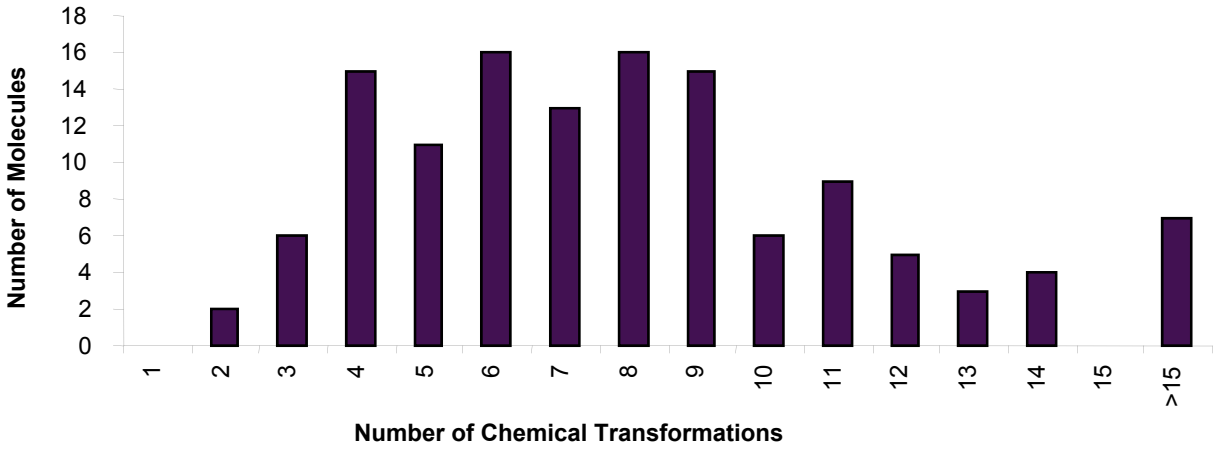
- Analysis of the reactions used for the preparation of drug candidate molecules
  - Survey of chemistry scaled up in AZ, GSK and Pfizer
  - 128 compounds, <1000 chemical transformations

J. S. Carey, D. Laffan, C. Thomson, M. T. Williams *Org. Biomolecular Chem.* **2006**, *4*, 2337-2347

- Shows the range of chemistries used in the manufacture of drug candidates and highlights certain gaps in current technologies

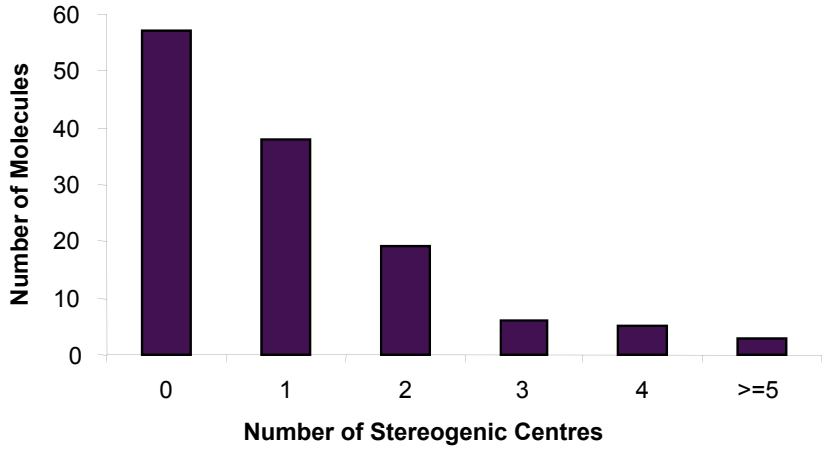
What Sort of Chemistries?
Chemical Complexity and Chirality

Step Count:

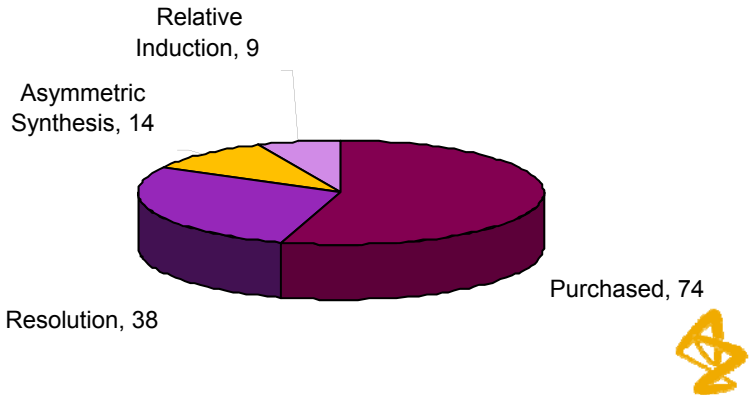


Average 8 steps per molecule

Chiral Centres:



Sources of Chirality:

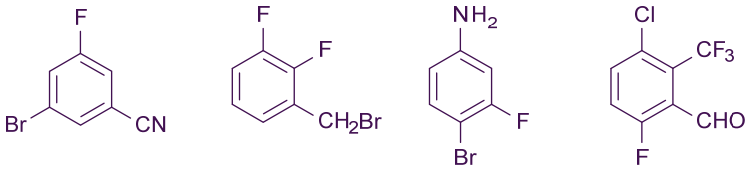


What Sort of Chemistries?
Analysis of Reaction Types Used

Reaction Category	Total	%
Heteroatom Alkylation/Arylation	196	19
Acylation	128	12
C-C Bond Forming	116	11
Aromatic Heterocycle Formation	52	5
Deprotection	159	15
Protection	61	6
Reduction	94	9
Oxidation	40	4
Functional Group Interconversion	104	10
Functional Group Additions	33	3
Resolution	30	3
Miscellaneous	26	3
	1039	

What Sort of Chemistries?
Aromatic Substitution - Not Trendy (or Easy!)

Substitution Pattern	Number of Examples	Frequency (%)
1,2-Ph	16	11
1,3-Ph	17	12
1,4-Ph	38	27
1,2,3-Ph	13	9
1,2,4-Ph	46	32
1,3,5-Ph	5	4
1,2,3,4-Ph	4	3
1,2,3,5-Ph	2	1
1,2,4,5-Ph	1	1
Total	142	100



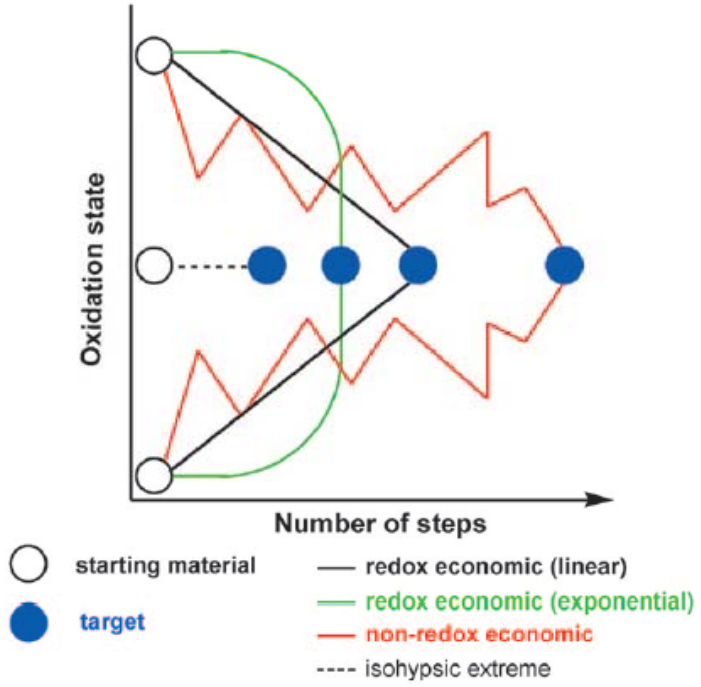
What Sort of Chemistries?
Protecting Groups

- Protections and Deprotections account for 6% (61 reactions) and 15% (159 reactions) of the total chemical transformations
  - Protecting Groups
    - Nitrogen (39%) - Boc and Bn/Cbz
    - Oxygen (30%) – Bn, SiR_3, Ac
    - Carboxylic Acid (28%)
- Between them account for >20% of all the transformations and almost 2 chemical transformations per molecule
- The reason that deprotections significantly out number protections is that many of the starting materials purchased contain the protecting groups in place
- On a positive note, 45 out of the 128 syntheses (35%) were achieved without the use of protecting groups

What Sort of Chemistries?
Oxidation and Reduction

- Carbon Oxidation
  - Relative rare reaction due to difficulties in controlling oxidation state
- Carbon Reduction
  - Observed much more frequently

- Links to Baran's proposals around 'Redox Economy in Organic Synthesis' (*ACIE* 2009, **48**, 2854 – 2867)



What Sort of Chemistries?
Conclusions in Paper

- Many common and important reactions are still difficult to perform at large scale
  - Poor selectivity
  - High levels of waste
  - Multiple steps for a single FGI
  - Toxicity associated with alkylating agents

Process Chemistry Preferences...

Process Chemistry Preferences... Functional Groups

- Dislikes
  - Aldehydes
    - Tend to be unstable and form hydrates
  - Chiral Fluorines
    - Expensive to put in and currently no reliable enantioselective methods
  - Azides/Triazoles/Tetrazoles
    - Explosivity risk
  - Azetidines
    - Difficult to source/prepare and poor stability
  - Thiols (low oxidation state sulfur)
    - Disulfide formation, oxidation potential
- Likes
  - Anything with good stability
    - Sulfonamides, Ethers, etc, etc

Process Chemistry Preferences...
Types of Reaction

- Dislikes
  - Protecting group introduction or removal
    - Adds steps to synthesis, but is often necessary
  - Oxidation or Reduction
    - Unnecessary changes in oxidation level of molecule
- Likes
  - Amide bond formations
    - Direct Ester to Amide
  - Transition Metal Catalyzed Reactions
  - Nucleophilic Aromatic Substitution
  - Classic Heterocycle Synthesis
  - Diels-Alder Reactions

Process Chemistry Preferences... Oxidation

- Dislikes
  - Hypervalent iodides
    - Difficult to source, variable strength, can be explosive, iodine waste
  - Chromium reagents
    - Presence of toxic metal
  - Oxygen
    - Flammability issues in plant, but 5% O_2 in N_2 can be used
- Likes
  - TEMPO/H_2O_2 or Na_2WO_4/H_2O_2
    - Cheap oxidant and reliable scale-up
  - DMSO oxidations (Swern, etc)
    - Effective on smaller scales, just need to minimize the smell!
    - (Can depend on who you talk to…)

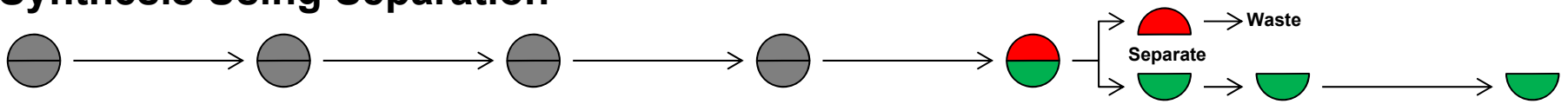
Process Chemistry Preferences...
Reduction

- Dislikes
  - Solid Reducing Agents
    - Difficult to handle on a large scale and add to reactions (eg $NaBH_4$)
  - DIBAL-H
    - Difficult to deal with Al waste in work-up
- Likes
  - Reducing Agents in Solution
    - Easy to use and charge accurately (eg $LiBH_4$)
  - Hydrogenation
    - Atom efficient and simple work-up
    - Always use specific grades of catalyst
    - JM Catalyst Handbook

Process Chemistry Preferences...
Chiral Synthesis

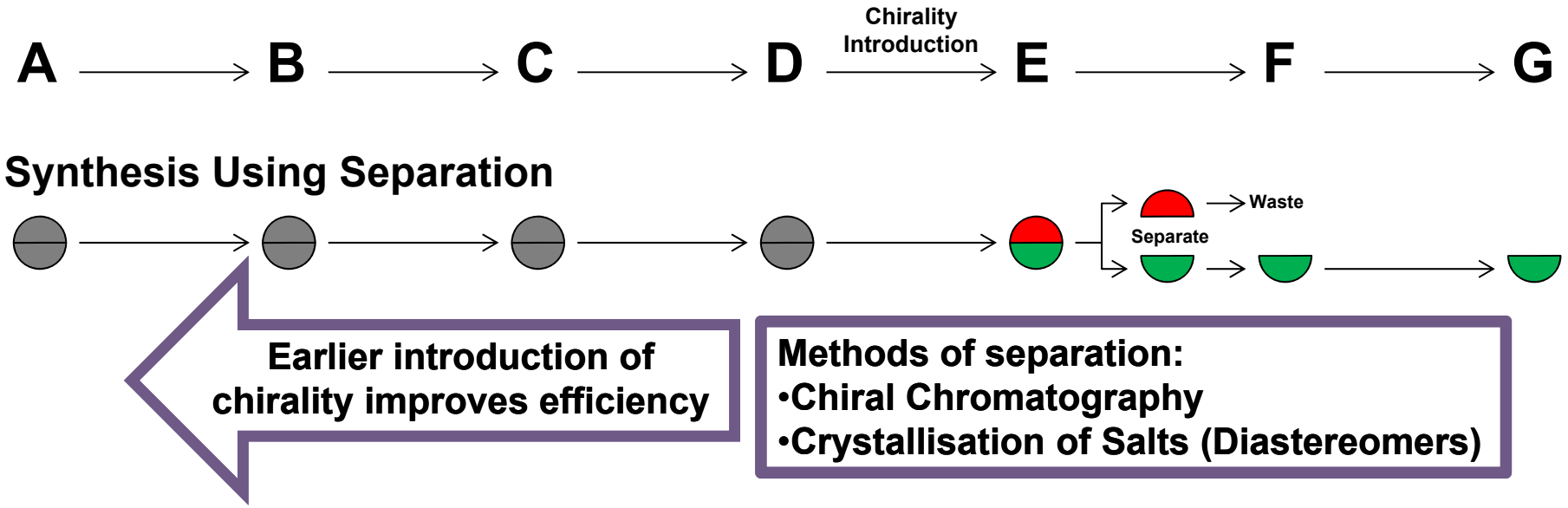
How to Access Single Enantiomers?

Synthesis Using Separation



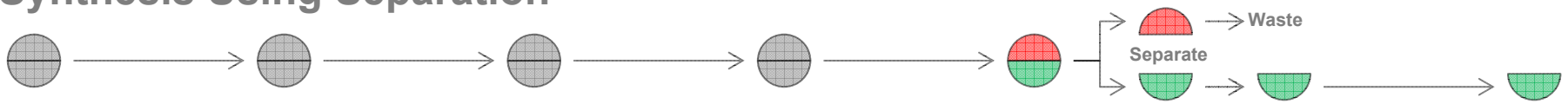
Asymmetric Synthesis

Synthesis using Separation



Asymmetric Synthesis

Synthesis Using Separation



Chirality can be introduced at any stage

Asymmetric Synthesis

Methods of chirality introduction:
- **Chiral Hydrogenation**
- **Enzymatic**
- **Plus lots more…**

Process Chemistry Preferences...
Chiral Synthesis

- Dislikes
  - Auxillary Chemistry
  - Late Stage Resolutions
  - Chromatography
- Likes
  - Purchase Chirality (59% measured by Carey *et al*)
  - Chiral Hydrogenations
  - Biotransformations
    - Dynamic Kinetic Resolution
  - Catalytic Reactions
    - Sharpless AD Reactions (Sharpless AE Reactions)
    - Jacobsen Epoxidiation and Aziridination
  - Early Stage Resolutions

Preferred Conditions

Generic Conditions
Where Would You Start?

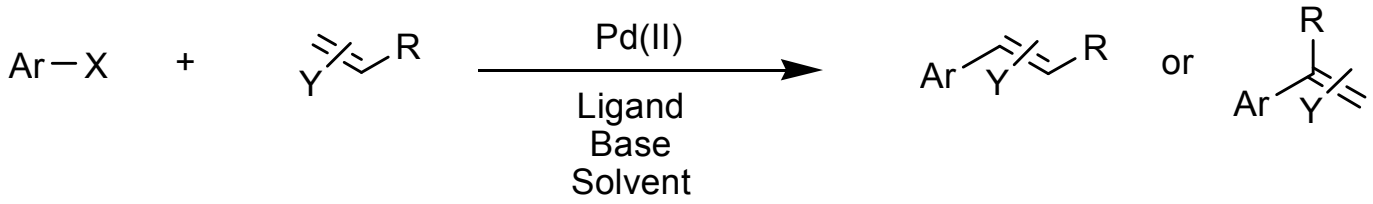
- When undertaking a ‘standard’ transformation on a new substrate, which set of conditions would you use?
  - Last set that you used
  - Latest set from the literature
  - One used on nearest substrate in SciFinder
  - A ‘old favourite’ set
  - One the person in the fumehood next door recommends

- What happens when it doesn’t work?
  - Is it due to the conditions?
  - Is it due to the substrate?

Generic Conditions

- Focussed piece of work looking to identify sets of conditions that:
  - Work reliably across a range of substrates
    - Allows a quick view as to viability of transformation
  - Provide ‘easy to use’ conditions
  - Use commercially available reagents

Generic Conditions
The Heck-Mizoroki Reaction



R. F. Heck, J. P. Nolley *J. Org. Chem.* 1972, *37*, 2320–2322;
T. Mizoroki, K. Mori, A. Ozaki *Bull. Chem. Soc. Jpn.* 1971, *44*, 581

Generic Conditions
The Heck-Mizoroki Reaction

- Catalyst Selection

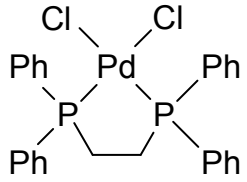
Pd/C

$Pd(PPh_3)_4$

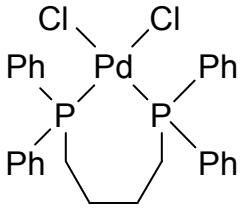
$PdCl_2(P[o\text{-}Tol_3])_2$

$Pd(OAc)_2$

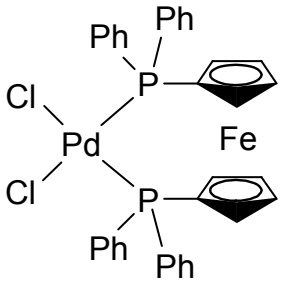
$Pd(^tBu_3P)_2$



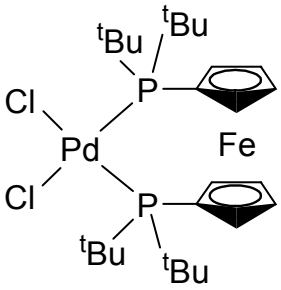
$Pd(dppe)Cl_2$



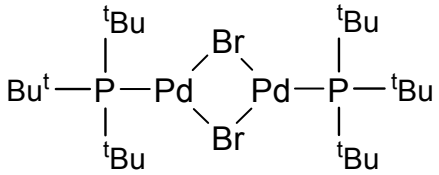
$Pd(dppb)Cl_2$



$Pd(dppf)Cl_2$



$Pd(dbpf)Cl_2$



$[Pd(^tBu_3P)Br]_2$

Generic Conditions
The Heck-Mizoroki Reaction

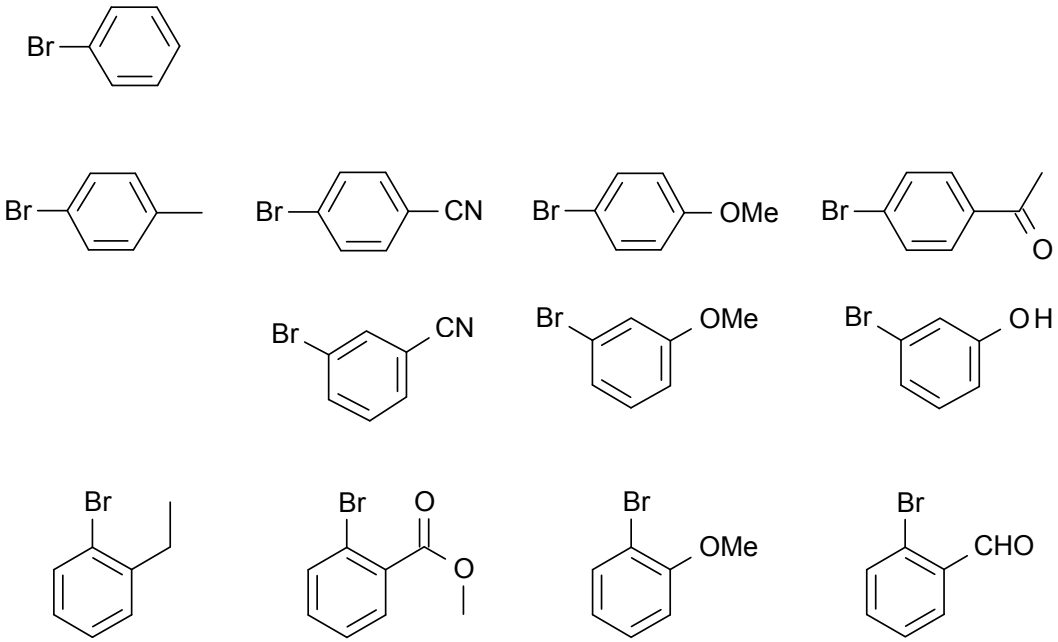
- Other Reaction Conditions
  - *Solvent* – Wide range of solvents possible, DMAC chosen in preference to DMF or dioxane
  - *Base* - Typically carbonate or tertiary amine, Cy_2NMe chosen for screen (exemplified by Buchwald[1] and Fu[2]) as it accelerates reductive elimination
  - *TBAC* - Added at 4 times Pd loading to increase catalyst activity

1. C. Gürtler, S. L. Buchwald *Chem. Eur. J.* 1999, *5*, 3107.
2. A. F. Littke, G. C. Fu *J. Am. Chem. Soc.* 2001, *123*, 6989.

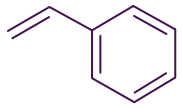
Generic Conditions
The Heck-Mizoroki Reaction

- Initial Substrate Scope

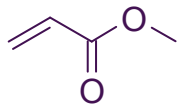
Aryl Bromide:



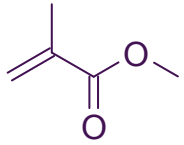
Alkene:



Styrene



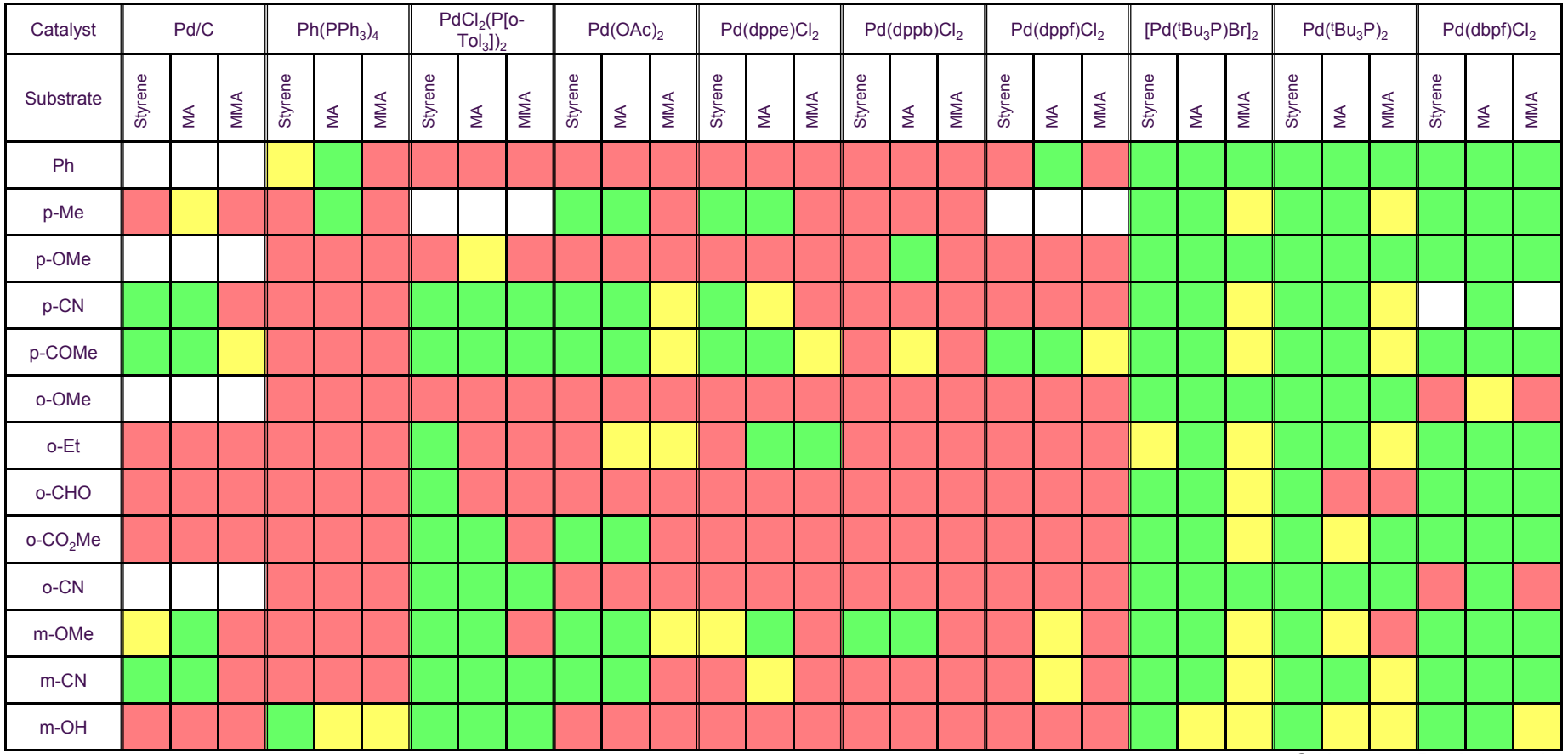
Methyl Acrylate (MA)



Methyl Methacrylate (MMA)

