How to make the best out of Process R&D

What Exactly Does PR&D Do?

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The Role Of Chemical Development

- To discover and develop robust, economic manufacturing processes for Candidate Drugs (CDs)
- To provide supplies of Active Pharmaceutical ingredient (API)to fund development
- To Transfer those processes to commercial manufacture
- To provide CMC documentation to satisfy external regulatory authorities.

GPR&D Project Operating Model

Develop Processes

Pre-CD Work → Route Selection → Process Definition → Process Optimisation → Tech Transfer → Life Cycle Management

Detailed Process Freeze

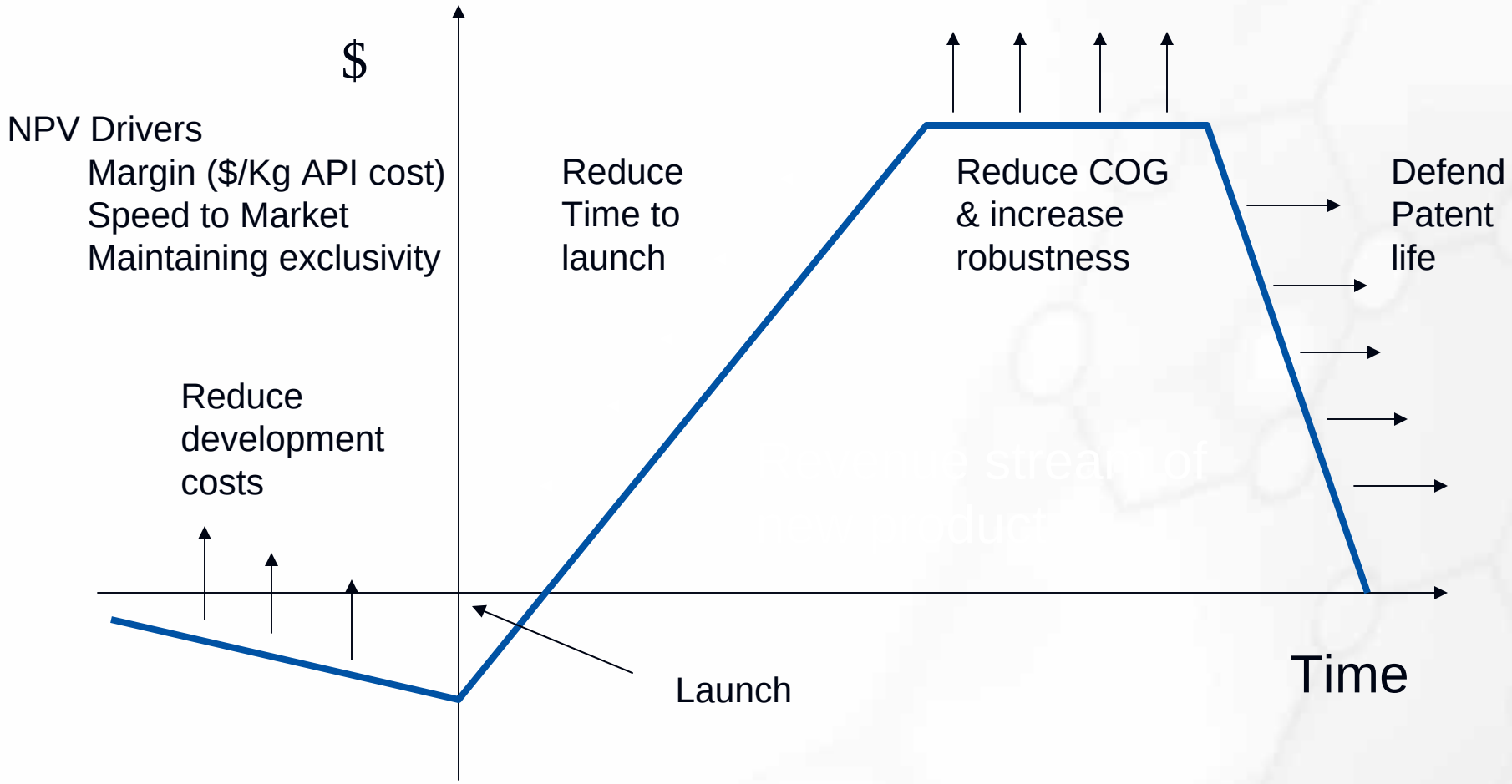
Supply of Development API

C-2 | C-3 | C-4 | C-5 | TT 1 | TT2

Generate Documentation

IND 1 | IND 2 | IND 3 | NDA

Value Chain Analysis for Chemical Development

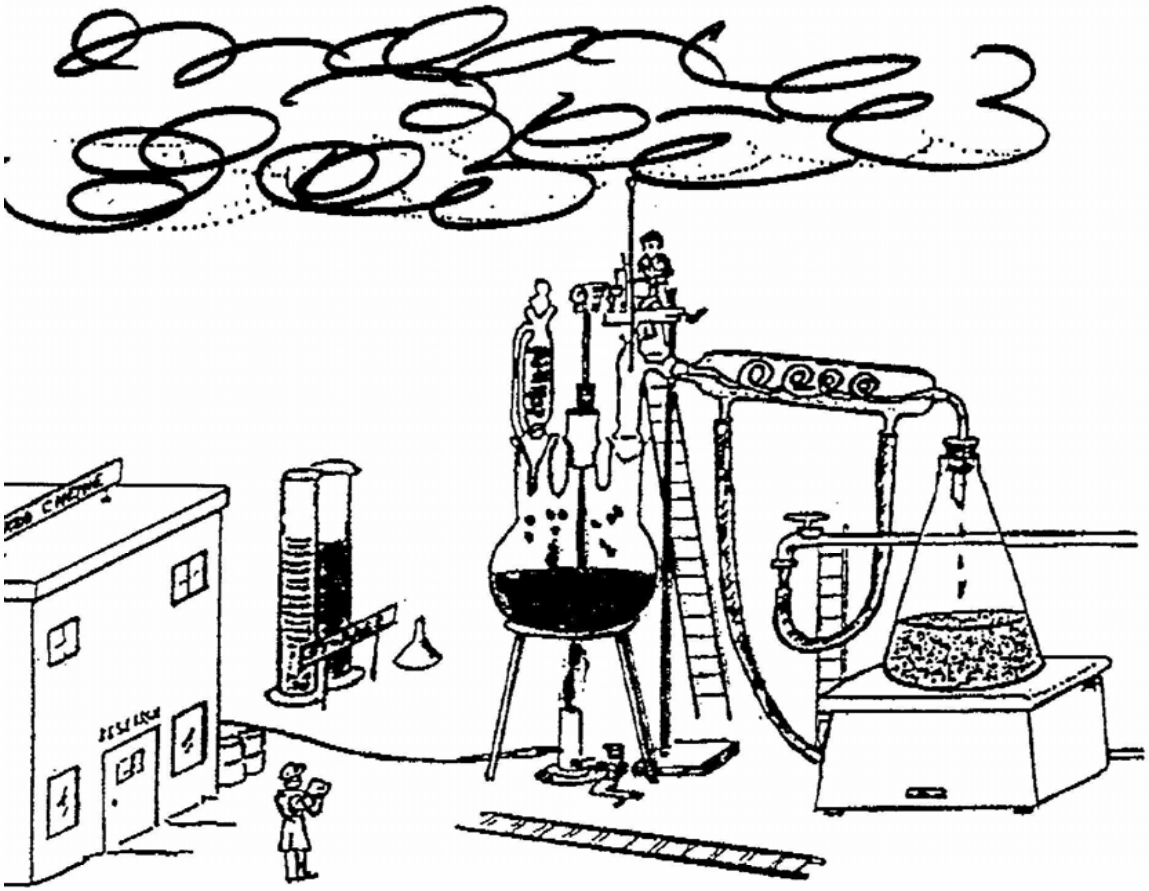


Introduction to Chemical Development

- How to get the best out of Process R&D?
  - Discovery support /Phase I supply
  - Form selection
  - Route selection
  - Scale up and optimisation
  - Validation

Discovery Support

and early Phase supply



The lab results were so good we **bypassed** process development

What's the point?

- Any interaction has to answer the following questions
  - Is this molecule any good from a CMC perspective?
  - How fast can we get it to a decision point and what's it going to cost?
- At this point in time , any penalty flags will be about the molecule, not the current manufacturing process
- We have to be able to extrapolate
- We have to understand the scientific objectives of the overall project

The molecule

- Is the molecule's structure consistent with the scientific and commercial objectives of the project?
- Two main drivers
  - Cost of goods (CoG)
  - Stability and Bioavailability of the physical form
    - Toxicology and PGIs sometime raise issues
- Are there any other show stoppers like intellectual property for example?
- Net Present Value of project ?