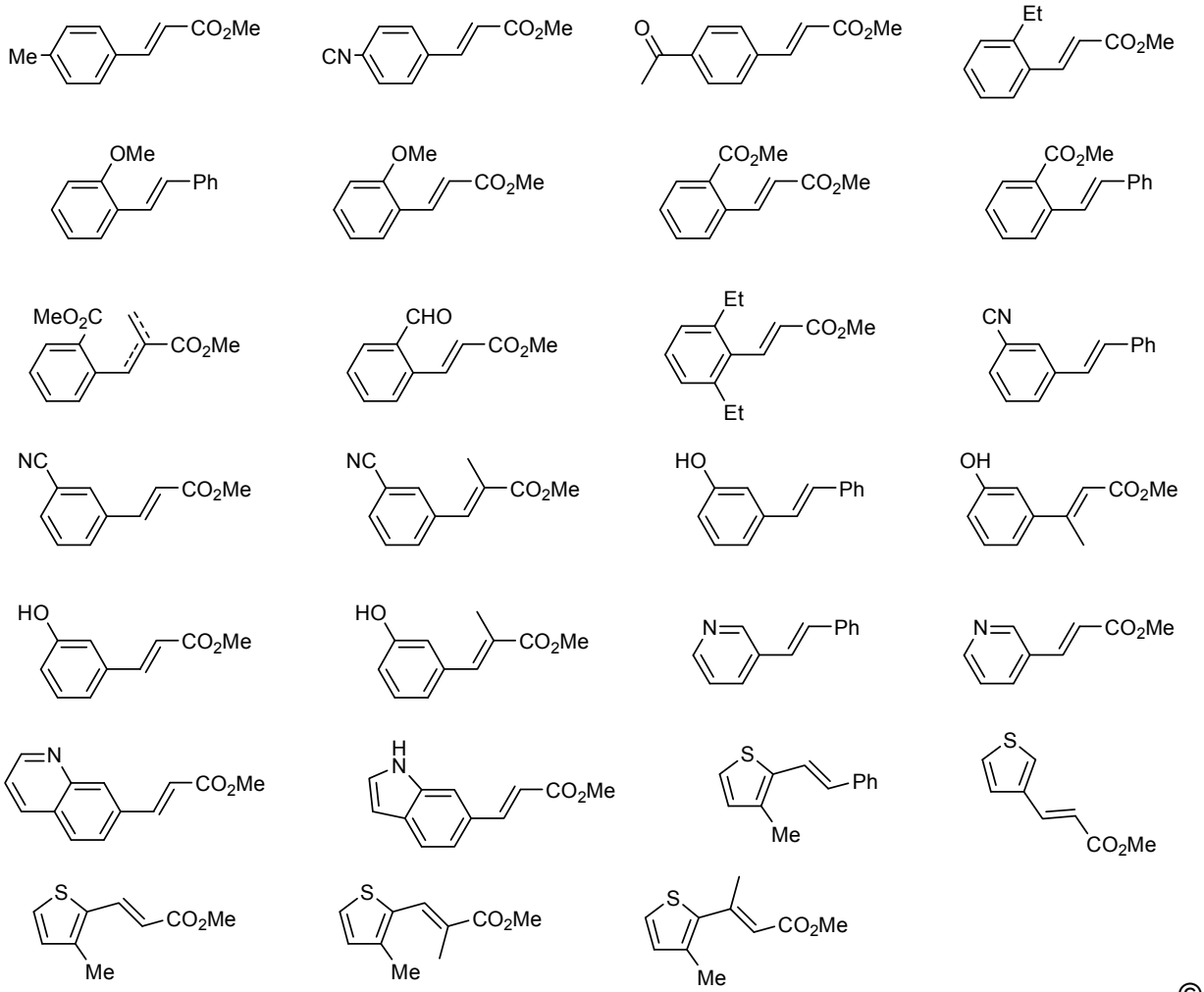
Generic Conditions
The Heck-Mizoroki Reaction

- Results



Generic Conditions
The Heck-Mizoroki Reaction

- Broader Substrate Scope



Generic Conditions
The Heck-Mizoroki Reaction

- Heck-Mizoroki Reaction
  - From the screening work completed, $Pd(dbpf)Cl_2$ was selected as the catalyst of first choice:
    - Catalyst is air stable
    - Works on majority of substrates investigated
    - 50-80°C
    - 10 relative volumes Dimethylacetamide
    - 1-5 mol% catalyst
    - 2-4 eq TBAC/TBAB relative to catalyst
  - For more challenging substrates $Pd(P^tBu_3)_2$ should be considered. This is an extremely active catalyst and is stable enough to weigh in air and use in chemistry. However, this catalyst must be stored under inert conditions

P. M. Murray, J. F. Bower, D. K. Cox, E. K Galbraith, J. S. Parker, J. B. Sweeney
Org. Process Res. Dev. 2013, *17*, 397-405

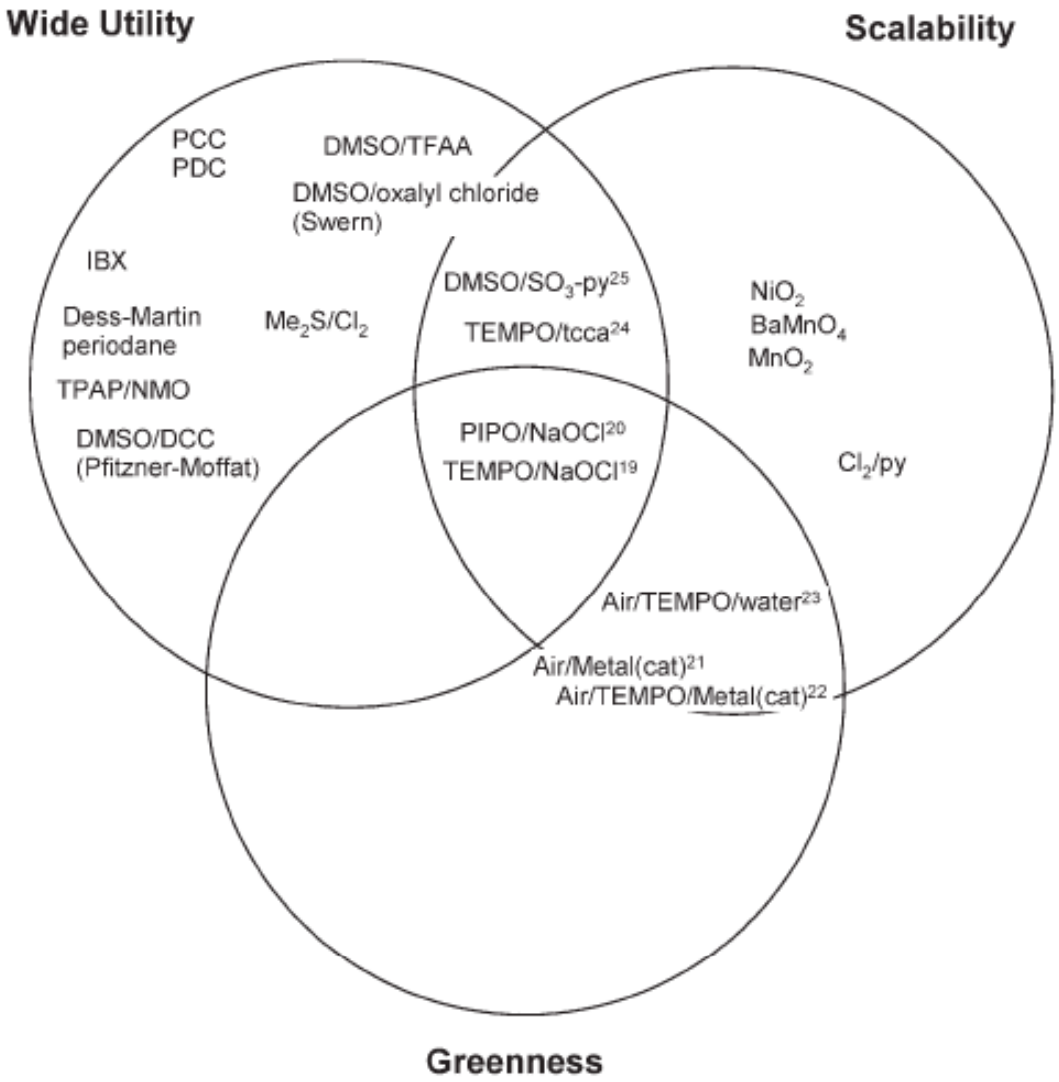
Generic Conditions
The Suzuki Reaction

- J. D. Moseley, P. M. Murray, E. R. Turp, S. N. G. Tyler, R. T. Burn
  Tetrahedron 2012, *68*, 6010-6017

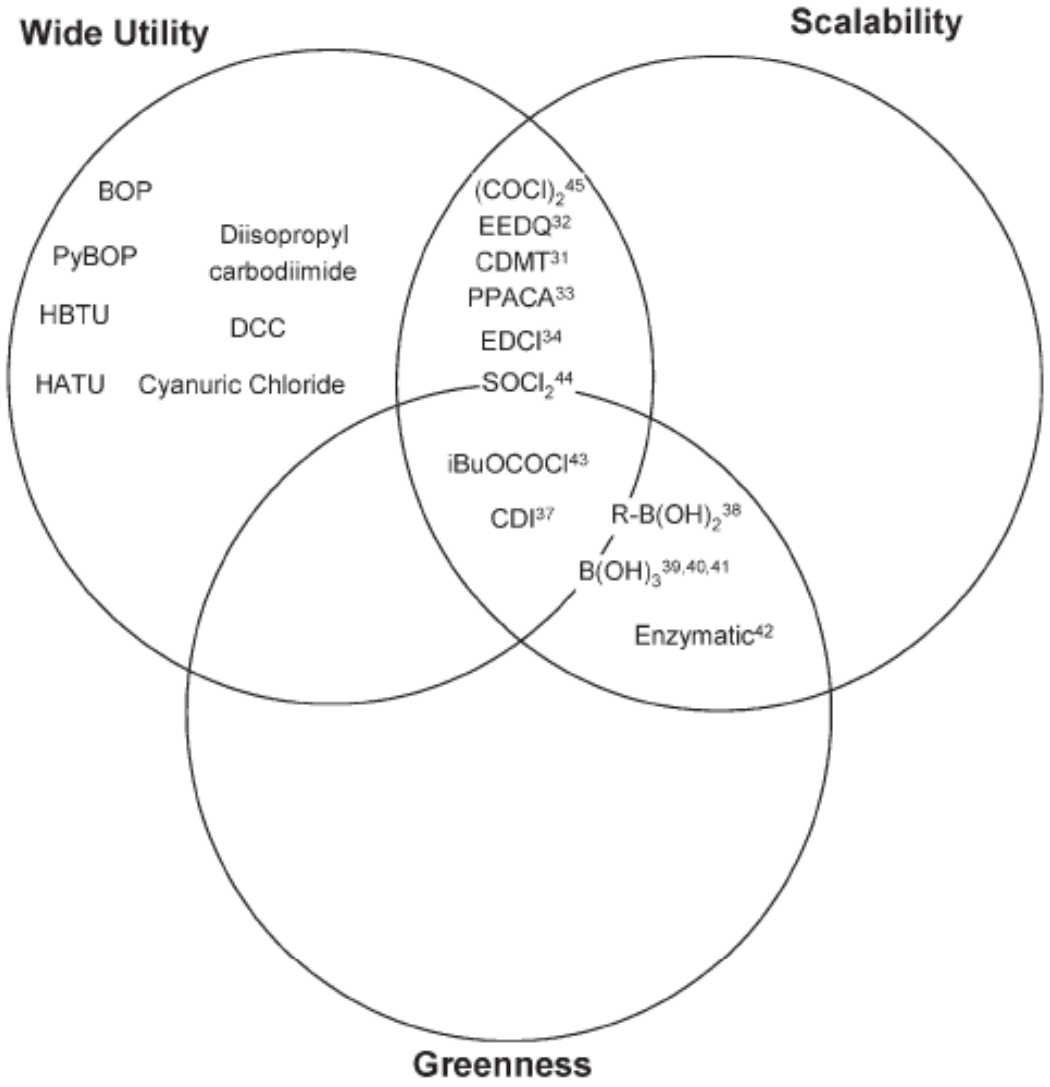
Reagent Guides

- Idea initiated by Pfizer but now being progressed by a Cross-Company Green Chemistry Network
  - *Green Chem.*, **2008**, *10*, 31-36

Reagents Guide
Oxidation of Alcohols to Aldehydes



Reagents Guide
Amide Formation from Acids and Amines



Process Design

Process Design
Unit Operations of a Process

Process Design
Equipment

Reaction → Quench → Solvent Swap? → Washes → Solvent Swap? → Crystallisation → Drying

Materials in
Solids/liquids/gas
Addition point (above surface/below surface/specific point)
Sampling points

The Batch Reactor - Reaction, Workup & Crystallisation all in one pot!

Process Design
Reaction

1. Addition of Solid Reagents
   - Avoids issues with solvent vapours
     - Solids can't be added to reactors containing solvents >50°C
   - Avoid issues with breaking reactor inerting
   - Assuming that solid is dissolved in a solvent prior to reaction this avoids issues around solid reagents dissolving/reaction on solid surfaces, etc

- If a solid does need to be added during the reaction it should be dissolved in a solvent and charged as a solution

- Reaction inerting will follow after solid addition
  - All large scale reactions are typically run inert for safety reasons

Process Design
Reaction - Solvents

2. Addition of Reaction Solvent
   - Aim to run reaction in <10 volumes of solvent
     - 1 volume = 1 ml of solvent per 1 g of starting material
     - Reducing the volumes as much as possible is always of benefit
   - Process solvents are not ‘dried’
     - Chemistry should be robust enough to run in standard solvents
     - Likely to be water introduction from solids and process equipment
     - Water content can be measured and contingency actions put in place
   - Some solvent retained for washing in reagents, etc

Solvents Selection

There is no such thing as a very good solvent, but there is also no such thing as a very bad solvent - simplistic view:

Water
Acetone
Ethanol
2-Propanol
1-Propanol
Heptane
Ethyl Acetate
Isopropyl acetate
Methanol
MEK
1-Butanol
t-Butanol

Cyclohexane
Toluene
Methylcyclohexane
TBME
Isooctane
Acetonitrile
2-MeTHF
THF
Xylenes
DMSO
NEP
Acetic Acid
Ethylene Glycol

Pentane
Hexane(s)
Diisopropyl ether
Diethyl ether
Dichloromethane
Dimethoxyethane
Chloroform
NMP
DMF
Pyridine
DMAc
Dioxane

Dichloroethane
Benzene
Carbon Tetrachloride

Solvents Selection

ICH (International Committee on Harmonisation) limits for solvents in Drug Substance:

Class 1	Limit (ppm)	Class 2	Limit (ppm)	Class 3
Benzene	2	Acetonitrile	410	Acetic Acid
Carbon Tetrachloride	4	Chlorobenzene	360	Acetone
1,2-Dichloroethane	5	Chloroform	60	Anisole
1,1-Dichloroethene	8	Cumene	70	1-Butanol
1,1,1-Trichloroethane	1500	Cyclohexane	3880	2-Butanol
		1,2-Dichloroethene	1870	Butyl Acetate
		Dichloromethane	600	tert-Butylmethyl Ether
		1,2-Dimethoxyethane	100	Dimethyl sulfoxide
		N,N-Dimethylacetamide	1090	Ethanol
		N,N-Dimethylformamide	880	Ethyl Acetate
		1,4-Dioxane	380	Ethyl Ether
		2-Ethoxyethanol	160	Ethyl Formate
		Ethyleneglycol	620	Formic Acid
		Formamide	220	Heptane
		Hexane	290	Isobutyl Acetate
		Methanol	3000	Isopropyl Acetate
		2-Methoxyethanol	50	Methyl Acetate
		Methylbutyl ketone	50	3-Methyl-1-butanol
		Methylcyclohexane	1180	Methylisobutyl Ketone
		N-Methylpyrrolidone	530	2-Methyl-1-propanol
		Nitromethane	50	Pentane
		Pyridine	200	1-Pentanol
		Sulfolane	160	2-Pentanol
		Tetrahydrofuran	720	2-Propanol
		Tetralin	100	Propyl Acetate
		Toluene	890	
		1,1,2-Trichloroethane	80	
		Xylene	2170	

Solvents
Process Solvents

- Alcohols
  - Mostly very good solvents
  - Higher alcohols can be partitioned with water
  - Glymes often good as high boiling but water soluble
- Ethers
  - Acyclic
    - Peroxidisable ethers (Et_2O, iPr_2O) typically avoided
    - MTBE usual replacement
  - Cyclic
    - THF considered to be a good solvent
    - THF can be partitioned with aqueous phases containing <2M NaCl
    - 2-Methyl THF preferred due to better partitioning and azeodrying
    - Cyclopentyl Methyl Ether is a new addition to range

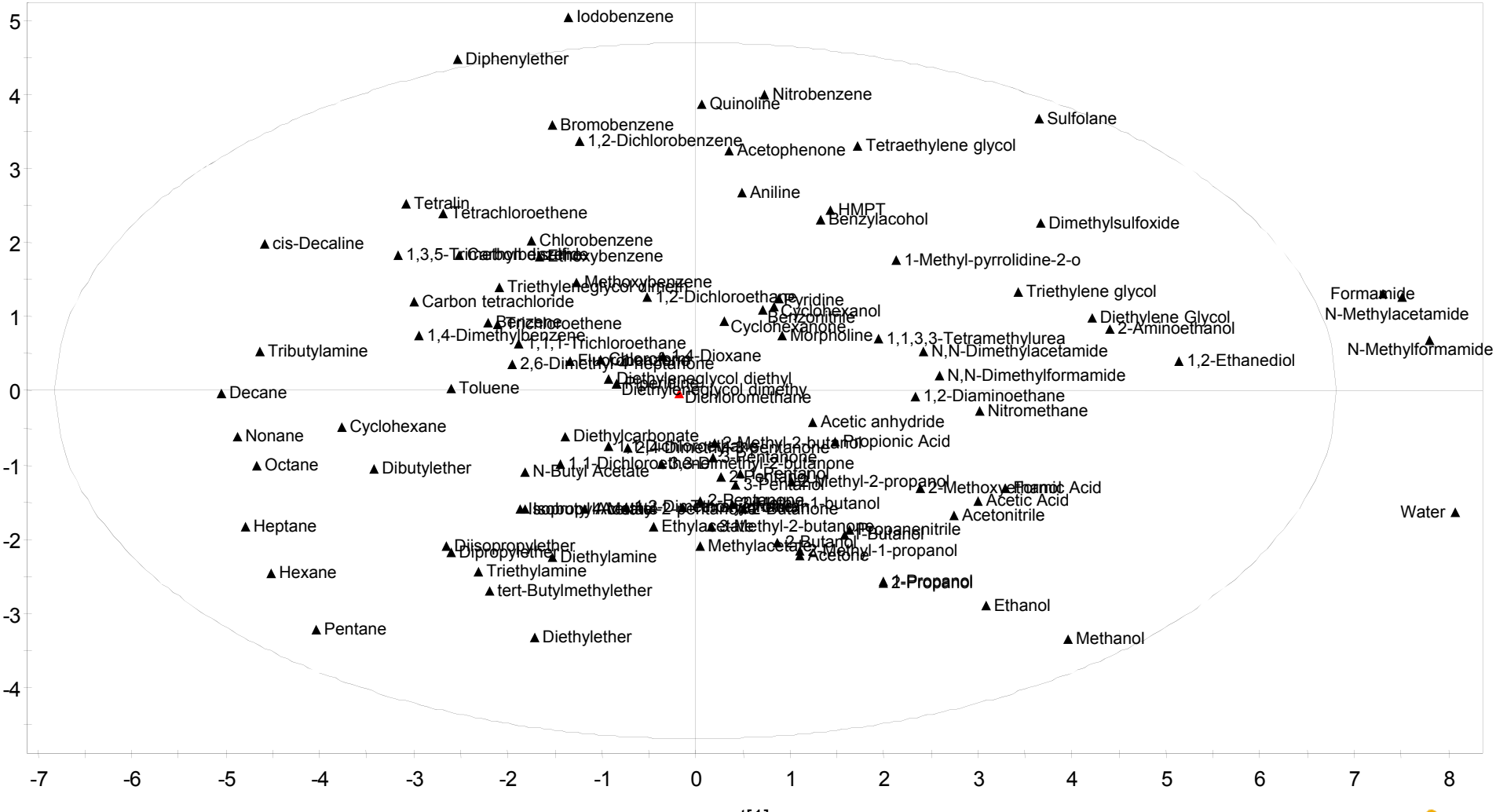
Solvents
Process Solvents

- Hydrocarbons
  - Hexane and Pentane should be avoided
  - Isohexane is better, but n-heptane is currently best option
  - Toluene
    - Class 2 solvent
    - Remains aromatic hydrocarbon of choice (excellent azeodrying)
- Esters
  - EtOAc obvious choice
    - Some water solubility
    - Significant saponification when using high or low pH washes
  - iPrOAc (IPAC) or nBuOAc preferred Process choice
    - Lower water solubility and better azeodrying
    - But higher boiling point

Solvents
Process Solvents

- Polar Aprotics (DMF, NMP, (NEP), DMAc, DMSO, MeCN)
  - Excellent solvents in terms of solubility
  - Benefit from ability to wash out in aqueous layer during work up
  - Toxicity remains a problems (DMF, NMP and DMAc)
    - NMP currently considered to be the best of these
    - Always think about DMSO (TH1) if possible
    - MeCN is a very good and versatile solvent
- Chlorinated
  - Toxicity and ecotoxicity are a major problem
    - DCE and Chloroform should be avoided
  - DCM remains the favoured solvent
    - Chlorobenzene or Dichlorobenzene are possibilities

Solvents
Principal Component Analysis

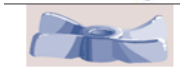
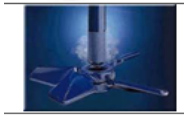


Process Design
Reaction

3. Dissolve Solid Reagents
   - In an ideal world the reaction is totally homogeneous
   - Often there will be undissolved reactants or reagents
     - Products or byproducts can precipitate out during reaction
   - Stirring is critical on heterogeneous reactions

Process Design
Equipment - Stirrers

Reaction → Quench → Solvent Swap? → Washes → Solvent Swap? → Crystallisation → Drying

	Tickler (or kicker) Impeller with close clearance to vessel bottom
	Anchor (ANC) 2-bladed tangential flow impeller
	Retreat curve impeller (RCI) 3-bladed radial flow impeller
	Curved blade turbine (CBT) 4-bladed radial flow impeller
	4-bladed pitched blade turbine (4PBT) Mixed flow impeller
	3-bladed pitched blade turbine (3PBT) Mixed flow impeller
	Hydrofoil (HYD) 3-bladed axial flow impeller, e.g. A310
	Turbofoil (TBF) 4-bladed glass-lined axial flow impeller
	4-bladed flat blade turbine (4FBT)
	6-bladed flat blade turbine (6FBT)

	Rushton disc turbine (RDT) 6-bladed radial flow impeller
	Ekato Intermig (IMG) Mixed flow agitator always used in pairs
	6-bladed pitched blade turbine pumping up (6PBT up)
	6-bladed pitched blade turbine pumping down (6PBT down)
	Chemineer CD-6 6-bladed gas dispersion impeller
	Chemineer Maxflo Y 4-bladed high solidity ratio impeller
	Chemineer HE-3 3-bladed axial flow impeller
	Chemineer BT-6 6-bladed gas dispersion impeller

Process Design
Equipment - Stirrers

- How the reactor is designed is a critical part of the efficiency of the mixing
  - Presence of thermocouples, addition lines, etc will affect the mixing
  - Baffles can be added to increase mixing effects
  - Recirculation loops provide significant additional mixing
  - Identifying hold-up points in the reactor can be important if solids collect/hold-up there

[Video Clips]

Process Design
Reaction

4. Adjust temperature
   - On the plant heating or cooling can take a number of hours
     - Needs to be considered as part of the process design
       - Does this time affect the contents of the reactor?
   - Careful monitoring of the temperatures (internal, external, HTF) is important during the reaction stage
     - Will identify exothermic events

Process Design
Reaction

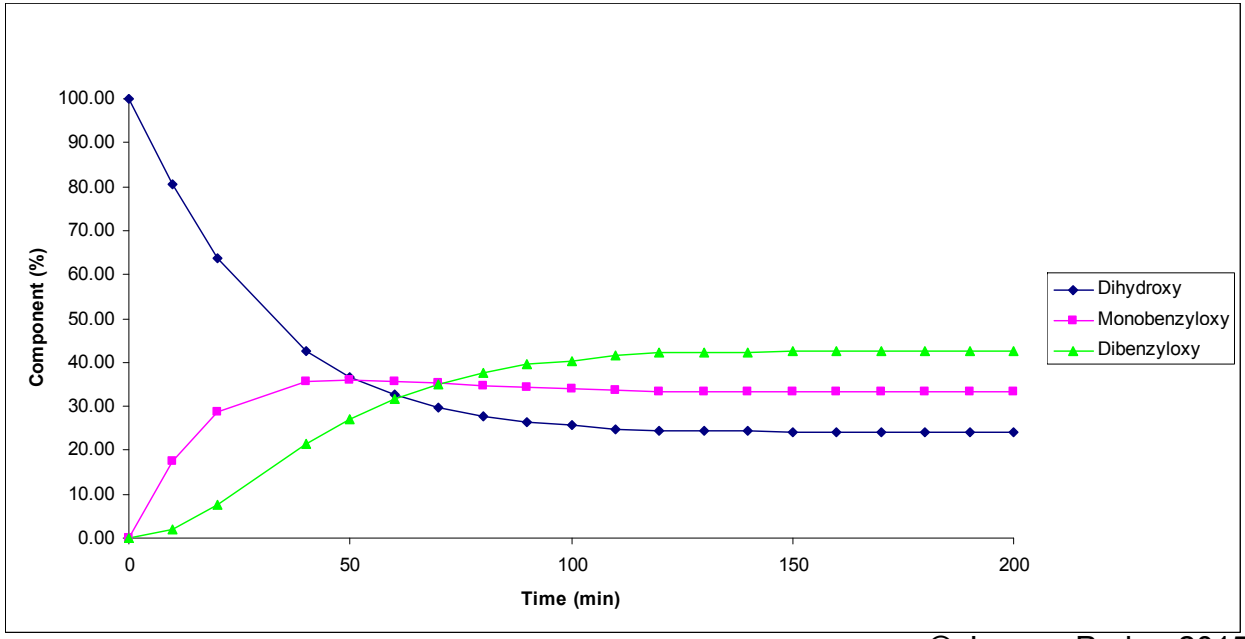
5. Add Liquid Reactants
   - Addition of liquid reagents/solutions should always be controlled
     - Typical basis of safety for Reaction Hazards
     - Syringe pump/dosing pump/etc
     - Check for exotherms during the addition of the first 10-20%

Process Design
Reaction

6. Run Reaction!
   - Investigate running reaction at *ca* 5ºC below reflux temperature
     - Uses about 20% of the energy required to run at reflux without making a major change to reaction rate
   - Reaction monitoring is extremely beneficial to understand profile
     - Remember to take a sample at t = 0
     - Use of internal standards can help ensure sampling consistency

Process Design
Reaction Profiling

- Reaction profiling is a critical technique for understanding your reaction
  - Kinetic Data
  - Formation of Intermediates and Impurities
- Number of ways of gathering data:
  - Sample reaction and analyse (HPLC, GC, etc)
  - PAT (Process Analytical Technology)



PAT
Drivers for Using PAT in Development

- Increase process understanding
  - Use information to help develop robust processes and using the knowledge to define design space
- Increase processing efficiency
- Shorten lead times
- Range analytical techniques can be used
  - PAT can be in/on/at/off-line

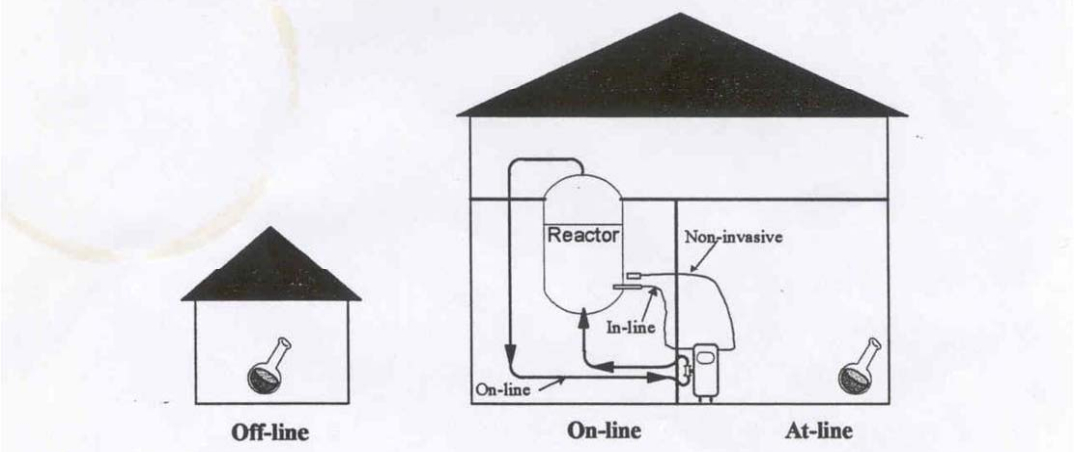
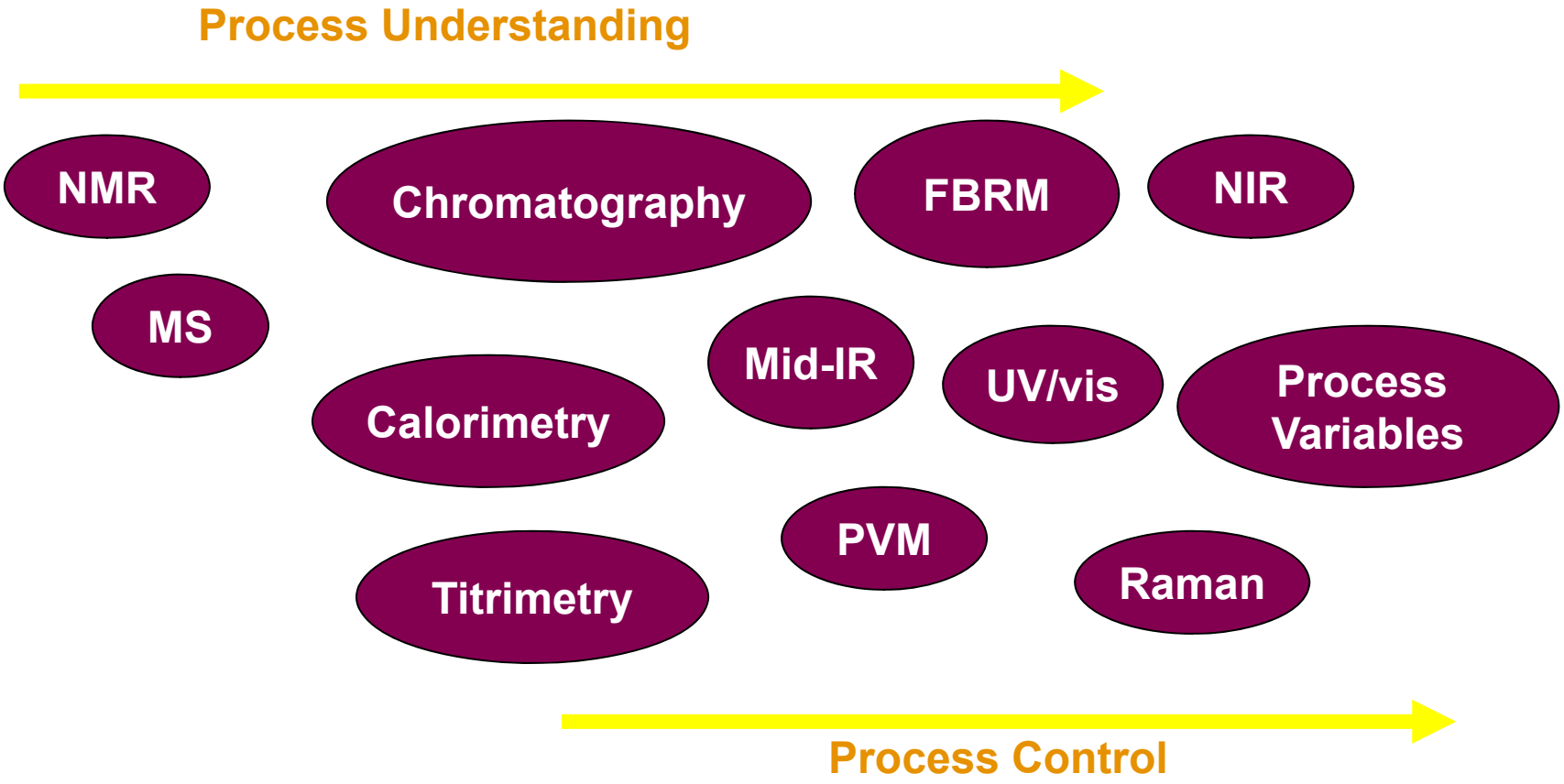


Figure 1 Process Analysis as defined by Callis

PAT
Benefits of Using In-Line Analysis

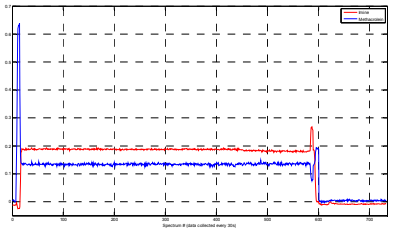
- Real-time data
  - Facilitate process understanding / product quality
  - Increase processing efficiency
  - Process optimisation on scale-up / troubleshooting
  - Opportunity for process control / real-time release
  - Monitoring continuous processes
- Sampling
  - Increased reproducibility
  - Minimise exposure to hazardous reagents
- Suited for process monitoring of:-
  - Heterogeneous reactions
  - Air/moisture sensitive reactions e.g. lithiation reactions
  - Cryogenic reactions
  - Pressure reactions e.g. hydrogenations
  - Vacuum distillations

PAT
Process Analytical Technologies



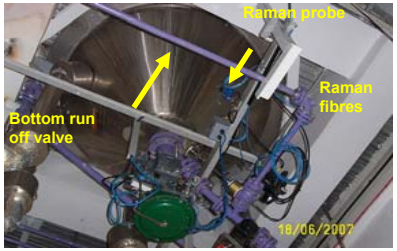
FBRM – Focussed Beam Reflectance Measurement
PVM – Particle Vision and Measurement

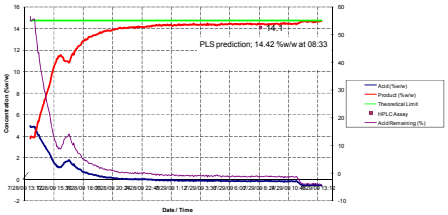
PAT Applications



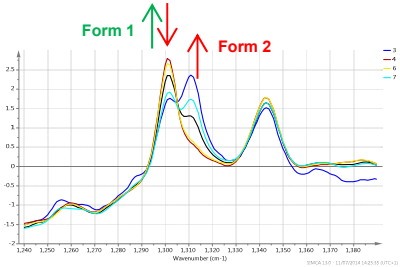
Continuous Process

How much?





Which polymorph?



Steady State

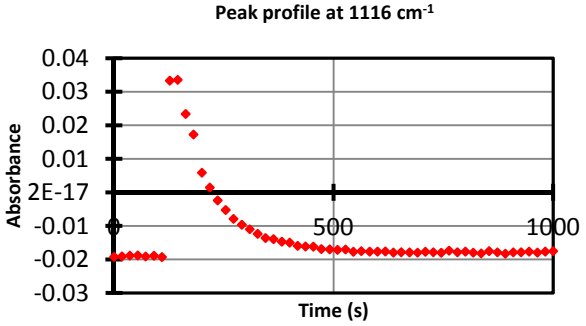
Heterogeneous

Quantitative

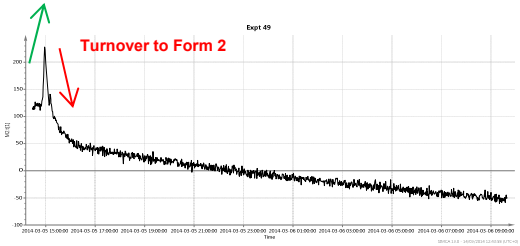
PAT

Rapid Kinetics

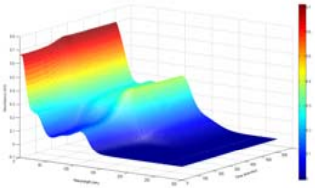
How Fast?

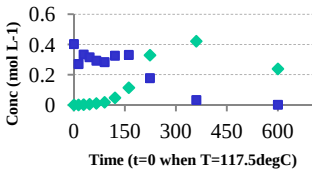


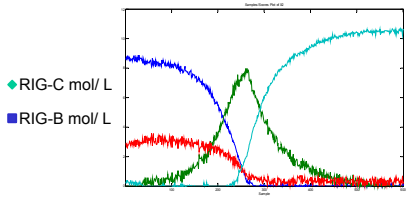
Form 1 nucleating



Reactive Intermediates

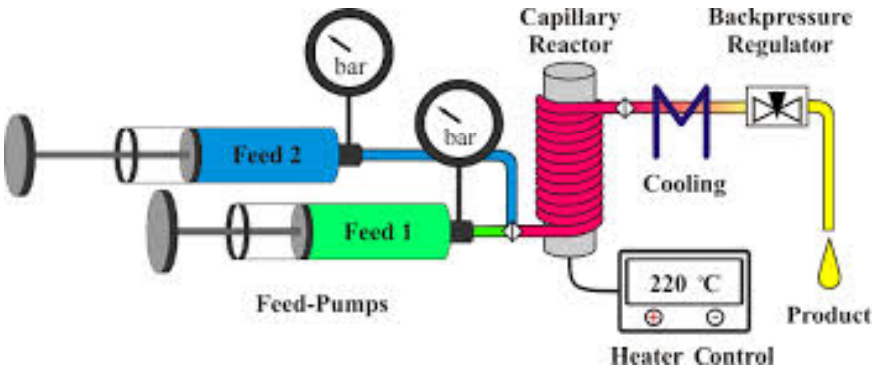






What can't I see?

Process Design
Flow Chemistry



- Flow Chemistry is becoming an important technique in Process Chemistry:

- Increased Chemistry Space (Safety)
  - Difficult/dangerous reagents
  - Extremes of temperature
  - Exotherms

- Improved Control
  - Poorly selective reactions
  - Unstable intermediates/reactants/products

- Economics
  - Make what you need
  - Switch off tap if there are problems
  - Scale up/out – reduce difficulties with increased demands.

- Environment
  - Use low boiling solvents – easier to recycle
  - Simpler processes (less complex reagents) – easier workups/less waste to dispose of

Flow Chemistry Equipment

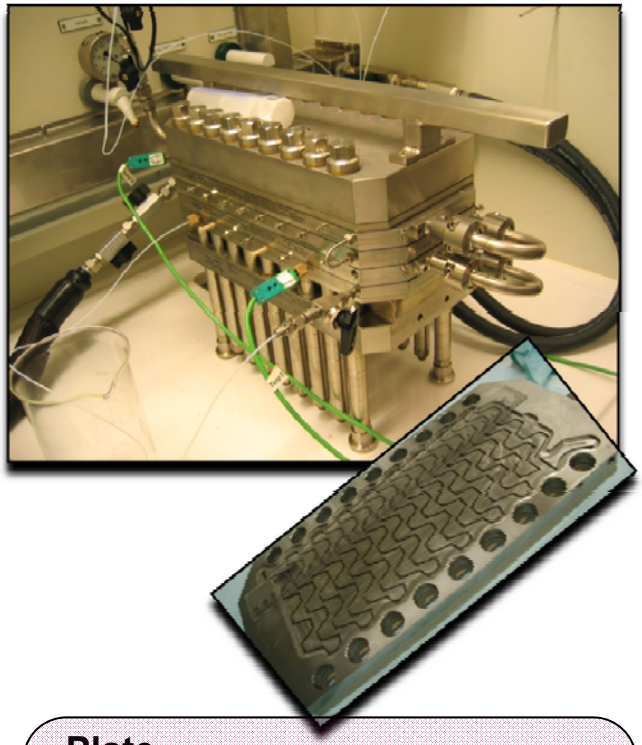
Future Chemistry

- Glass chip
- Flow 0.012 ul/min – 0.58ml/min
- Temp -5°C – 200°C
- Microchip – 100ul
- Syringe pump

Uniqsis

- Coil
- Flow 0.1 ml/min – 10ml/min
- Temp -35°C – 250°C
- Reaction vols 1ml to ~20ml
- Knauer dual piston pumps

Alfa Laval



- Plate
- Flow 0.1 ml/min – 50ml/min
- Temp -35°C – 200°C
- Reaction vols 3.5ml to ~34.6ml
- Knauer dual piston pumps

Process Design
Quench

- Reaction Quenching
  - Reacts with any reactive species
    - Understanding again required as to what new species will form and the reactivity of these
  - Often water or aqueous systems
    - pH buffered systems often used
  - 'Reverse Drown-Out' can be used
    - Controlled addition of reaction solution to a separate process stream
    - Typically water, as this is a good heat sink (if the quench is exothermic)

Process Design
Work-Up Solvent

- Work-Up Solvents
  - Changing from one solvent to another is a key part of Process Design
    - Often the solvent used for the reaction stage is not suitable for the work-up
    - More than one solvent swap might be required, thus a key activity is finding an effective set of solvents that result in the least number of solvent swaps
  - The easiest process is to add a high boiling solvent and distil out the low boiling solvent
    - Normally time consuming
    - There must be a reasonable separation in boiling points
  - Swapping from a higher to a low boiling solvent is not ideal
    - Typically materials are ‘evaporated to dryness’
    - This can only be done on a small scale (50 litres)
    - Issues with isolating dry materials which can be explosive

Process Design
Work-Up Solvent

- Solvent for washes needs to be immiscible with water
- Preferred work-up solvents
  - nPrOAc
    - Improved partitioning with water
    - EtOAc has a 8.7% solubility in water vs 0.7% for nPrOAc
  - MTBE
    - Eliminates peroxide risk of diethyl ether
  - 2-Methyl THF
    - Good partitioning with water compared to THF
  - Toluene
    - Noting that this is Class 2
  - Higher Alcohols and Higher Ketones

Process Design
Washes

- Washes
  - Washes are used for removing unwanted reagents and by-products
    - Materials need to be in a water immiscible solvent (ie forming two phases)
  - Specific washes for specific purposes…
    - Acidic washes (hydrochloric acid or citric acid) to remove basic species
    - Basic washes (sodium hydroxide or sodium hydrogen carbonate) to remove acidic species
    - Water washes to remove inorganic species
    - Brine (sodium chloride) washes to remove water
    - Other washes for specific purposes (oxidative washes, reductive washes, etc)
  - More complicated work-ups involve making salts of the desired product which are water soluble
    - Product transfers to aqueous phase
    - Impurities/reagents/by-products remain in the solvent
    - Conversion of salt back to neutral form (‘salt break’) allows product to be extracted back into new solvent (alternative to a solvent swap)
  - The target is to produce a clean solution of desired product in a solvent
    - Final solvent swap may be required before the final part of the work-up

Process Design
Washes

- Washes
  - Important to think about the purpose and effectiveness of each wash:
    - Are the correct number of equivalents of any reagent present?
    - Will extremes of pH cause sides reactions/degradation?
    - How much product is lost of washes?
      - Are losses acceptable if it produces a clean solution of the final product?
      - Analysis of relative amounts of material in the different phases is key

Process Design
Process Washes

- Process Washes
  - Ideal wash volumes are <10vol
  - Saturated NaCl (6.2M), Na_2SO_4, etc
    - Can't be made up on scale
    - Typically use 5M NaCl on scale which can be reliably prepared and handled
  - Acid and Base solutions
    - Typically use purchased solutions at 1M, 2M and 5M
    - Less of more concentrated is best
  - $NaHCO_3$ and Na_2CO_3 solutions
    - Typically avoided due to off-gassing issues
    - Neutralization to pH 7 preferred
  - Increasing density of washes tends to help improve separations
    - For example, 2M HCl/2M NaCl solution often used

Process Design
Process Washes – Equipment

Process:

- Add Washes to Vessel
- Agitate contents
  - Check Lab vs Plant performance
- Allow phases to settle
  - Critical to optimise in the lab
    - >10 minutes in the lab can be >1 day on the plant
    - Dispersion of phases can be critical

  [Video Clip]
    - Change density of phases to improve
- Run off lower aqueous phase

Process Design
Process Washes – Chlorinated Solvents

Reaction → Quench → Solvent Swap? → **Washes** → Solvent Swap? → Crystallisation → Drying

- Chlorinated solvents typically have a higher density than the aqueous phase
  - Process:
    - Remove organic phase
    - Remove aqueous phase
    - Recharge organic phase
  - Typically avoided due to time required
- Chlorinated solvents often have similar densities to aqueous washes leading to poor phase separations
  - DCM 1.40g/cm^3
  - Saturated brine 1.30g/cm^3

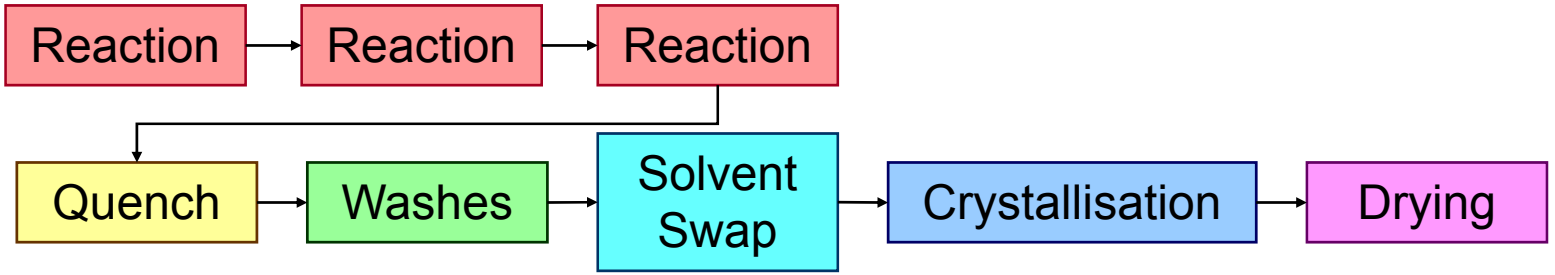
Process Design
Work-Up Solvent

- Further Solvent Swaps
  - Often required for during the overall work-up process
    - Ideal circumstance would be to use solvents in ascending boiling point...

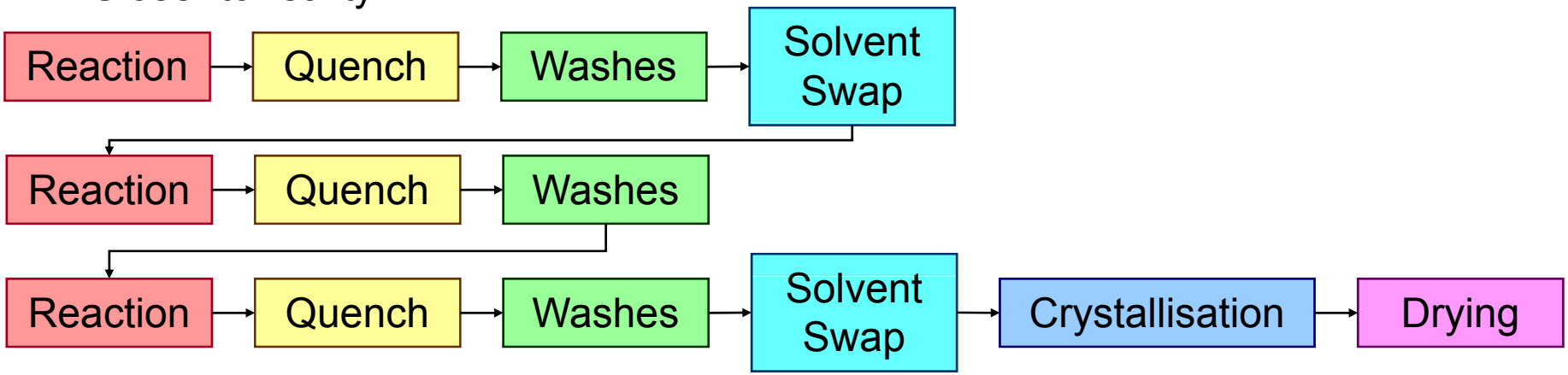
- Drying and Evaporation
  - Drying
    - $MgSO_4$ and Na_2SO_4 really can't be used on scale
    - Azeodrying of solutions often used (toluene, cyclohexane, ethanol, butyronitrile,…)
  - Evaporation
    - Solutions can't be evaporated to dryness on scale (>50L)
    - Hazard issues as well as getting material out of vessel
    - If no isolation required then material is typically 'solvent swapped' into next reaction solvent (telescoping)

Process Design
Telescopes

- Telescopes
  - Ideal world:



  - Closer to reality:



  - Extensively used when products are oils rather than solids

Process Design
Isolation

- Crystallisation is key technique in Process Chemistry
- There are however some other options...
  - Distillation
    - Always worth considering if boiling point low enough
  - Precipitation
    - Effective way of isolating solid from a solution without having to develop a crystallisation
      - Reduce solvent to a low volume
      - Slowly add miscible anti-solvent with good stirring
      - No significant control over particle size/formation
        - Filtration can be challenging
  - Triturations
    - Not practical on a large scale
    - Nearest equivalent is to slurry solid in solvent and isolate by filtration (slurry wash)
  - Chromatography
    - Only really viable on a small scale (kgs) due to high cost

Process Design
Crystallisation

- Key Benefits of Crystallisation
  - Acts a purification point for the synthesis
  - Allows analytical check of purity
  - Separates product from solvent/allows isolation of a solid
  - Allows control of particle size

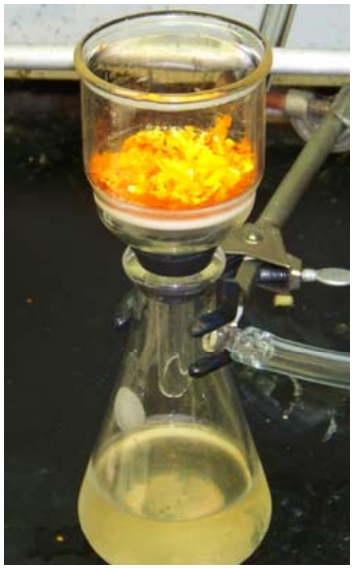
- Types of Crystallisation
  - Cooling Crystallisation
    - Crystals form as solubility changes with temperature
  - Evaporative Crystallisation
    - Crystals form as solvent concentration changes
      - Solvent composition can also change if more that one solvent is present
        - Close to a precipitation
  - Reactive Crystallisation
    - Crystals form as chemical composition changes
      - Includes changing pH to change species

Process Design
Crystallisation

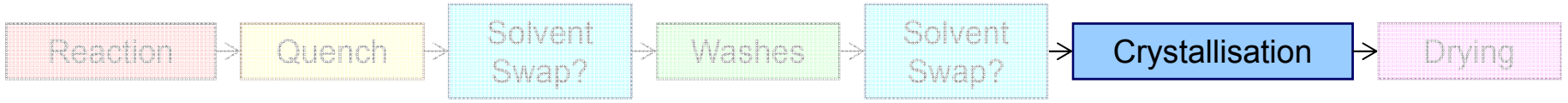
- Practical Approach
  - Determine approximate solubility of material in a range of solvents
    - Ambient temperature
    - Elevated temperature (70°C or 80°C)
  - Use solvents where solubility is low at low temperature and high at high temperature
    - Dissolve material in minimum amount of hot solvent
    - Cool (ideally in a controlled manner) to ambient temperature
    - Add a small amount of product (seed) at 10°C below high temperature
  - If this is unsuccessful then try solvent mixtures (anti-solvent crystallisation)
    - Dissolve material in minimum amount of a hot solubilising solvent
    - Add controlled amount of non-solubilising solvent (anti-solvent)
    - Cool (ideally in a controlled manner) to ambient temperature
    - Add a small amount of product (seed) at 10°C below high temperature