Cost of Goods

- Very hard to be definitive on this, so it's seldom a show stopper at the initial stages, although it kills between 5 - 10% of compounds in the long term
- I've only seen two drug candidates killed at nomination in over 20 years
- Both were complex, large dose antibiotics doses, TID, with a target cost of $2000/Kg

Iterative Loops for Compound Design Extend into Development

Speedier LO could mean a greater number of CDs produced in absence of new knowledge unless we can speed up the API delivery. This won't reduce attrition

Hypothesis

CD Selected

External data

200-300g prep

7 day rat & dog tox

1 month tox Rat and dog

FTIM SAD

MAD

CMC development 1st GMP prep

1-3 Months

12-24 months

24-36 months

Extending this Back into Discovery

- The faster we can go around the loops, the more likely CD 2 will be invented with new knowledge
- This will improve CD quality or stop programs earlier
- Ease of synthesis represents the biggest stumbling block to doing this routinely

Speed to decision point / market

- This is a more important issue if you are dealing with a family of candidate drugs
- If that's the case ,there is real value on the scientific collaboration between Med Chem. and Chem. Dev.
- When this works well it can save months (years) and a lot of money

Key Factors that Impact Speed

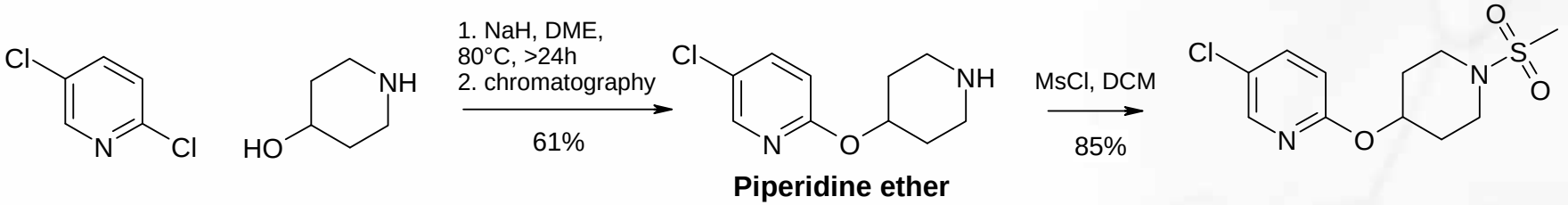
- **Process**
  - **Complexity (No of Steps)**
  - Yields
  - Dilution / throughput
  - Scalability
  - Convergent vs. divergent route of synthesis
  - Material Supply for experimentation
  - Purification strategy
    - Chromatography vs. crystallisation
    - Physical form issues

- **Plant**
  - 'hurdle'
  - Capacity
  - working hours
  - planning / scheduling / other projects

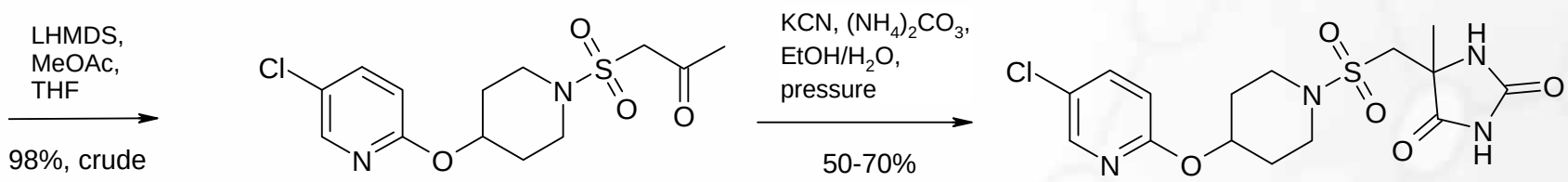
- **Project**
  - **Quantity**
  - Raw Material lead times
  - Specification target
  - Material supply from suppliers
    - Selection of tactical vs. catalogue
  - Phasing of CDs
    - Resource bulging
  - Risk taking