Process Design
Crystallisation

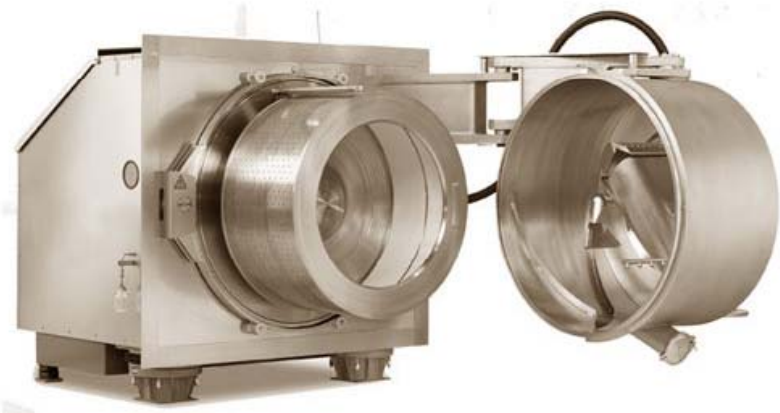
- Filtration
  - Size and properties of crystals will determine filtration properties
    - Large crystals will filter and deliquor rapidly
    - Small crystals and needles will filter and deliquor slowly
  - Washes are then applied to the filter cake
    - Wash out impurities
    - Remove water
    - Change final solvent present in solid



Process Design
Crystallisation - Equipment



Pressure Filter



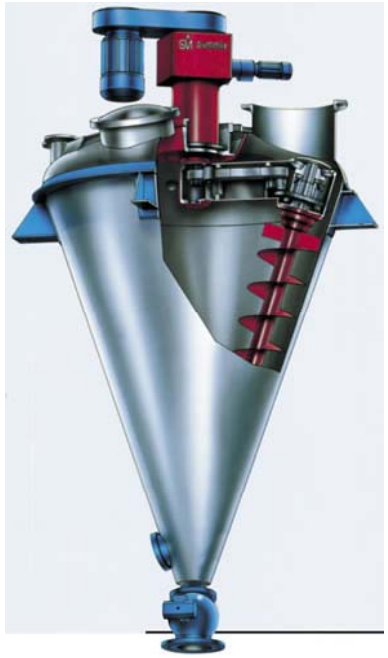
Centrifuge

Process Design
Drying

- The isolated product is normally dried
  - Removes any remaining solvent
  - Removes any remaining water
- Drying achieved by a combination of:
  - Heat
  - Inert Gas (nitrogen) Flow
  - Vacuum
  - Agitation

Process Design
Drying - Equipment

Tray Dryer



Cone Dryer

Double Cone Dryer

Process Chemistry
Process Optimisation

Jeremy Parker, Principal Scientist
Chemical Development, Pharmaceutical Development
AstraZeneca
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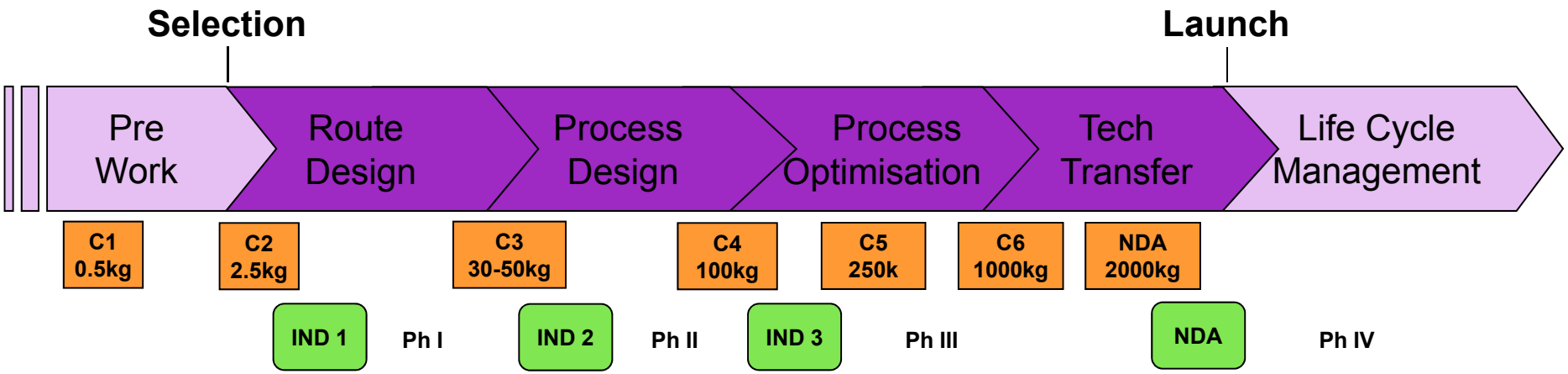
Process Development Overview



Process Optimisation
Definition

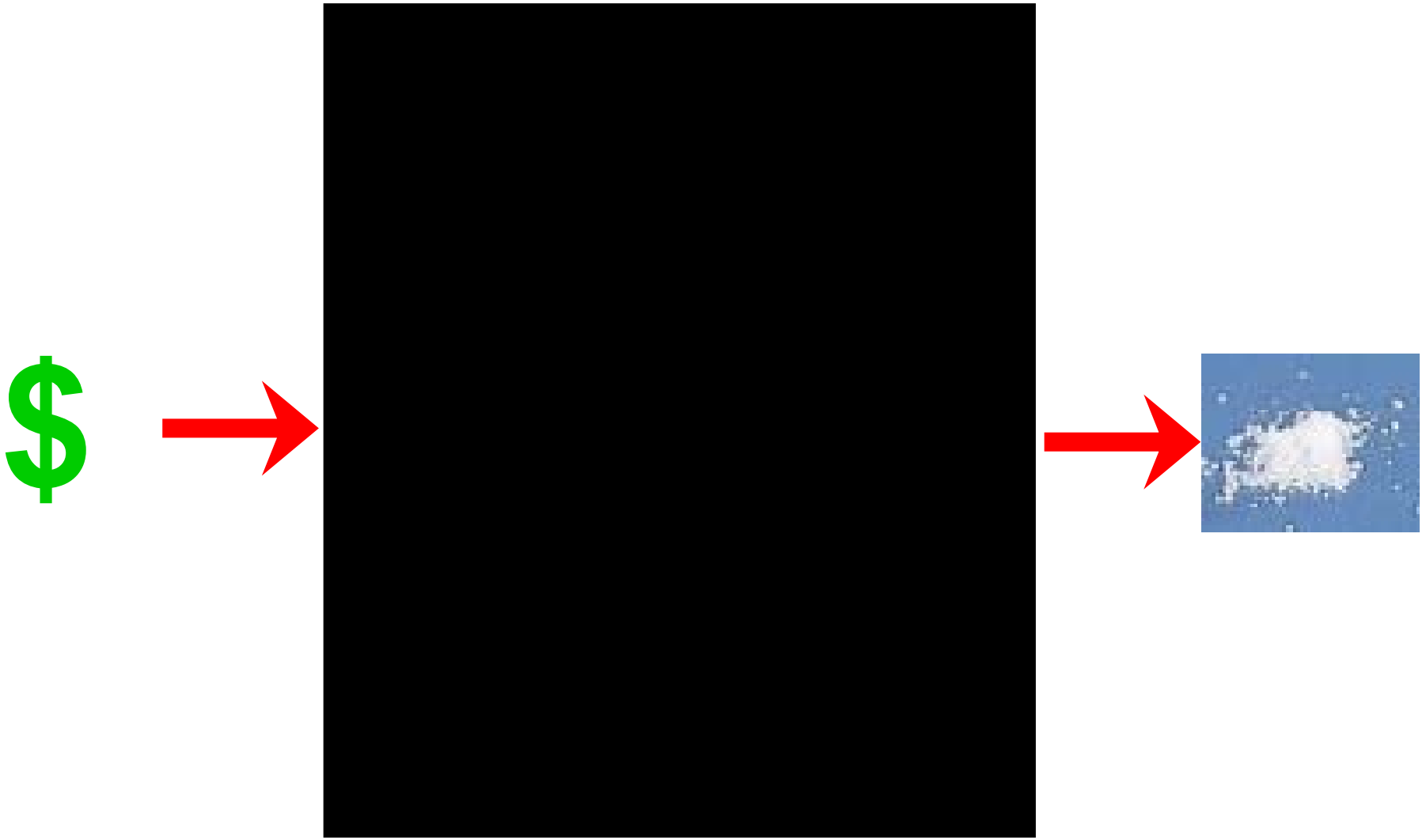
- **Process optimization** is the discipline of adjusting a process so as to optimize some specified set of parameters without violating some constraint. The most common goals are minimizing cost, maximizing throughput, and/or efficiency.

Process Optimisation
Activities

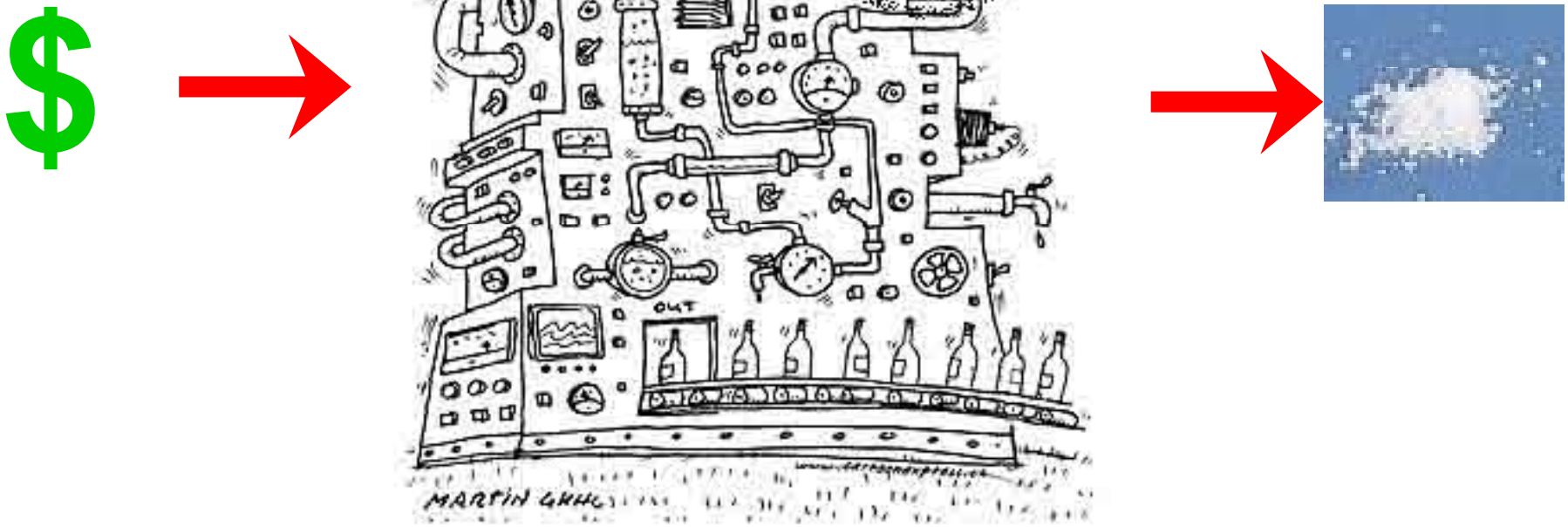
- Refine reagents
  - Reagents
  - Solvents
  - Additives
  - Catalysts
- Improved Reaction Understanding
  - Mechanism
  - Impurity profile
  - Improving control
- Define Parameters
  - Set points for reagents/solvents charges
  - Set points for other parameters (temp, addition times)
  - Set points for work up
  - Set points for isolation
  - Set points for drying

Process Understanding

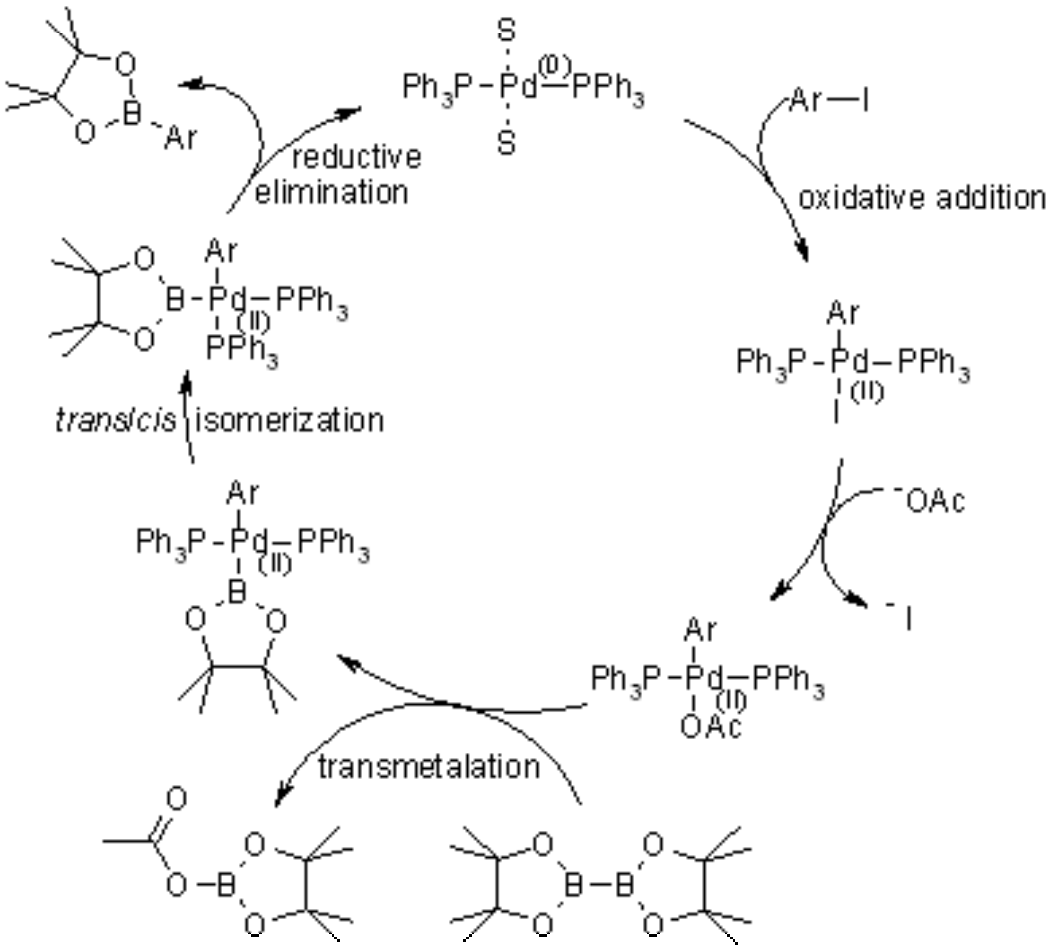
Process Understanding



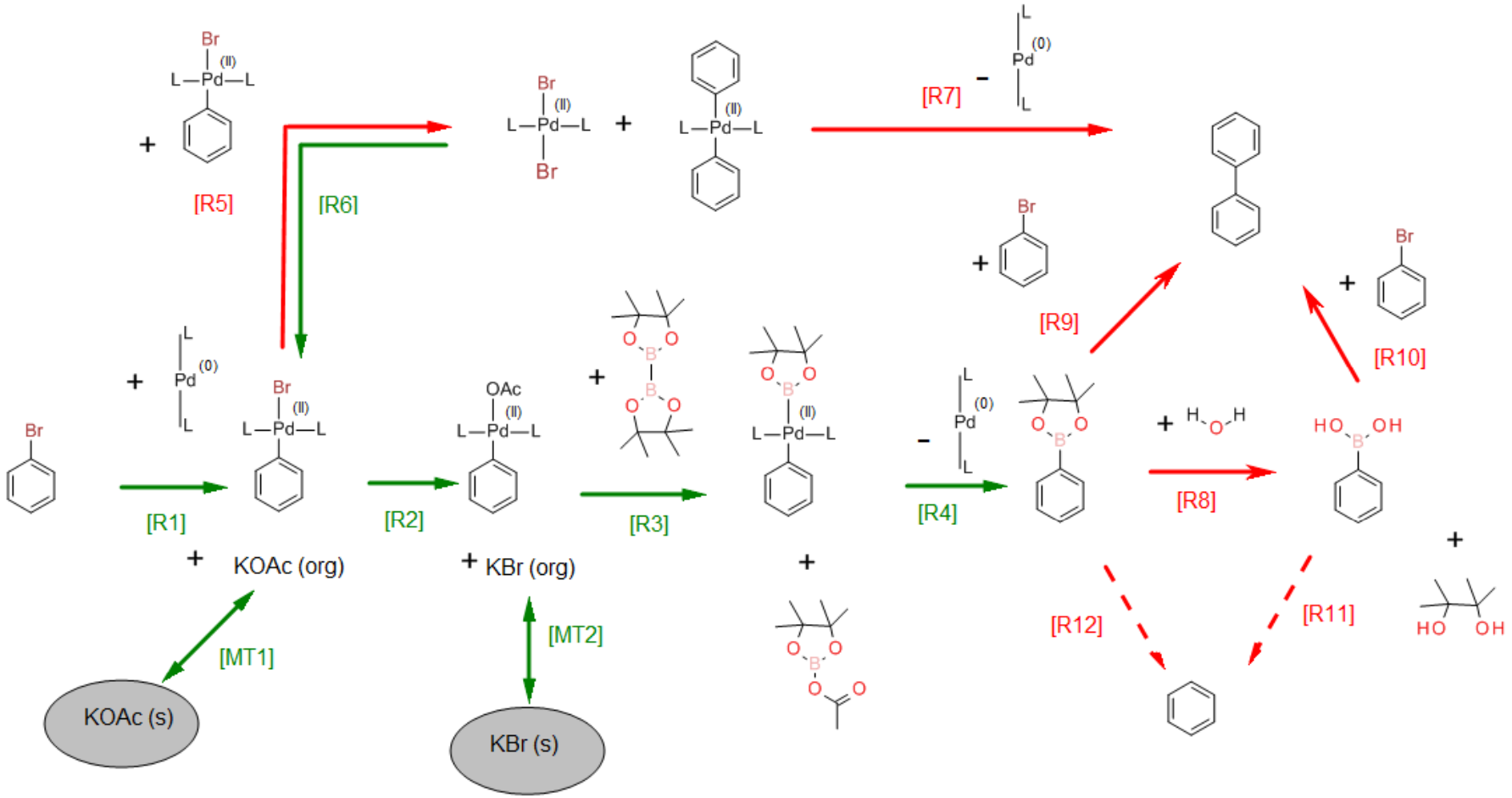
Process Understanding



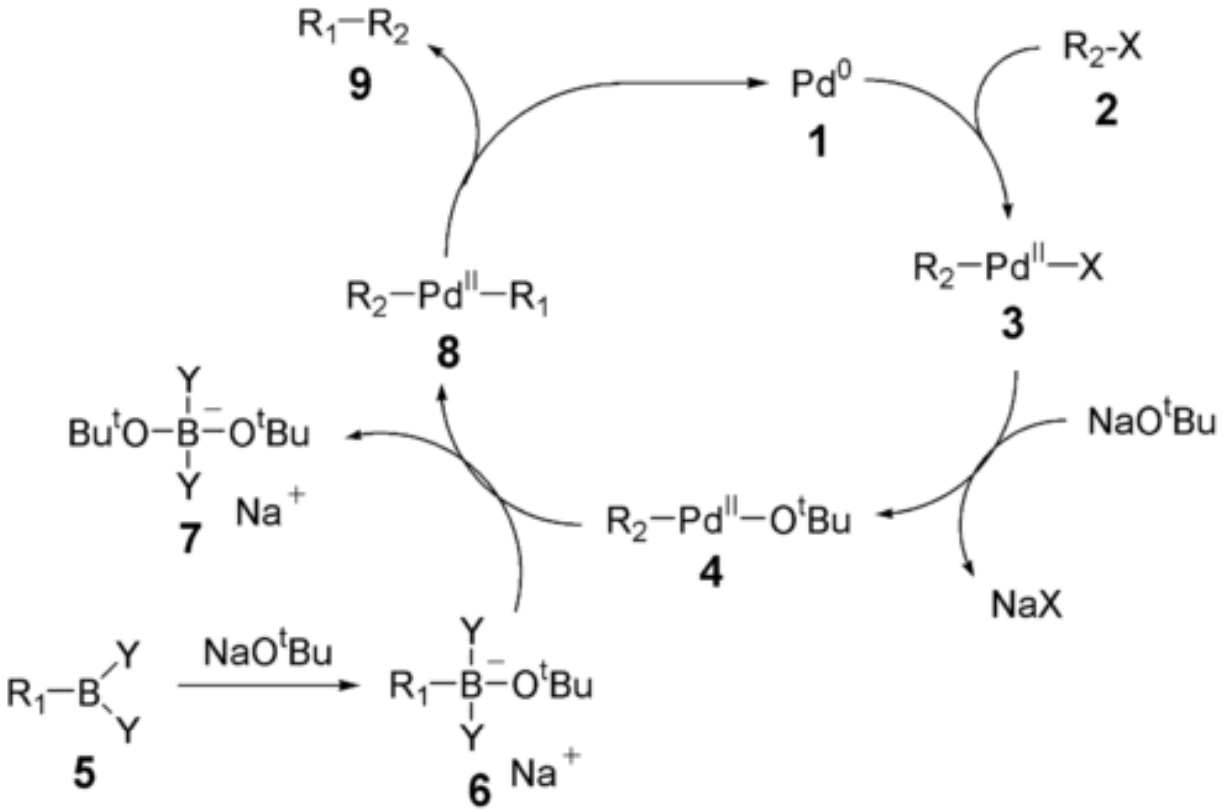
Understanding Reactions
Miyuara Borylation Catalytic Cycle



Understanding Reactions
Miyuara Borylation Transformations



Understanding Reactions
Suzuki Coupling Catalytic Cycle



Most cases now do not use NaOtBu, aq base e.g. K_2CO_3 is sufficient

Understanding Reactions
Suzuki Coupling Competing Oxidative Processes

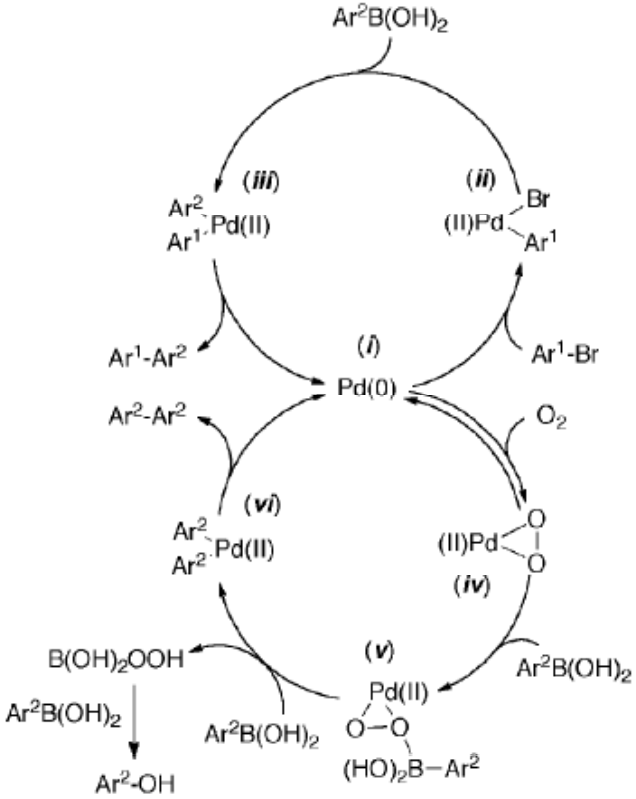
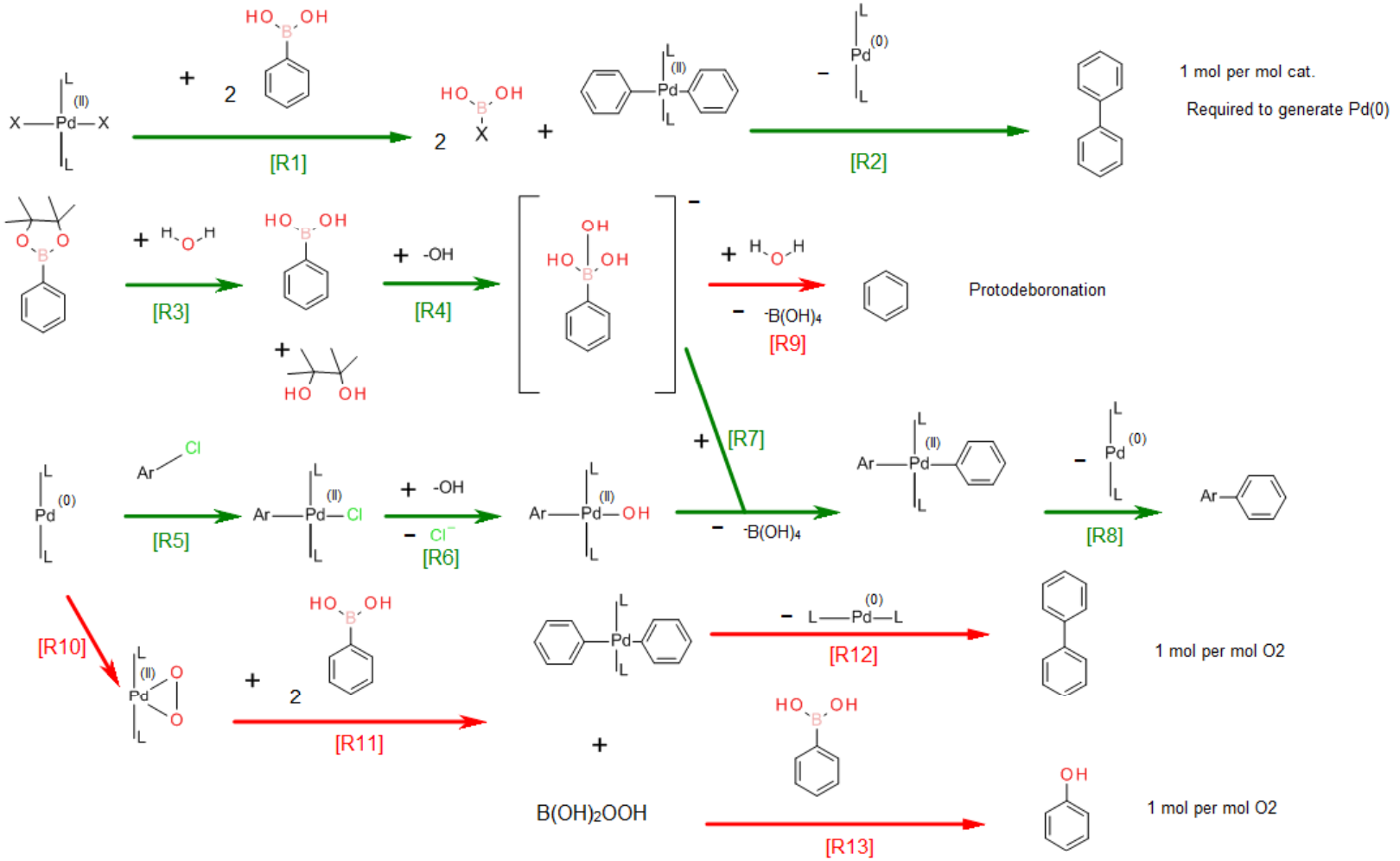


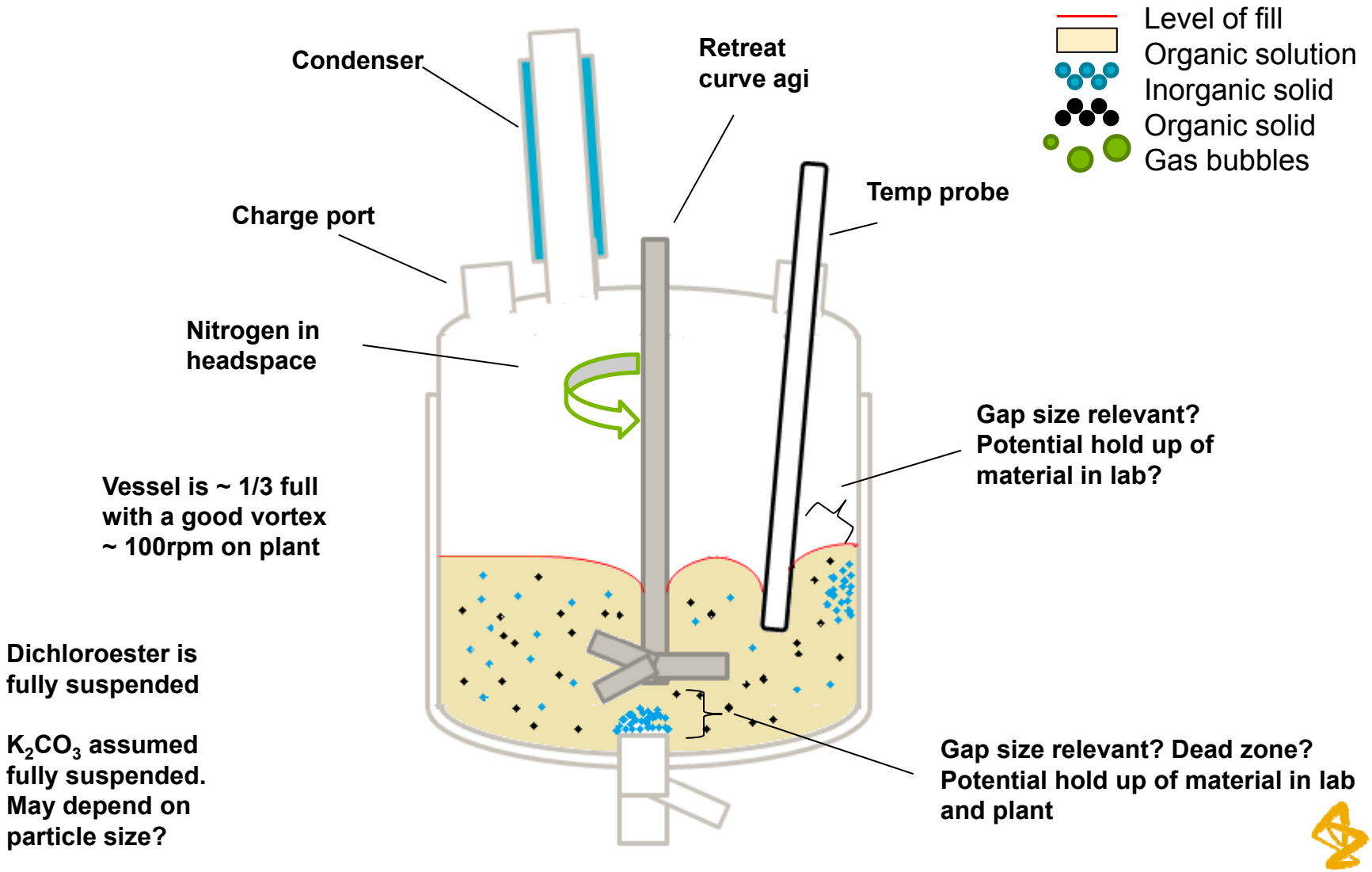
Figure 14. Competing cycles for Pd-catalyzed cross-coupling and oxidative homo-coupling of an aryl boronic acid.

A. J. J. Lennox and G. C. Lloyd-Jones Isr. J. Chem ***2010***, 50, *664-667*

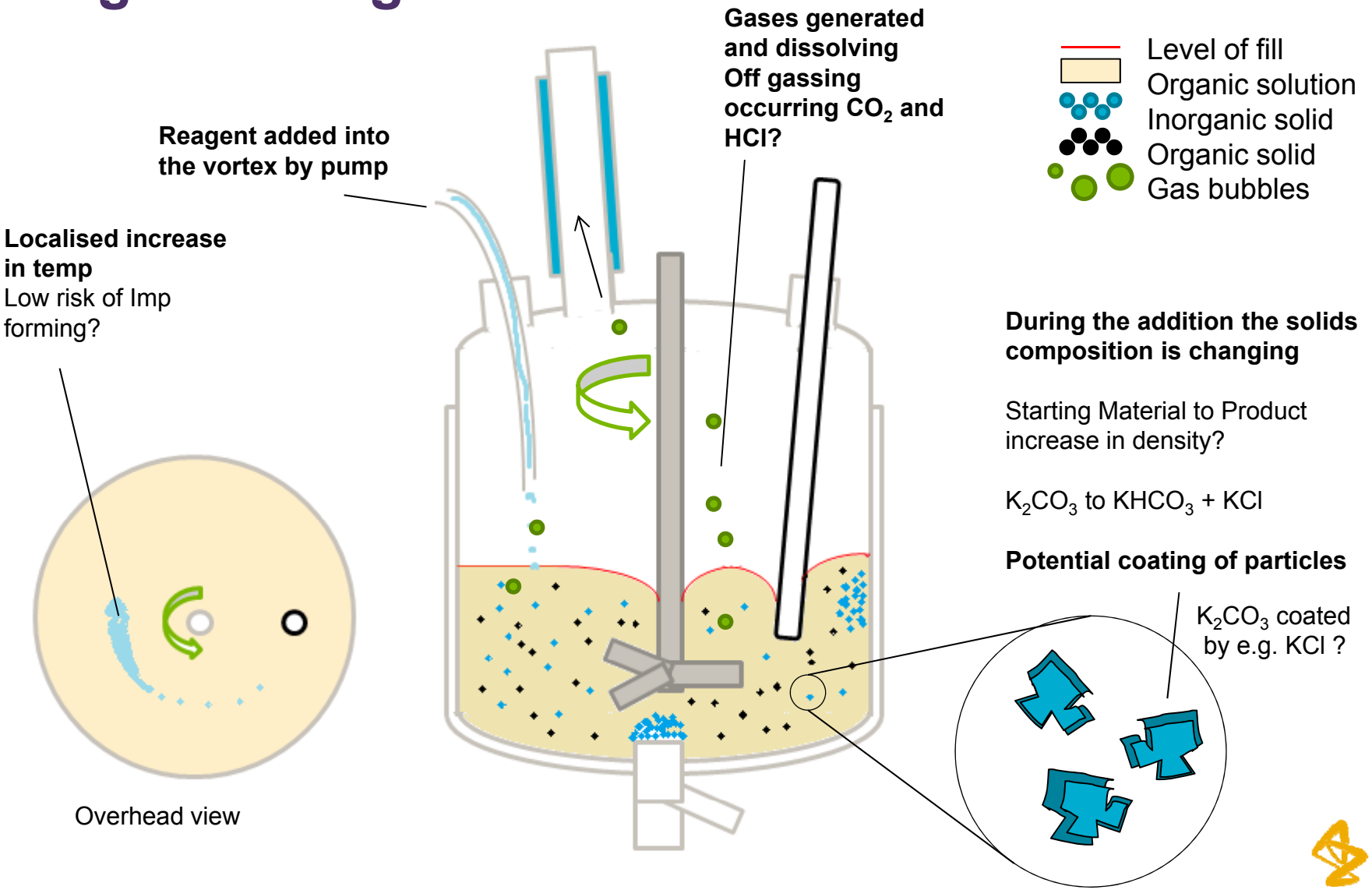
Understanding Reactions
Suzuki Coupling Transformations



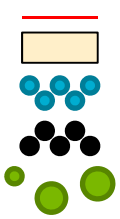
Visualisation/Insight
Vessel at 80°C Before Reagent Charge



Visualisation/Insight
Reagent Charge at 80°C

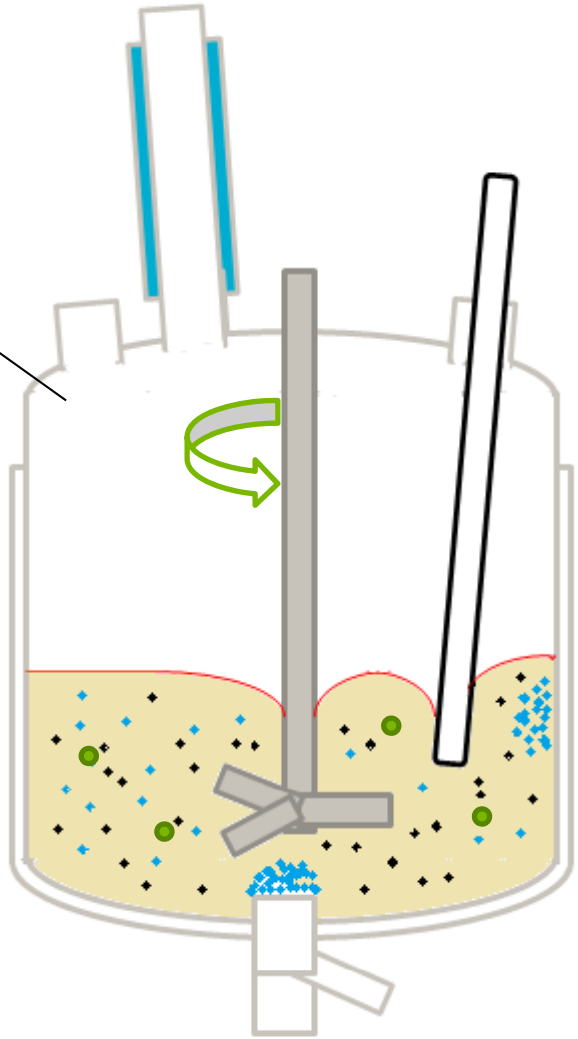


Visualisation/Insight
Vessel at 110°C to give ideal EOR



Level of fill
Organic solution
Inorganic solid
Organic solid
Gas bubbles

Headspace contains a mixture of gases
- **Nitrogen**
- **CO_2**
- **HCl**
- **Water**
- **Toluene vapour**



Yellow organic solution
Product organic soluble in neutral state
Are any organic HCl salts out of solution?

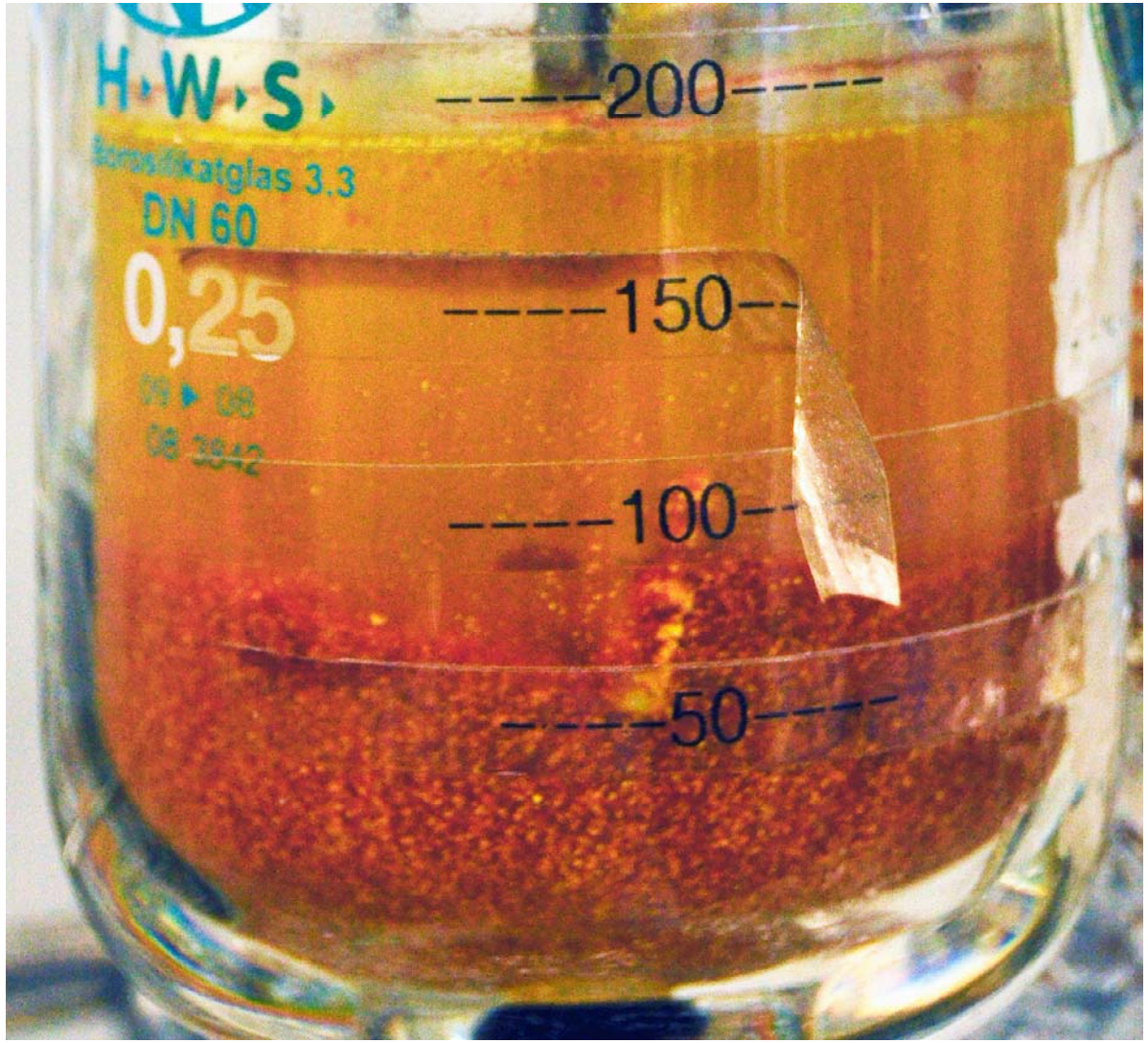
Inorganic solids assumed fully suspended

K_2CO_3, $KHCO_3$, KCl
Possibly KOH?

Dissolved gases
Some CO_2 in solution, assume HCl has either reacted or disengaged

Visualisation/Insight

When it goes wrong.....
using Sigma-Aldrich ACS grade K_2CO_3



Control of Impurities

Control of Impurities
Impurities in Process Development

Impurities Vs **Contaminants**

*Are species **generated** during the process, either during side reactions or due to stresses relating to processing*

*Are **already present** in an input material, but which persist or react further; contributing to the impurities in the final intermediate or API*

Heavy metals

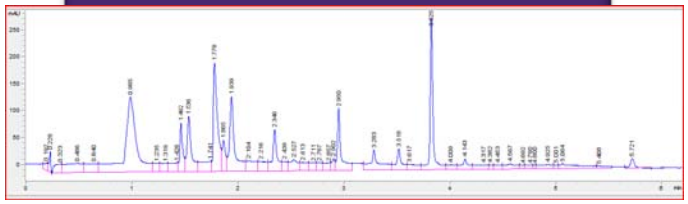
Residual solvents

Stereoisomers

Positional isomers

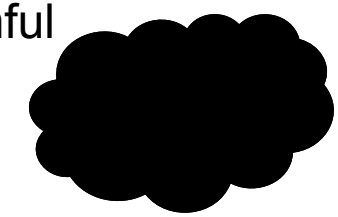
Structurally similar components

Impurity Profile



Control of Impurities
Importance of Impurities

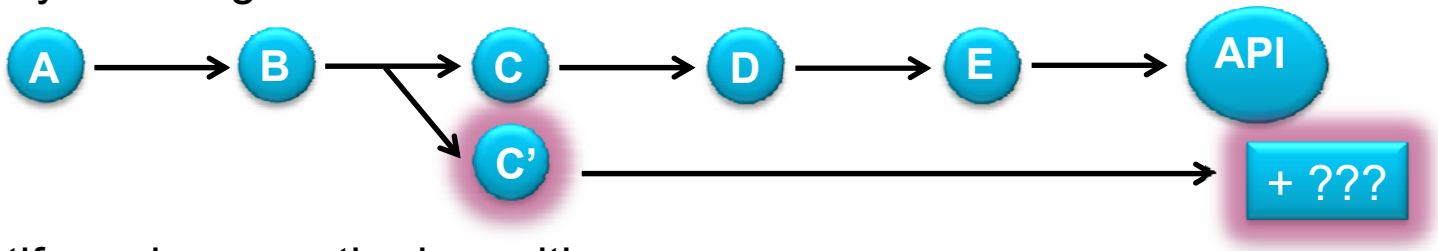
- Impurity profile is directly linked to the level of control we have over a process
  - *As we progress through development, we need a consistent impurity profile:*
    - *Related substances must have toxicological cover*
- Patient safety is of paramount importance: Impurities can be harmful
  - *Particularly reactive or toxic impurities*
    - *ie. alkylators can be carcinogenic*
    - *PGIs (potential genotoxic impurities)*



- Difficult or hard to remove impurities can severely limit your synthetic options
  - *Complex purifications*
  - *Inability to 'telescope'*
  - *Can add uncertainty, time and cost..* SELE_cCT
- Identification of Impurities can give valuable insight into the process
  - *Mechanism of the desired reaction*
  - *Minimise an unwanted reaction*
  - *Reduce formation of the impurity itself...*

Control of Impurities
Coping with Impurities

- Identify impurities in your product by normal spectroscopic methods (NMR, LC-MS, UV, IR etc...)
  - Isolate the impurities prior to analysis?
- Impurity Tracking:



- Quantify and assess the impurities
  - *Are they at the threshold of toxicological concern (TTC)?*
  - *What are the toxicological implications of the drug itself?*
  - *Patient safety?.. might not be compromised*
- Process control
  - *Suppress or predict formation?*
- Removal by purification
  - *Can the isolation steps cope with the predicted levels?*
- Deliberate chemical synthesis of impurity
  - *Confirms earlier findings and supports impurity tracking*

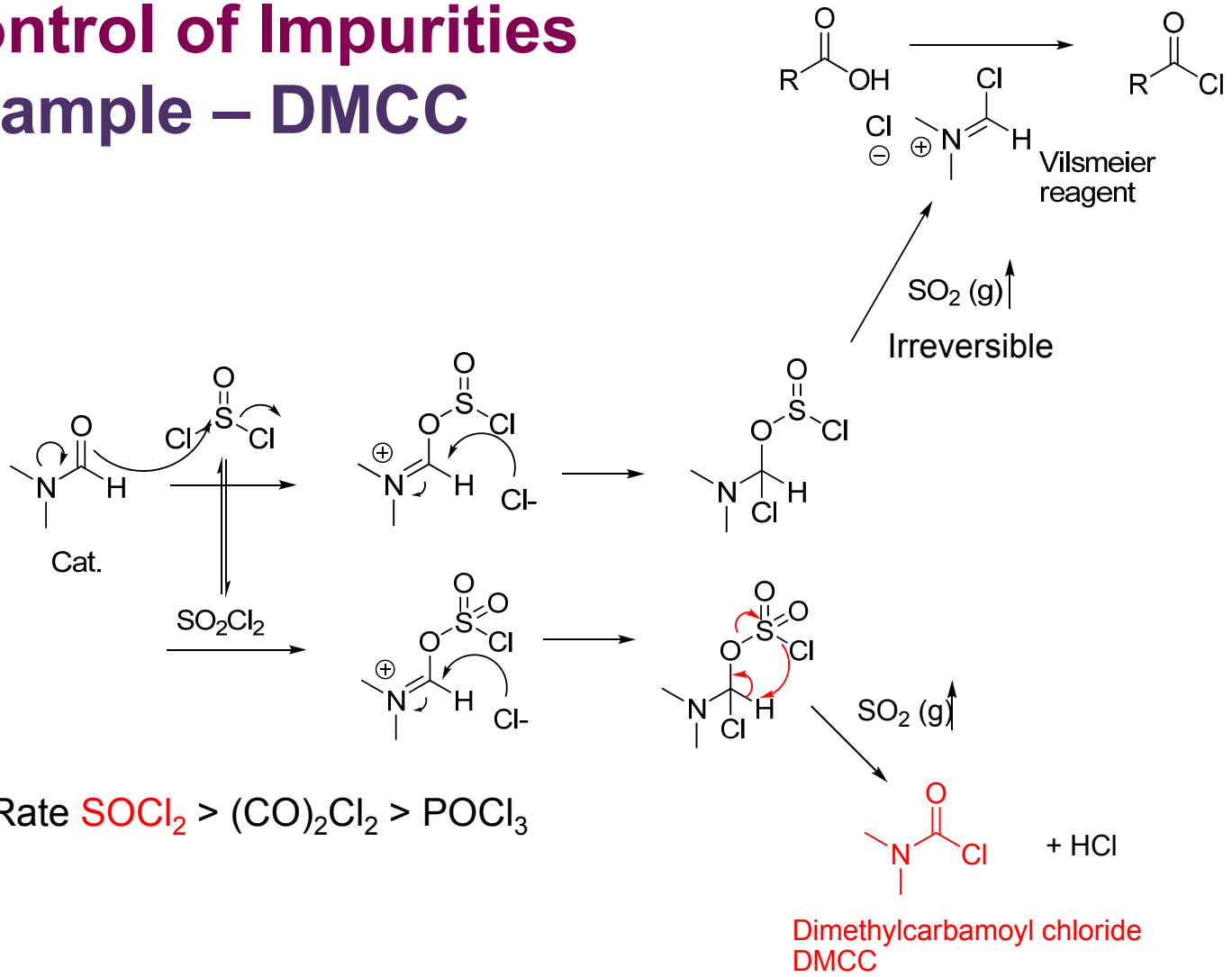
Control of Impurities
Removal of Impurities

*Always aspire to **control**, but often **removal** is more realistic*
A mixture of approaches is often applied throughout a synthetic sequence....

- Control Options:
  - Alter Process
    - Reagents
    - Solvents
    - Temperature
    - Time
    - Order of addition
    - Equivalents
    - Derivitisation
  - Reactor Considerations
    - Batch process *Vs* continuous

- Removal Options:
  - Crystallisation
  - Recrystallisation
  - Liquid/liquid extraction
  - pH control
  - Physical Separation
    - Distillation
    - Chromatography

Control of Impurities
Example – DMCC

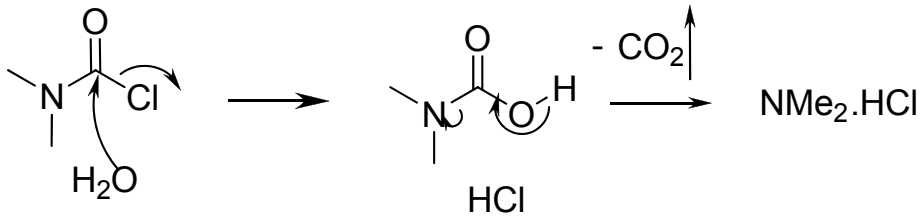


Rate $SOCl_2$ > $(CO)_2Cl_2$ > $POCl_3$

- Known animal carcinogen
- Potential human carcinogen
- Has to be controlled at ppm levels!
- Organic Process Research & Development, 1997, *1*, 182

Control of Impurities
Example – DMCC

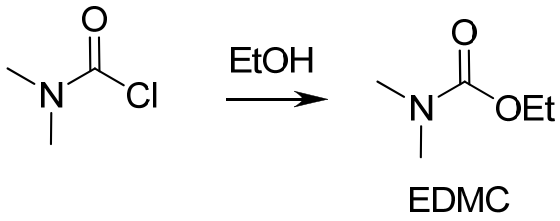
1. Consider Removing Reaction Altogether
2. Alter Process
   - DMCC hydrolyses rapidly during aqueous workup
     - Organic Process Research & Development, 2009, *13*, 857



     - Hydrolysis for 30 mins reduced DMCC from 87 ppm to <1 ppm (half life 6.8 min)
3. Layers of Protection
   - Consider position of the DMCC formation in synthetic sequence

Control of Impurities
Example – DMCC

4. Reaction Monitoring
   - Analyse reaction mixture for DMCC after derivitisation



EDMC

   - GCMS analysis allows quantitative assessment of EDMC levels via selected ion monitoring against a standard
   - Linearity and Limit of Quantification were both confirmed – method has been Qualified
5. Analysis of Intermediates or API
   - Last Resort

Process Chemistry

Design of Experiments for Process Optimisation

Jeremy Parker, Principal Scientist
Chemical Development, Pharmaceutical Development
AstraZeneca
jeremy.parker@astrazeneca.com

Process Optimisation
Activities

- Refine reagents
  - Reagents
  - Solvents
  - Additives
  - Catalysts
- Improved Reaction Understanding
  - Mechanism
  - Impurity profile
  - Improving control
- Define Parameters
  - Set points for reagents/solvents charges
  - Set points for other parameters (temp, addition times)
  - Set points for work up
  - Set points for isolation
  - Set points for drying

Time for Tea?

Objective: Make the perfect cup of tea!

Brainstorm all the Factors that can be varied…..

- Additive yes or no: Milk, Lemon, Sugar.
- Tea: Type e.g. Assam; bag or leaves.
- Addition order: Milk, Sugar etc
- Milk: Type e.g. skimmed
- Sugar: Type e.g. Castor; particle size.
- Caffeinated?
- Stirring.
- Pot warming.
- Water hardness.
- Type of mug.

Discrete variables

Continuous variables

- Quantities: Water, Milk, Tea, Sugar.
- Temperature: Water, Milk.
- Brewing time.

Time for Tea?

- Select which Factors to Fix and which to Vary
- Decide on Factor Levels (simplify as H or L)
- What about Reponses?
  How will we *measure* these? (Tea is difficult!)

If did every combination of your plan…how many experiments?

a) 4330….but that's impossible!
b) 82 Million!!!

Design of Experiments (DoE) = Factorial experimental design (FED) approach

- Confine to available ingredients and equipment
- Carry out minimum number of 'experiments' ie. 10?

To extract the maximum information

Introduction

DoE is used extensively in other areas

- **Engineering/Manufacturing**
- **Formulation / Analytical Chemistry**

Sole requirement:
Varying the levels of input factors results in a change to a response

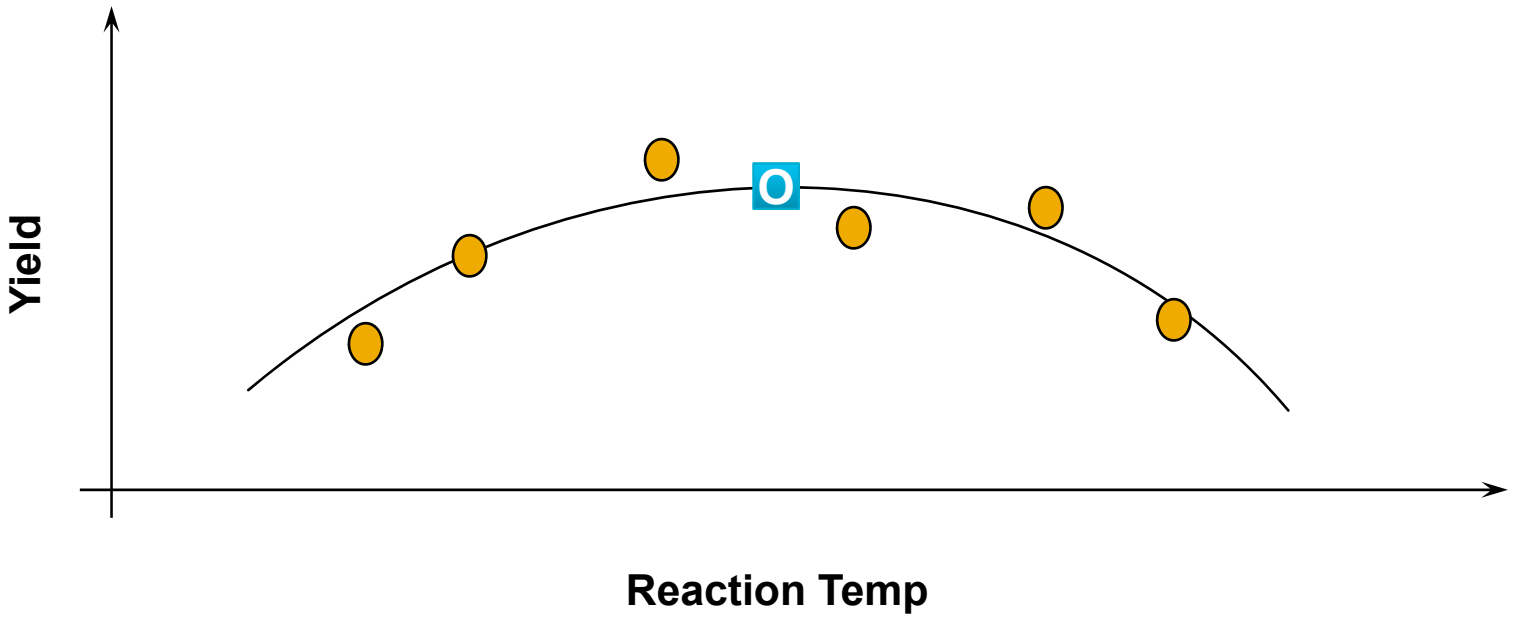
…….most experiments could be done in DoE approach.

2 Main uses of DoE in organic chemistry:

But... DoE is not the traditional approach...

Traditional approach...
One-Variable-At-A-Time (OVAT); Iterative approach

Vary temperature keeping concentration fixed:



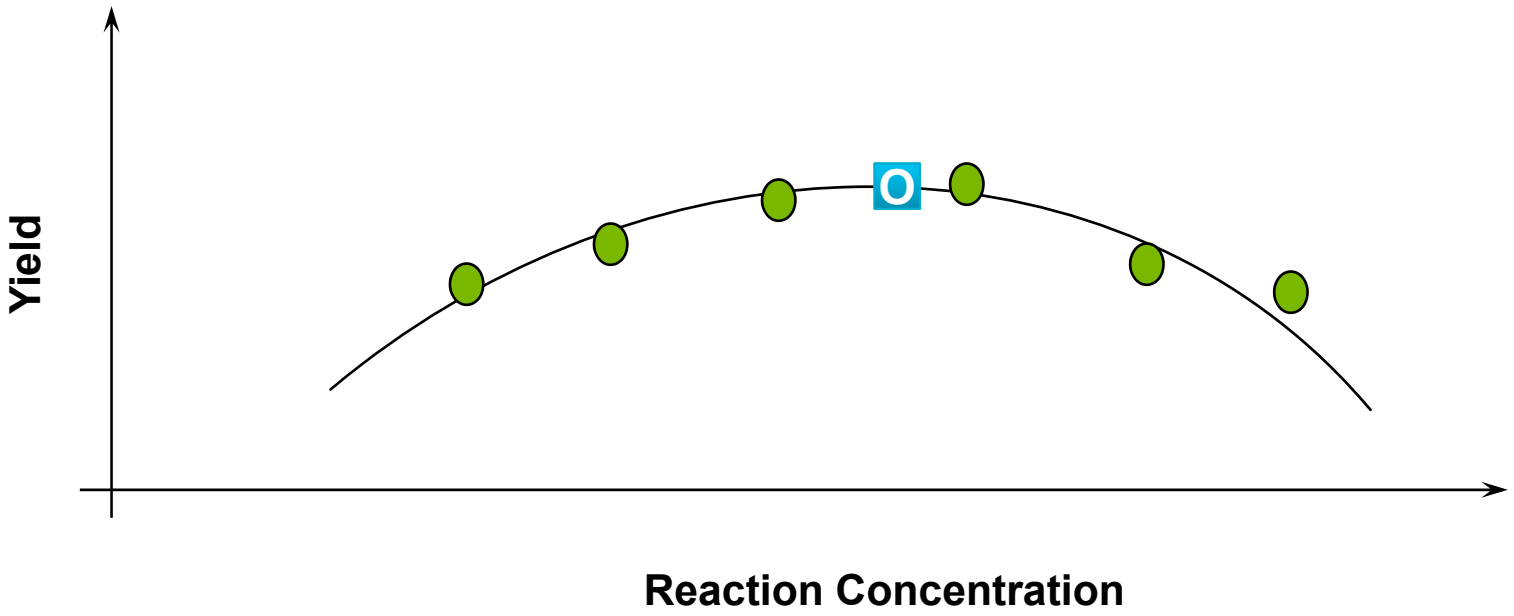
O = Optimum yield at fixed concentration

Traditional approach...

One-Variable-At-A-Time (OVAT); Iterative approach

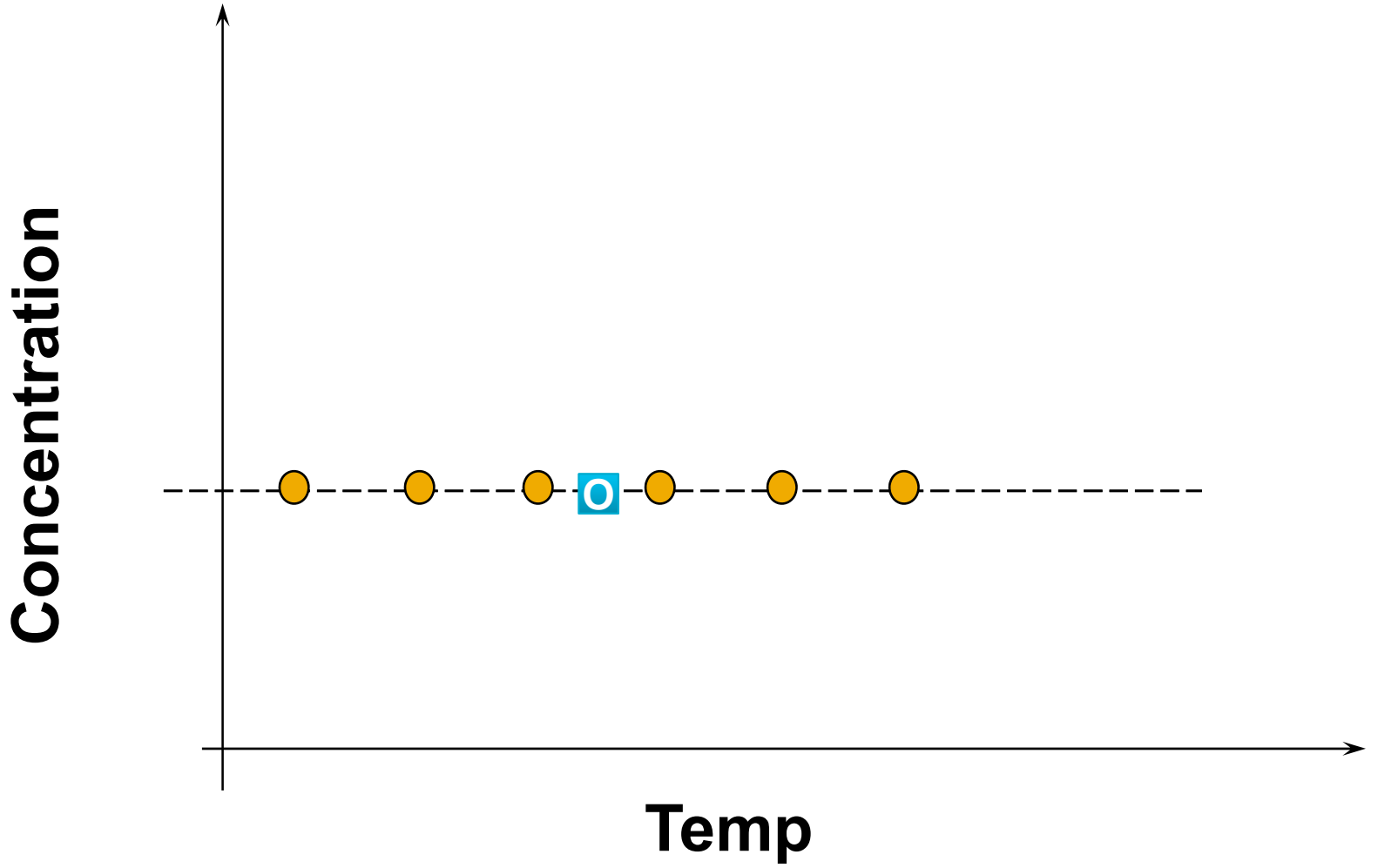
Now we've found our 'optimum' temperature...

Vary concentration keeping temperature fixed:

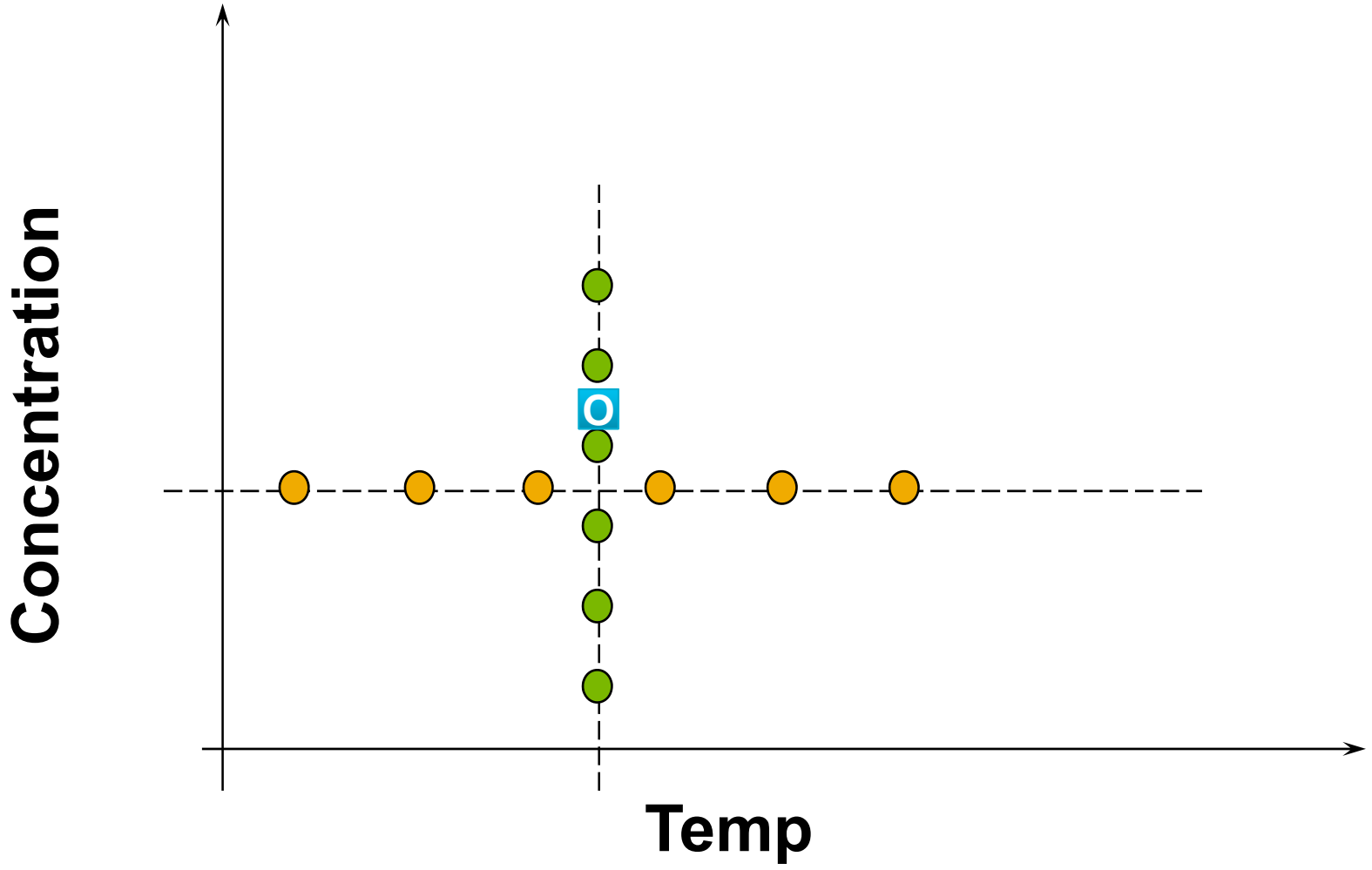


O = Optimum yield at fixed concentration and temperature

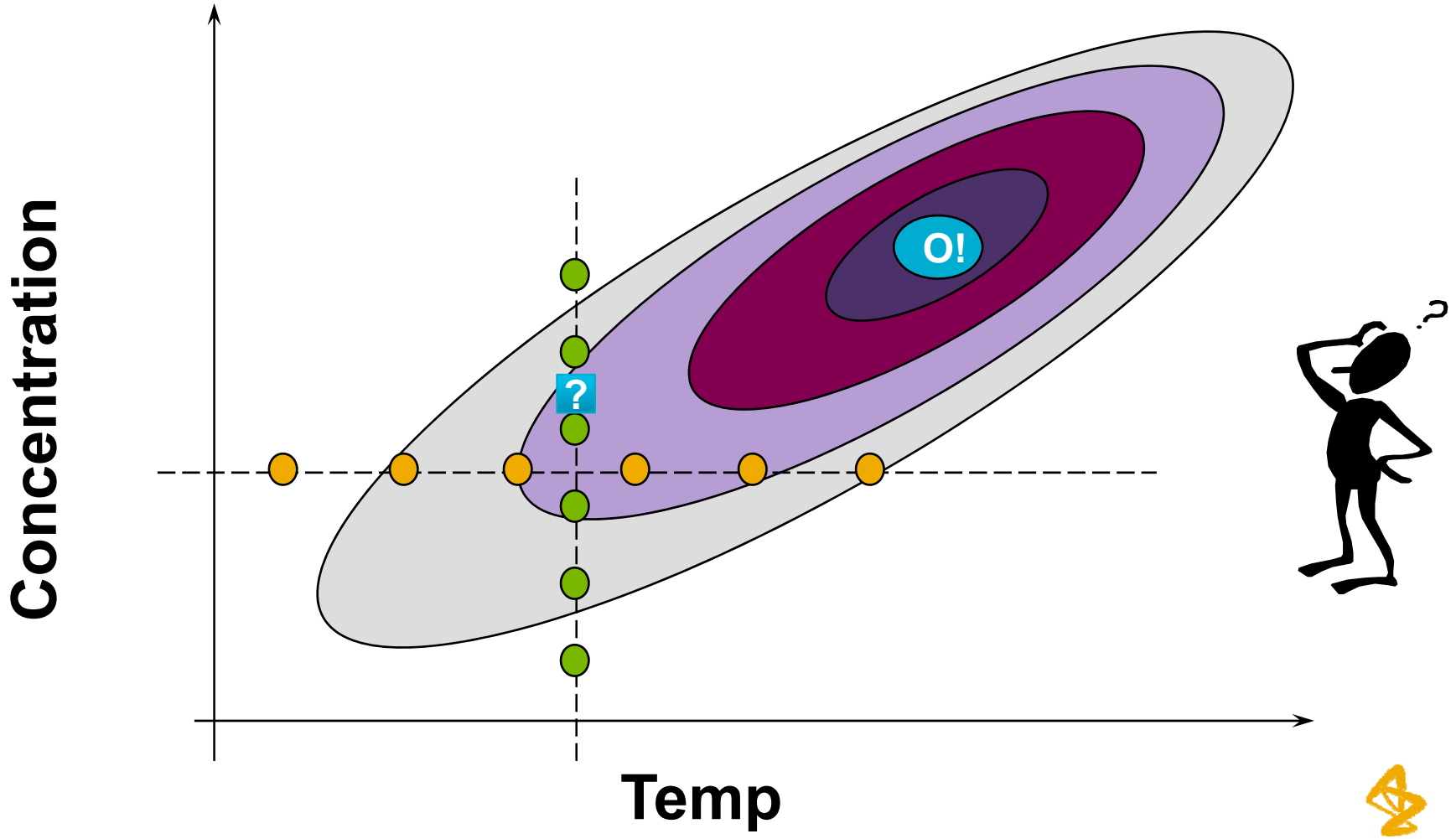
Traditional approach...
One-Variable-At-A-Time (OVAT)



Traditional approach...
One-Variable-At-A-Time (OVAT)



Limitations
One-Variable-At-A-Time (OVAT)



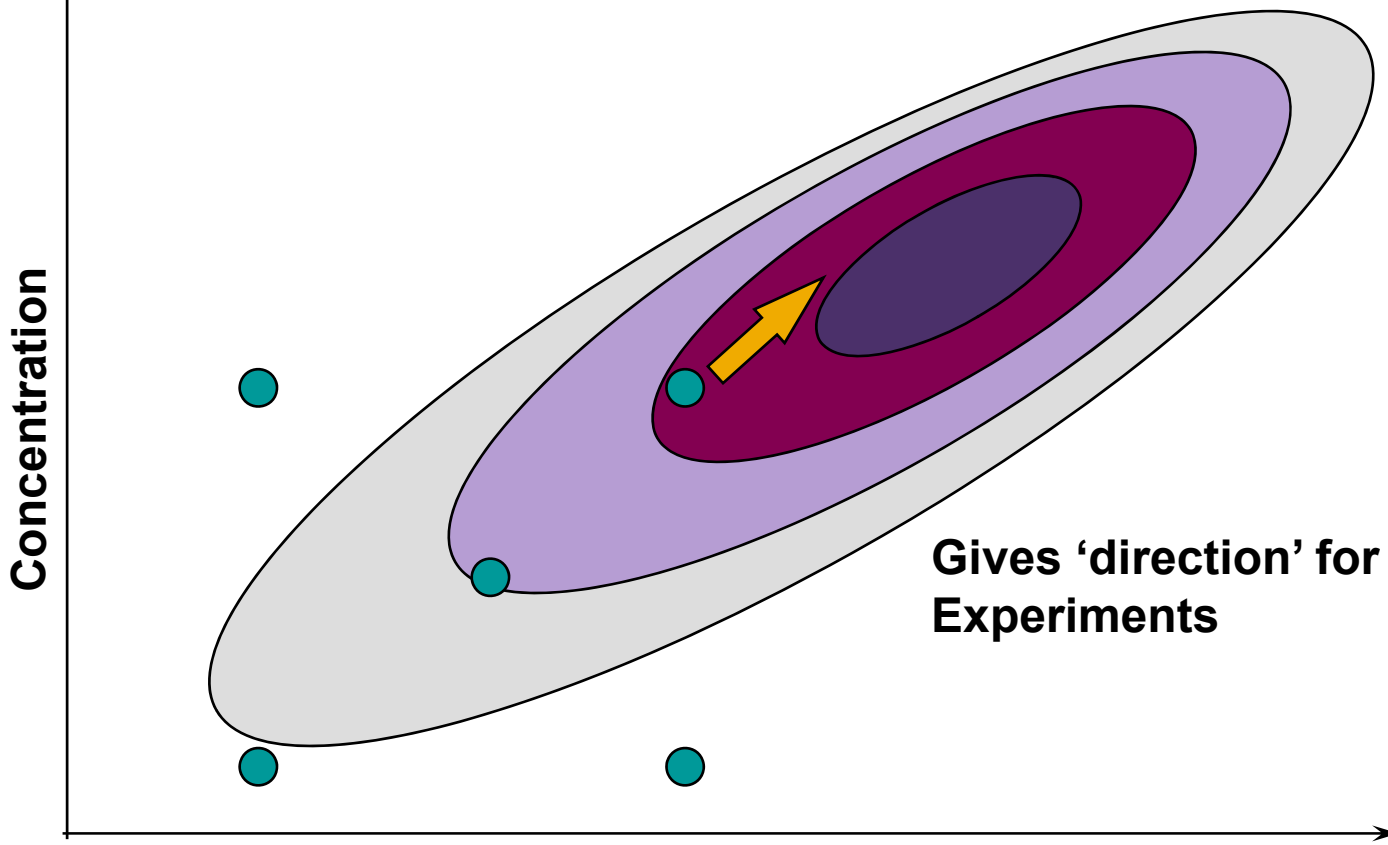
Background
Dangers of OVAT

- **Can lead you to think you've found the optimum**
  .....when in reality you have not
- **Can be inefficient (use of people, resources)**
- **Limited coverage of 'chemical space'...Think three dimensions...**
- **Does not allow interpretation of *interactions***
  ..understanding dependency of one parameter on another

What Could I Have Done Instead...DoE

Choose suitable *range ...H and L*

Carry out *extremes* and *centrepoint*

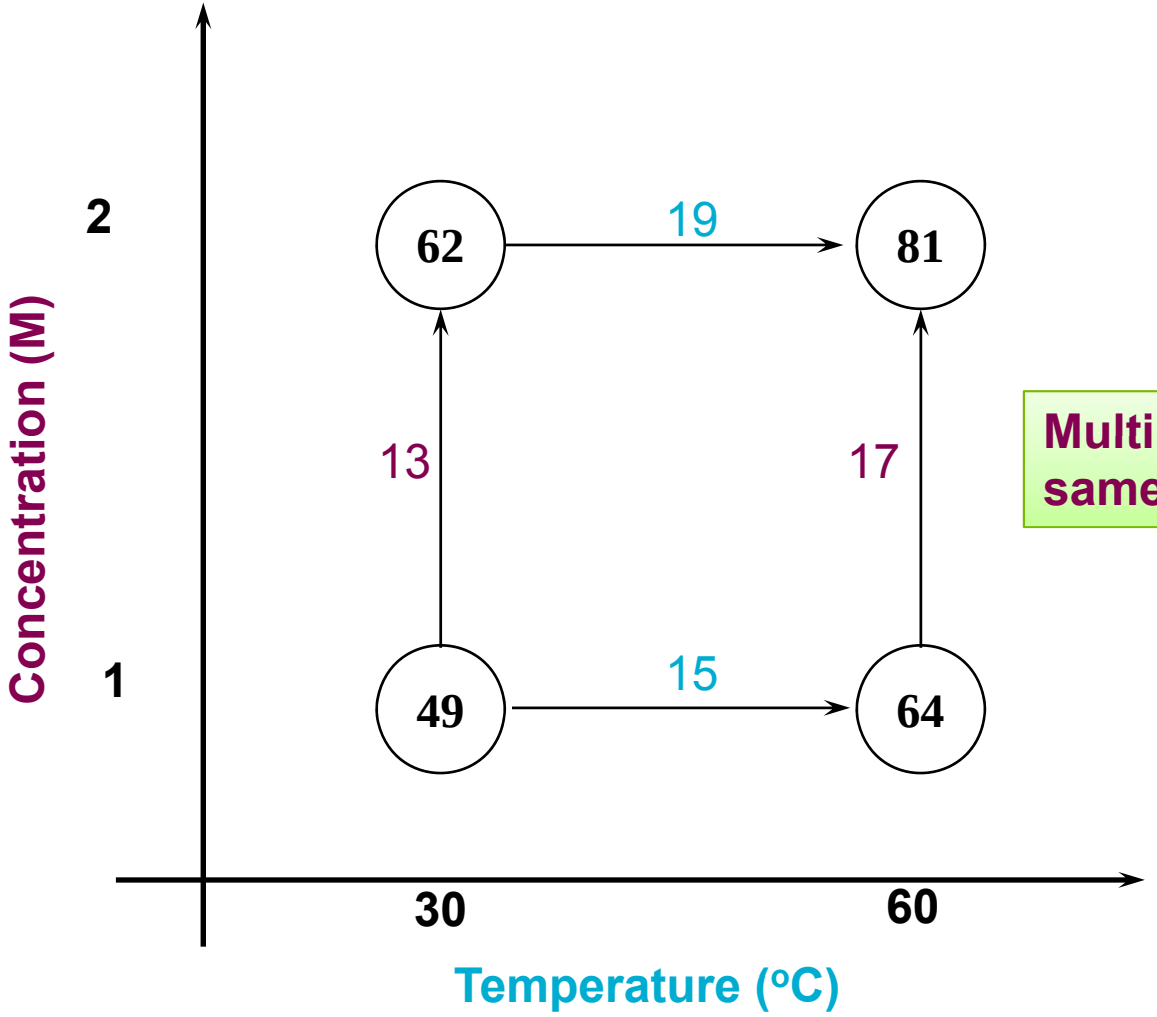


Gives 'direction' for Further Experiments

Design of Experiment
Two Factors; '2-squared' design

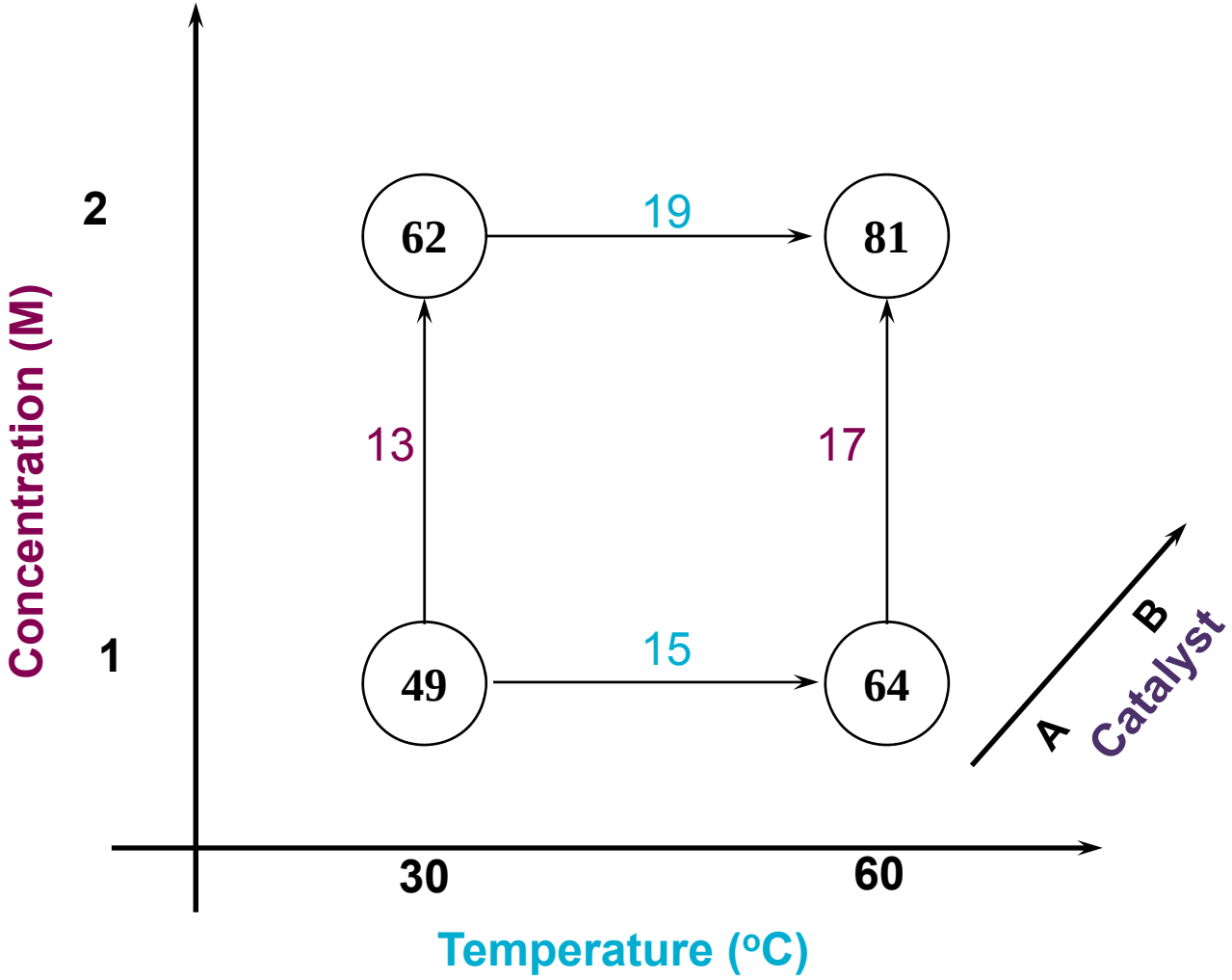
Average Effect of Temp = 17

Average Effect of Conc = 15



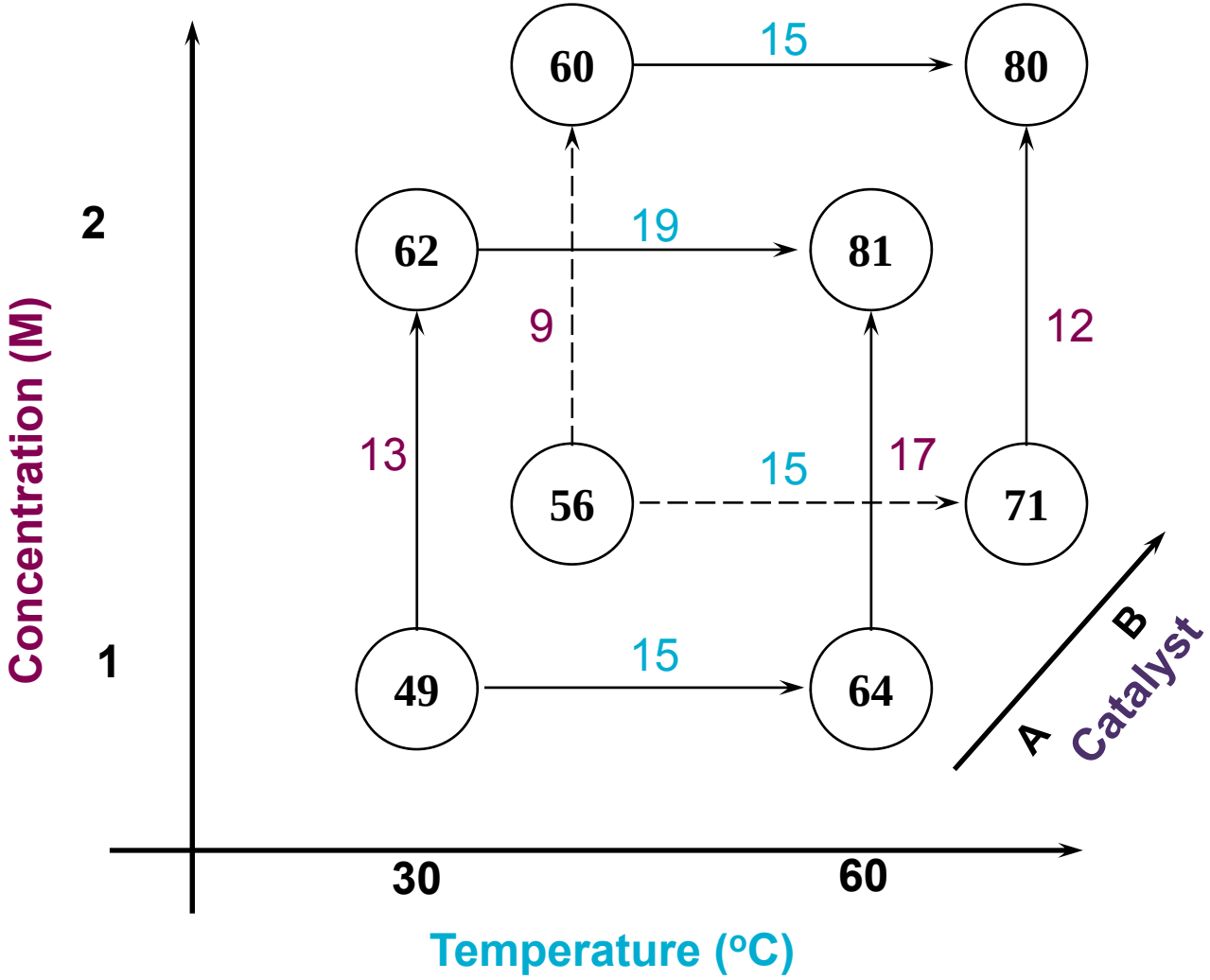
Multiple uses of the same data set

Design of Experiment
Three Factors; '2-cubed' design



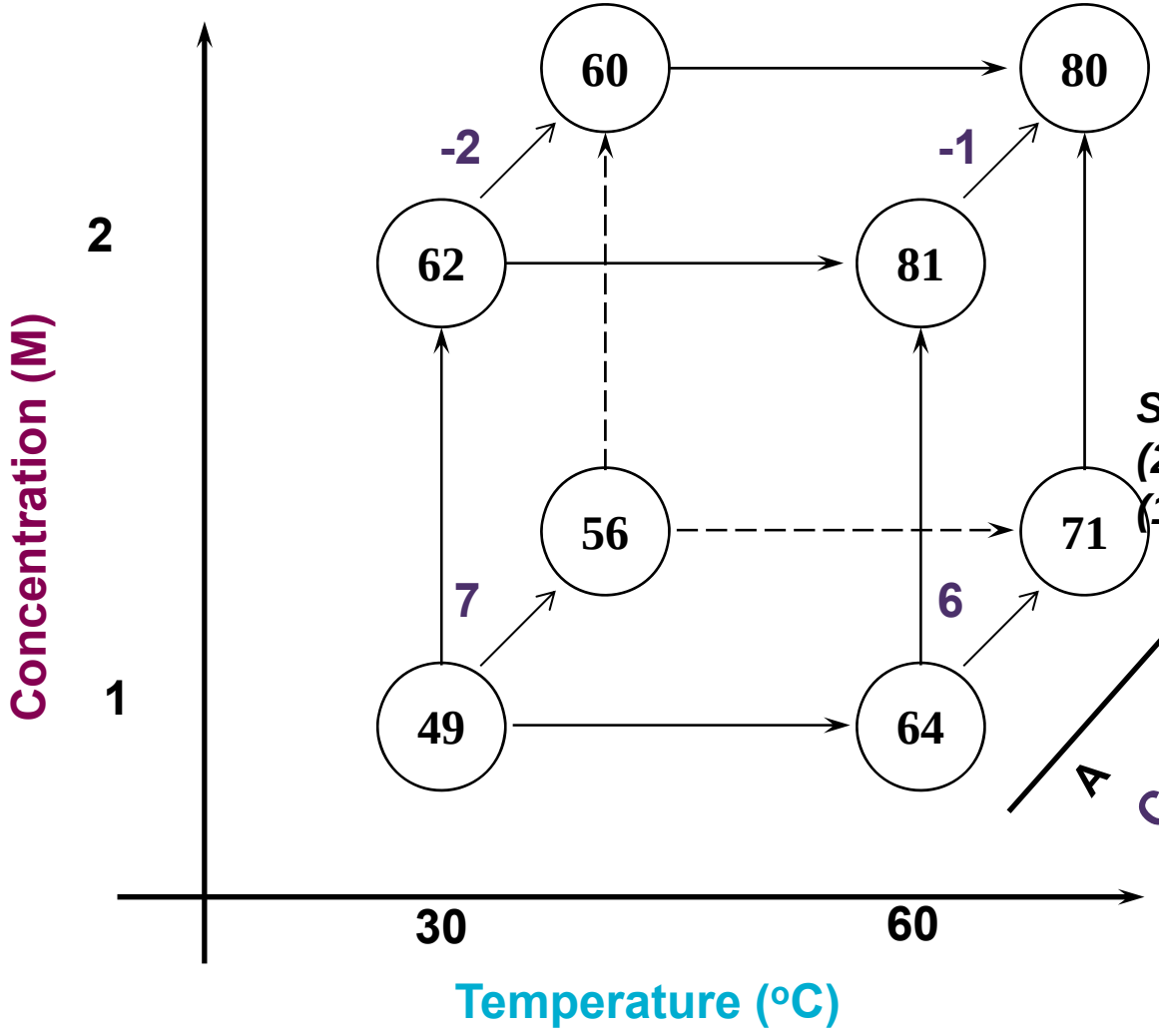
Design of Experiment
Three Factors; '2-cubed' design

Average Effect of Temp = 16
Average Effect of Conc = 13



Design of Experiment
Three Factors; '2-cubed' design

Average Effect of Catalyst:
-2 and -1, 7 and 6 = 2.5



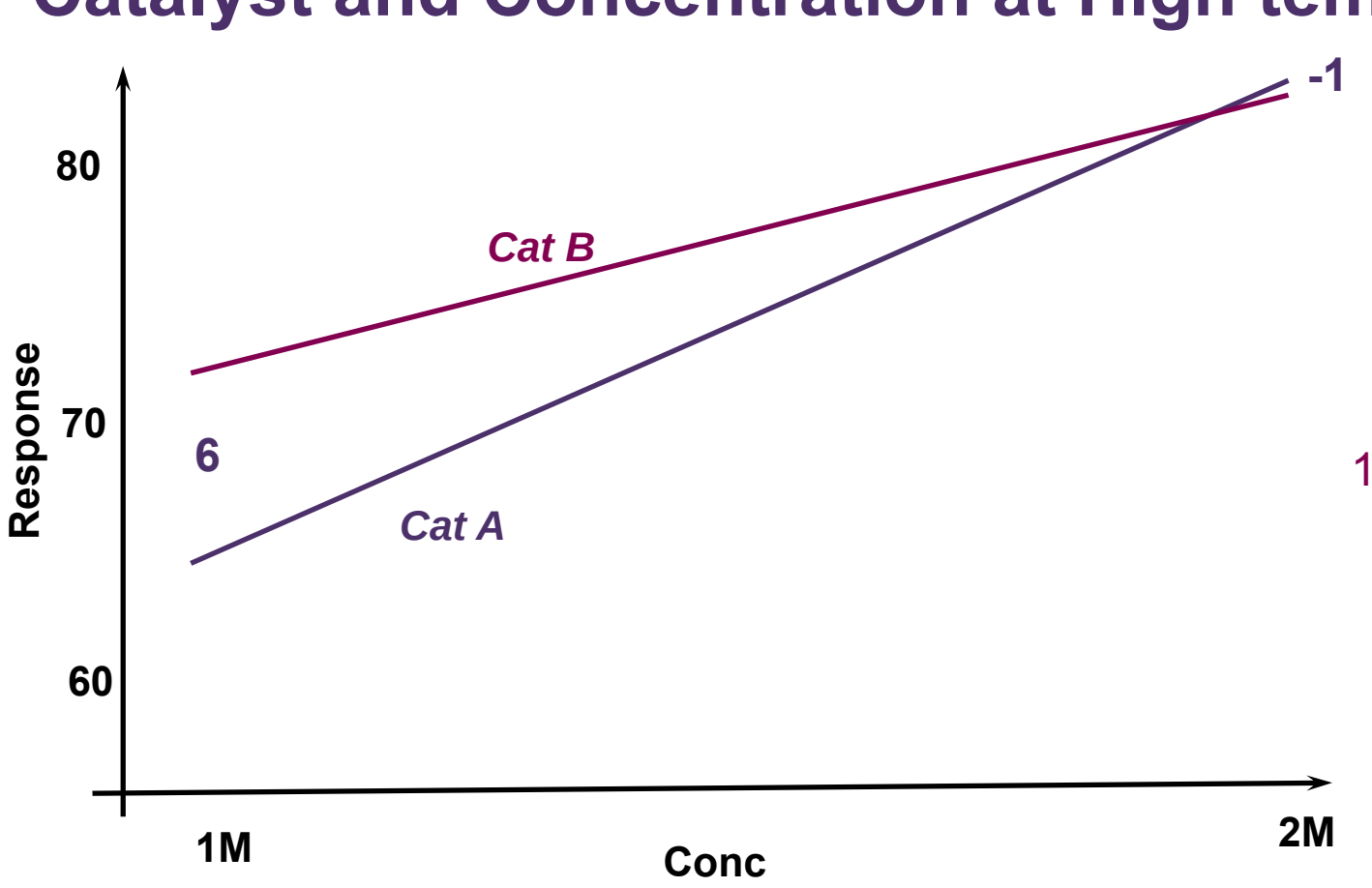
This is an Interaction

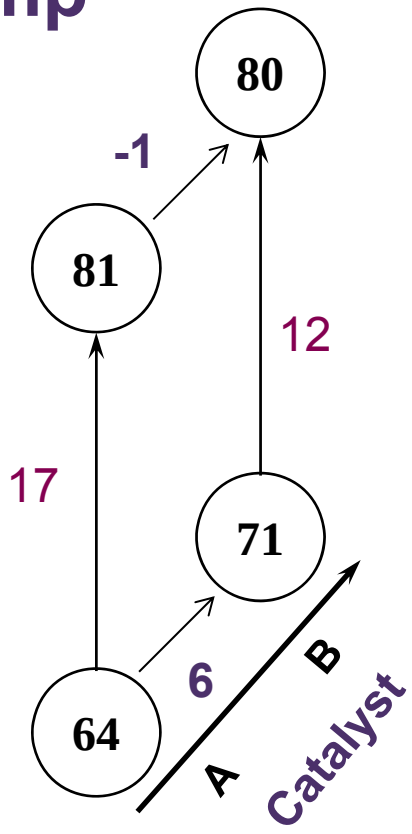
Relative performance of cat A vs B depends on concentration

Suggests...
(2M: Independent of Catalyst)
(1M: B is better)

Interaction Plot

Catalyst and Concentration at High temp





'Catalyst A is half the cost of B': Use catalyst A & high conc

'We have to run at low concentration': Analyse CoG; yield loss vs cat cost

All this info from 8 experiments!!!

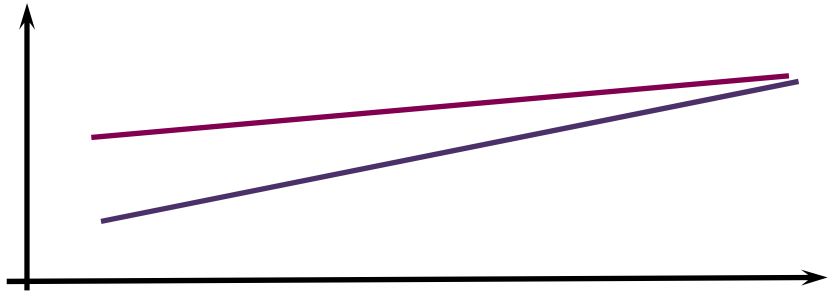
Visualisation

From Table…..

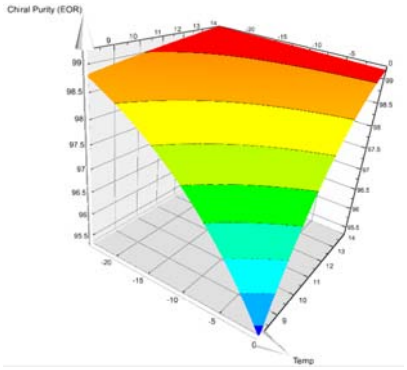
Temp / °C	Conc (M)	Catalyst	Yield /%
-	-	A	49
-	+	A	62
+	-	A	64
+	+	A	81
-	-	B	56
-	+	B	56
+	-	B	71
+	+	B	80

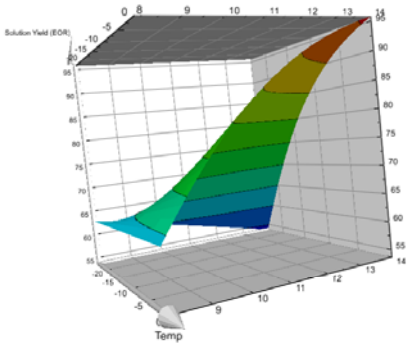
To Knowledge of Main Factors:
Temp and Conc have equal +ve effects

To Knowledge of Interactions



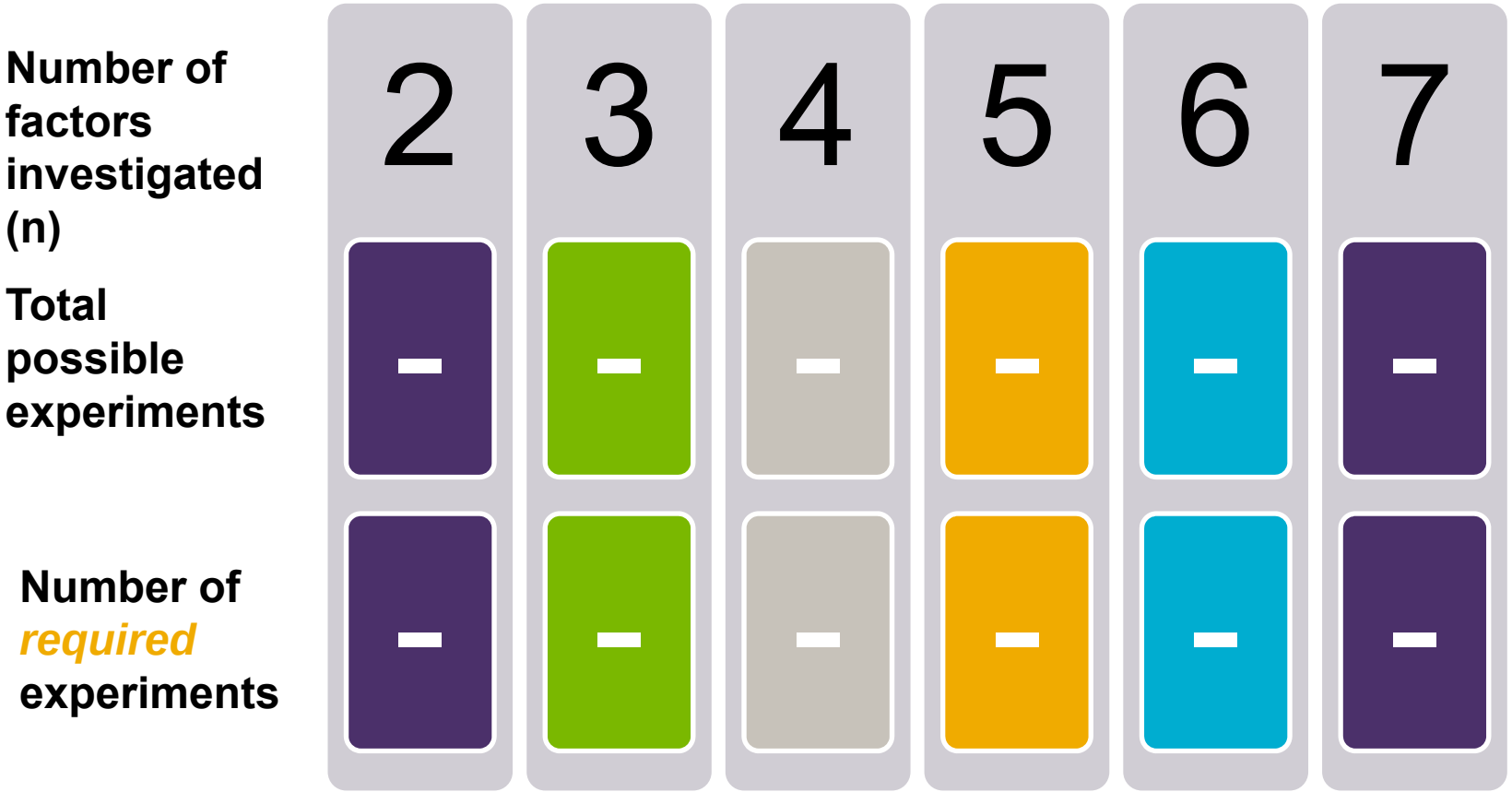
To Full Contour Plots





Easy to Visualise 2 and 3 Factors...
...But not 4 or more!
Need Software to do this

Design of Experiment
Fractional Designs (Factors at 2 levels)



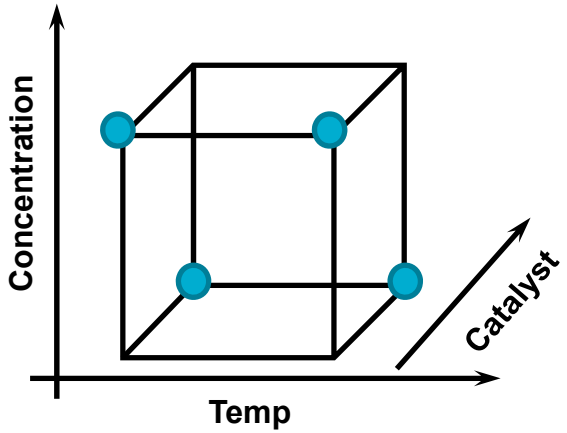
Design of Experiment
Fractional Designs (Factors at 2 levels)

Design of Experiment
Fractional Designs (Factors at 2 levels)

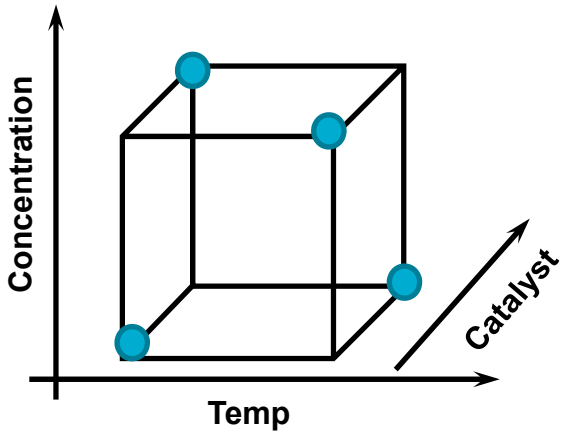
Maximise chemical space...

You can do 4 experiments...
Fractional Designs – which would you choose?

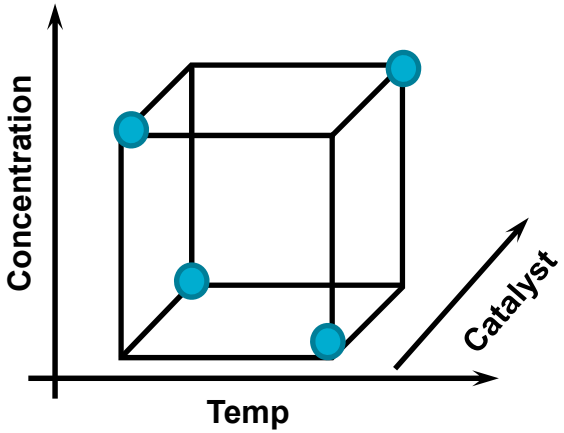
1



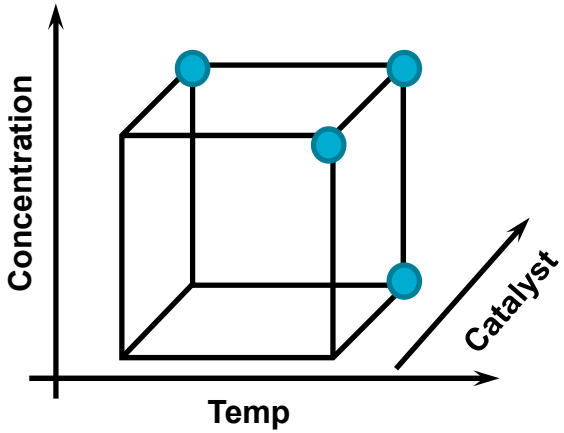
2



3

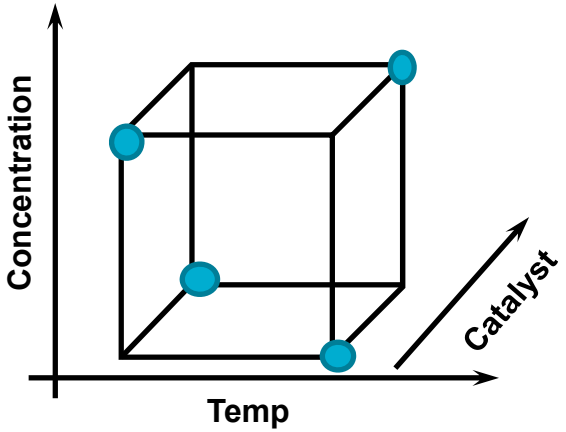


4

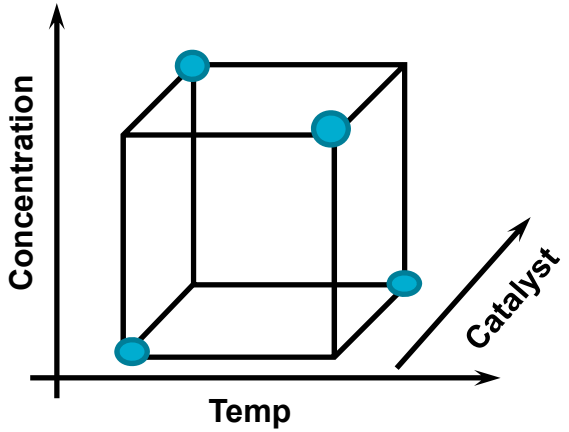


Design of Experiment
'Half fractions'– 2 possibilities

'Fraction 3'



'Fraction 2'



Tetrahedron arrangement...Why these?
Think of as '**maximising chemical space** in 3D'...
Or... 'covering each factor at **both levels**

In reality, start with half fraction (good approximation of full design)
Analyse results

- May have all info
- Or do selected experiments
- Or complete other half

Increasing 'effort'

Need to also plan for repeats and centrepoints...

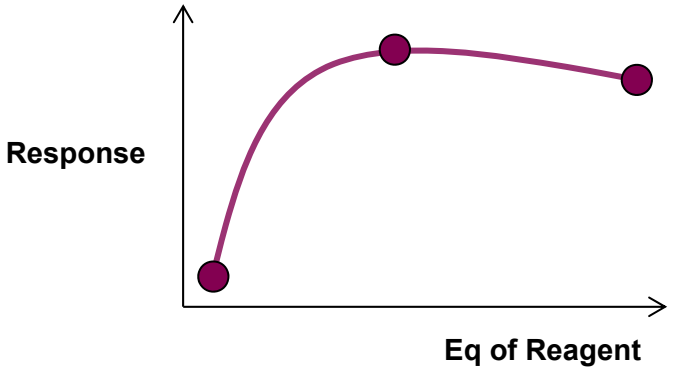
Standard Practice
Repeats

Run Repeats

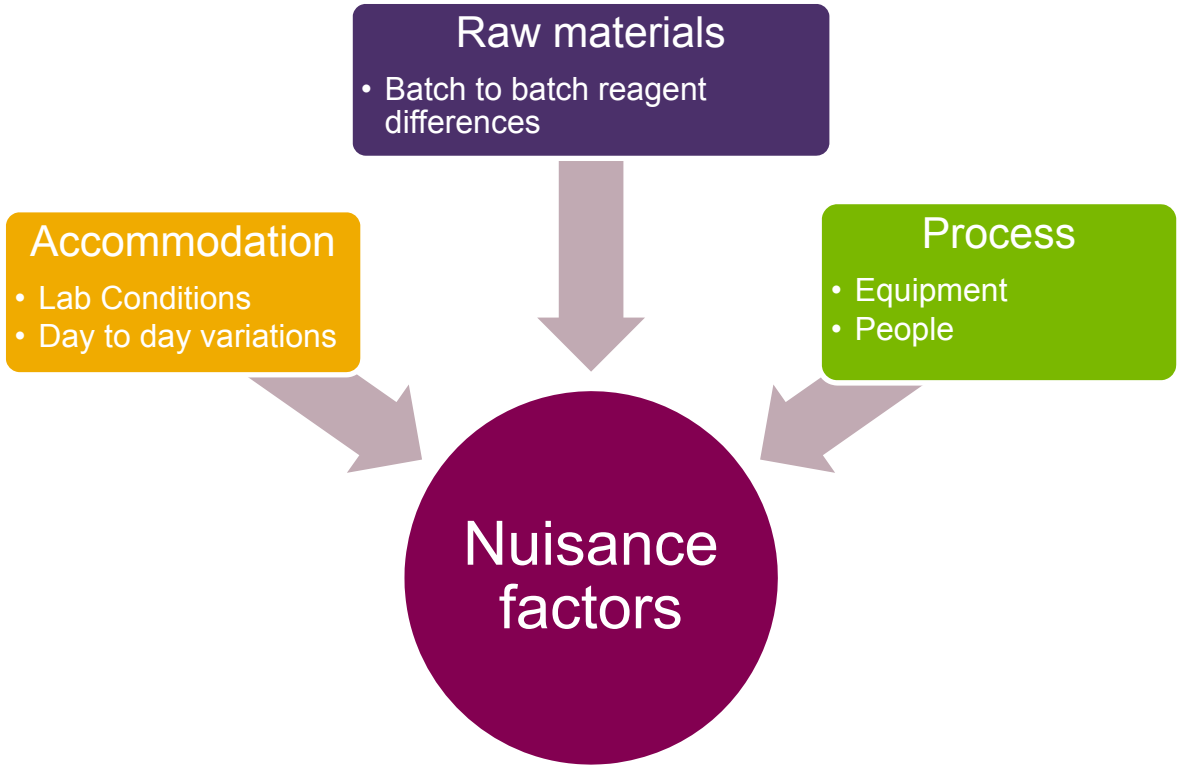
- Min 2 or up to 4 depending on design
- Quick check to ensure consistency
- Need for statistics to measure error
- Especially important when design split between chemists/input material

Repeats are often Centre Points

- If Centre Point in not in the middle – 'curvature' is present
  = irregularity, showing lack of understanding of reaction model



Control of Nuisance factors



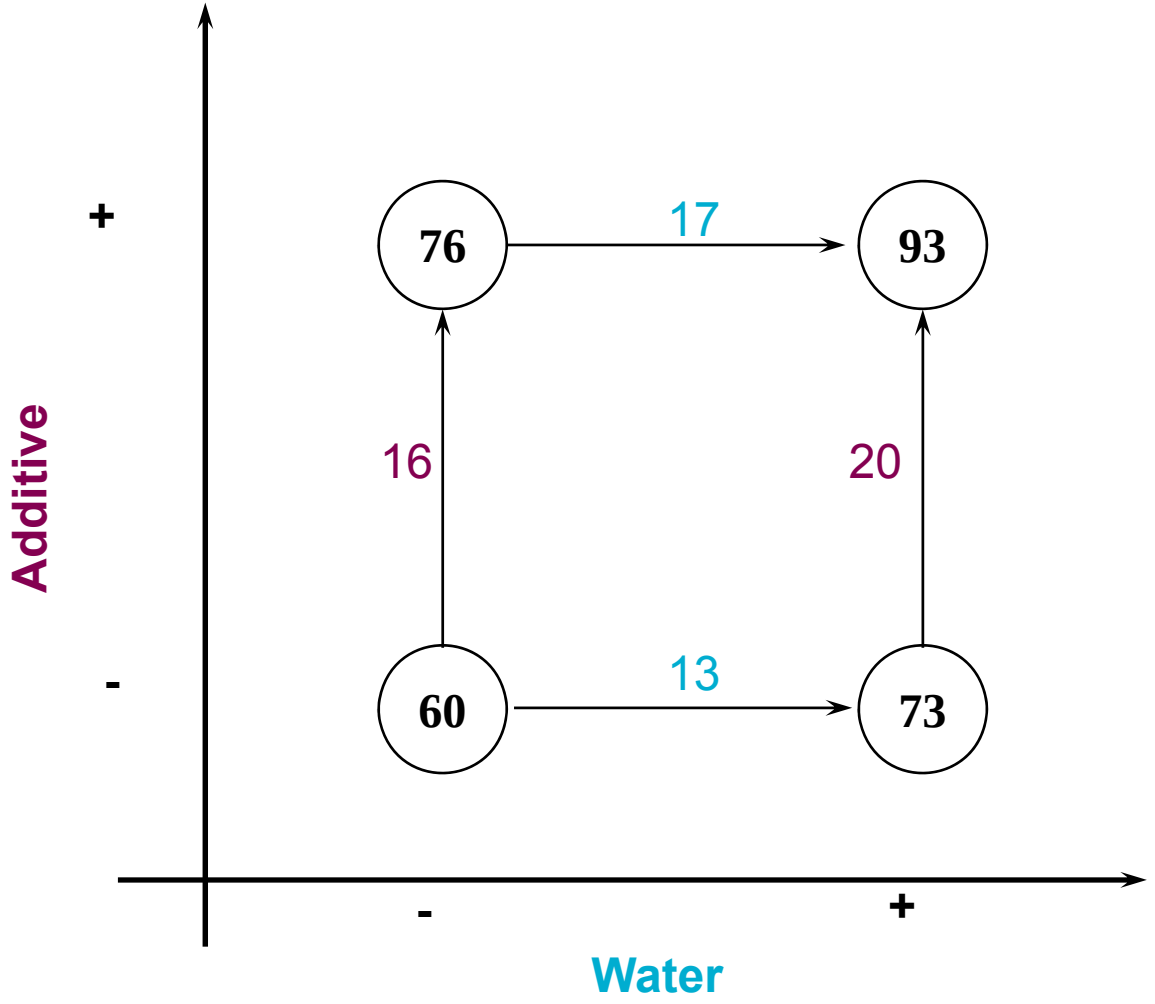
Randomisation is key...

- Neutralises inconsistencies across run (ie. unstable reagent)
- Takes away any bias chemist has on interpreting results.

Blocking...
Two Factors; '2-squared' design

Average Effect of Water = 15

Average Effect of additive = 18



A ‘Blocked’ Design
Neutralises ‘day to day’ variability

Water	Additive	Response	Day
-	-	60	1
-	+	76	1
+	-	73	1
+	+	93	1

Av effect of water
= [(73-60)+(93-76)] / 2 = 15

Av effect of additive
= [(76-60)+(93-73)] / 2 = 18

What if we carry these out over two days, and day 2 leads to spurious results? +10% yield...

Water	Additive	Response	Day
-	-	60	1
-	+	86	2
+	-	83	2
+	+	93	1

Av effect of water
= [(83-60)+(93-86)] / 2 = 15

Av effect of additive
= [(86-60)+(93-83)] / 2 = 18

Carrying out the *right* experiments on day 1 vs day 2 means you can knock out (or block) these effects...

A ‘Blocked’ Design
Neutralises ‘day to day’ variability

Water	Additive	Response	Day
-	-	60	1
-	+	76	1
+	-	73	1
+	+	93	1

Av effect of water
= [(73-60)+(93-76)] / 2 = 15

Av effect of additive
= [(76-60)+(93-73)] / 2 = 18

What if we carry these out over two days, and day 2 leads to spurious results? +10% yield...

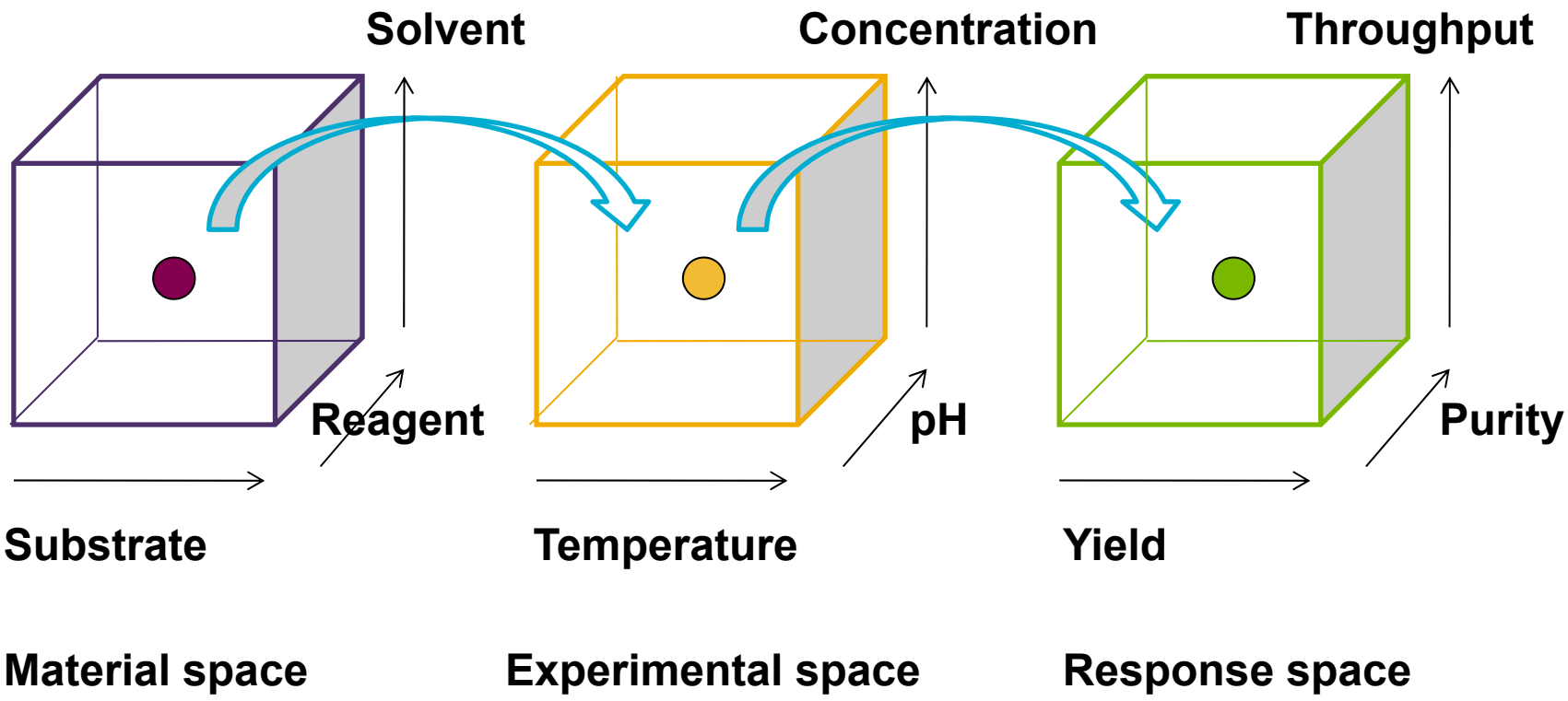
Water	Additive	Response	Day
-	-	60	1
-	+	76	1
+	-	83	2
+	+	103	2

Av effect of water
= [(83-60)+(103-76)] / 2 = 25

Av effect of additive
= [(76-60)+(103-83)] / 2 = 18

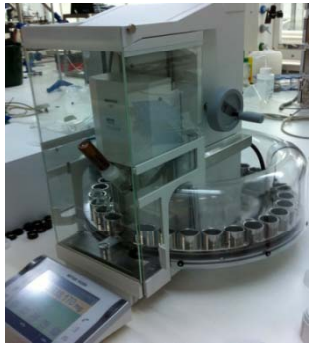
Carrying out the *right* experiments on day 1 vs day 2 means you can knock out (or block) these effects...

How to Optimise a Reaction
Ideal Development



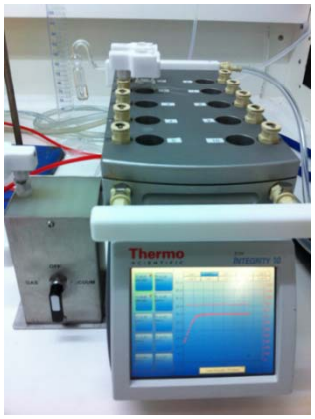
Opportunity to exploit **blocks** of experiments, rather than single one-offs...

Driving Use
New Equipment



Automated Weighing
(Quantos)

Stem Blocks / Carousels
(Same Temp)



Integrity 10:
Different Temps
All Inerted and
Condensing

Tube Size:
10ml or 2ml (above)

4 x 250 ml

Amigo and SK233
Automated Sampling
Automated Additions

Design of Experiment – Conclusions
Benefits

- **Structured**
  Enforced through planning
- **Efficient**
  Each experiment gives information on every factor.
  Recycling of results...
- **Interactions**
  See how the effect of one parameter depends on others
- **Information on Robustness**
  Will the process work on scale?
- **Spans a Variety of Conditions**
  Which can sometimes throw up surprises!
- **Confidence**
  All the above lead to greater confidence in conclusions

This approach helps to optimise experimental development but still leaves significant uncertainty in arriving at a successful working process.
A high degree of scientific thought and input is still required.

Process Chemistry Technology Transfer

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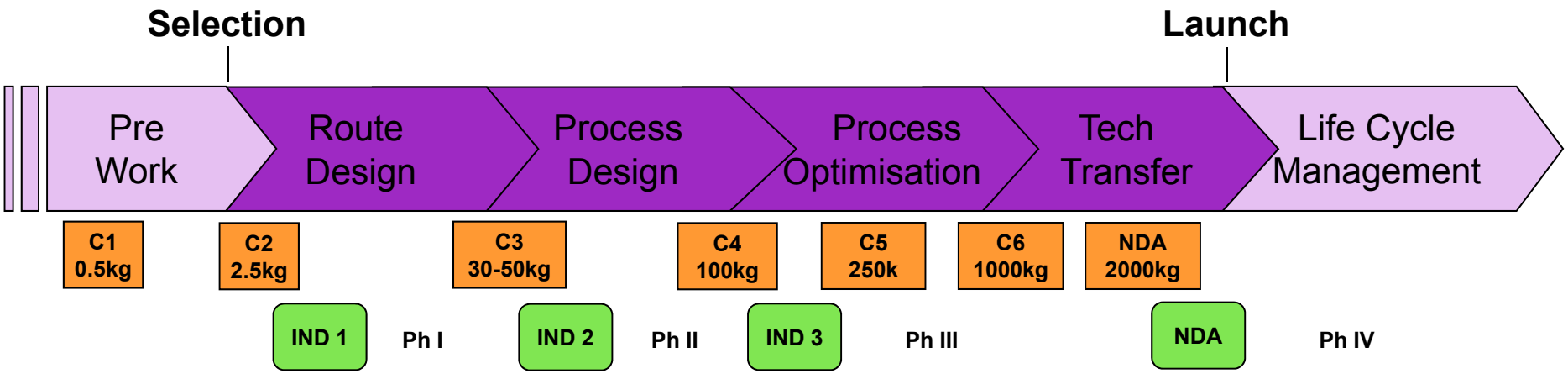
Process Development Overview



Technology Transfer
Definitions

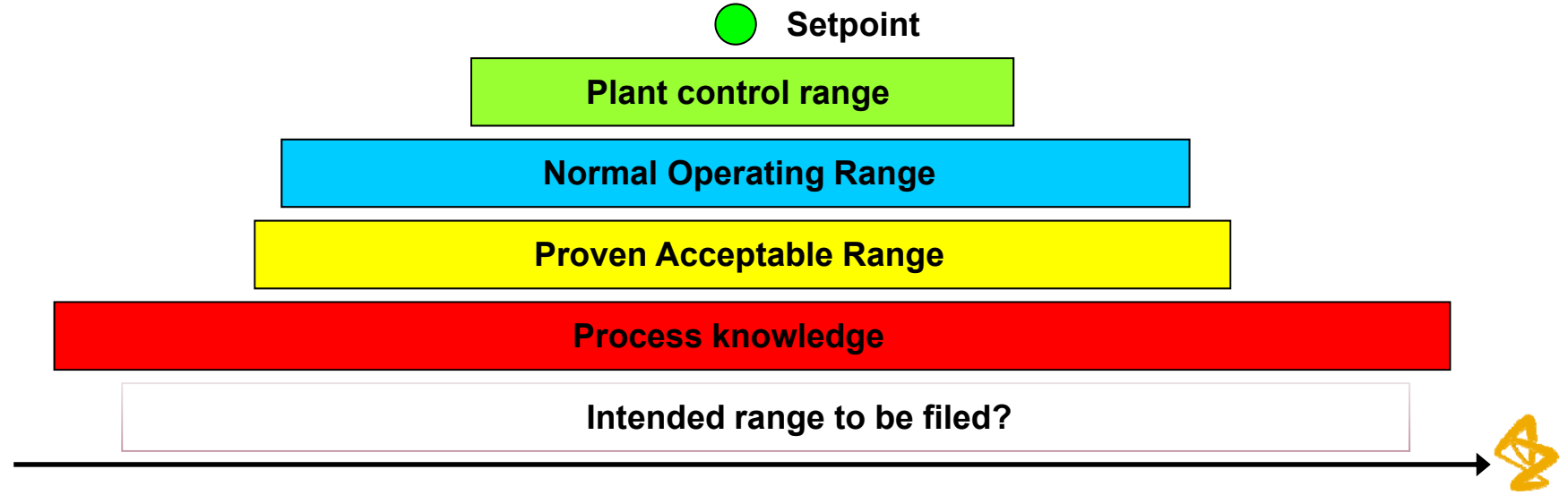
- Technology Transfer
  - Transfer of processes to site for long-term manufacturing
  - Establishment then Validation
- Establishment
  - Demonstration that processes work on long-term manufacturing plant
- Validation
  - Demonstration of reproducibility on long-term manufacturing plant

Technology Transfer
Establishment and Validation

- Information transferred to commercial site:
  - Overall synthetic route
  - Process descriptions
  - Process Ranges & Rationale documents
  - In-process analytical methods
  - Equipment cleaning processes
  - Plant requirements
  - Packaging & transport requirements
  - Sampling plans
  - Specifications
  - QC methods for raw materials, intermediates, drug substance and cleaning
  - Stability methods for the drug substance

Technology Transfer
Set Ranges

- Ranges must be within the process capabilities
- Ranges must be wide enough to cover plant, analytical instrument and procedural capabilities i.e. plant control range of the supplier
  - Knowledge of suppliers limitations
- Differences in terminology and definitions
- Limits set so they give the correct response in the suppliers quality system
- Ranges should allow for process optimization/improvement as much as possible



Technology Transfer
Establishment

- Operating the process for the first batch(es) at the commercial manufacturing facility.
- Done prior to Validation
- Requires an Establishment Plan & Report
  - Acceptance criteria
- After this stage, the process is fixed ready for validation

Technology Transfer
Validation

AZ Definition:
Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

ICH Definition:
The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specification and quality attributes.

FDA Definition of Process Validation:
The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

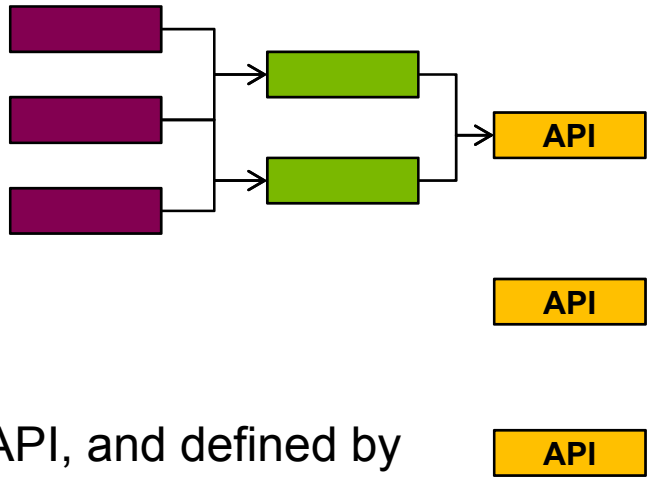
AZ Process Validation = FDA Process Qualification

Technology Transfer
Validation

What are we trying to achieve?

- To demonstrate process robustness for commercial manufacture, & show we are in control

- by proving the CMO can manufacture
  - (at least) 3 consecutive batches
  - with the intended process
  - at the commercial facility
  - at the commercial scale.



- We validate the stages critical to the quality of the API, and defined by the RSM strategy.

Technology Transfer
Validation Success Criteria

Part of the Validation Plan
Requires Critical Parameters and Critical Activities to have been identified

Typical success criteria include:

- Validation batches all to pass specification
- All Critical Parameters to be within the parameter ranges and all Critical Activities to be carried out
- All critical in-process controls to be within specified limits
- Homogeneity – Beginning, middle, end and composite samples all to pass specification, and all to pass in-process test for drying
- No Major Deviations (process related) which could impact the quality
- Yield