At least 1 of the above is going to impact your project

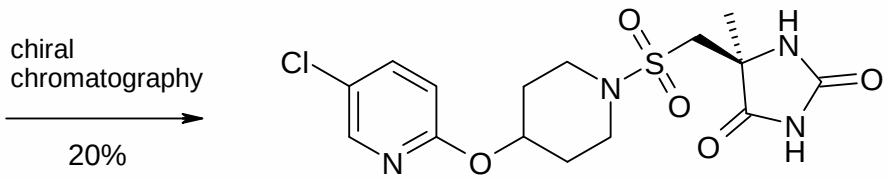
Inefficient Chemistry



Piperidine ether



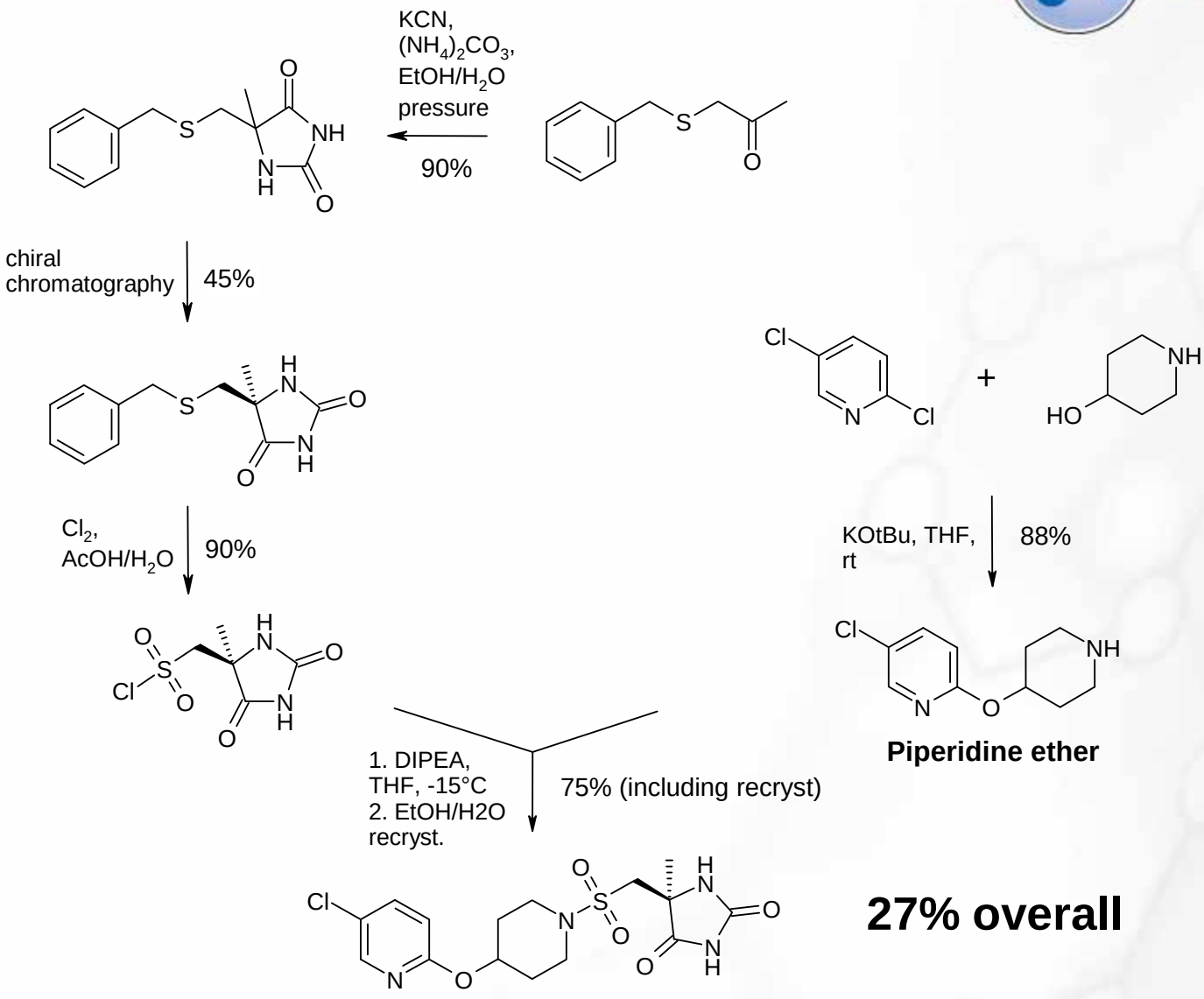
(racemate)



(S)-Piperidine hydantoin

5% overall yield

Efficient Chemistry



Outcome

- Initial lab work to demonstrate efficient chemistry took less than 2 weeks!
- Because of route improvement:
  - Discovery rapidly delivered 40g of API for initial tox
  - Chemical Development delivered 297g of API delivered in 4 week (cf 18 weeks predicted with original process)
  - Savings on 1st GMP manufacture over $700K

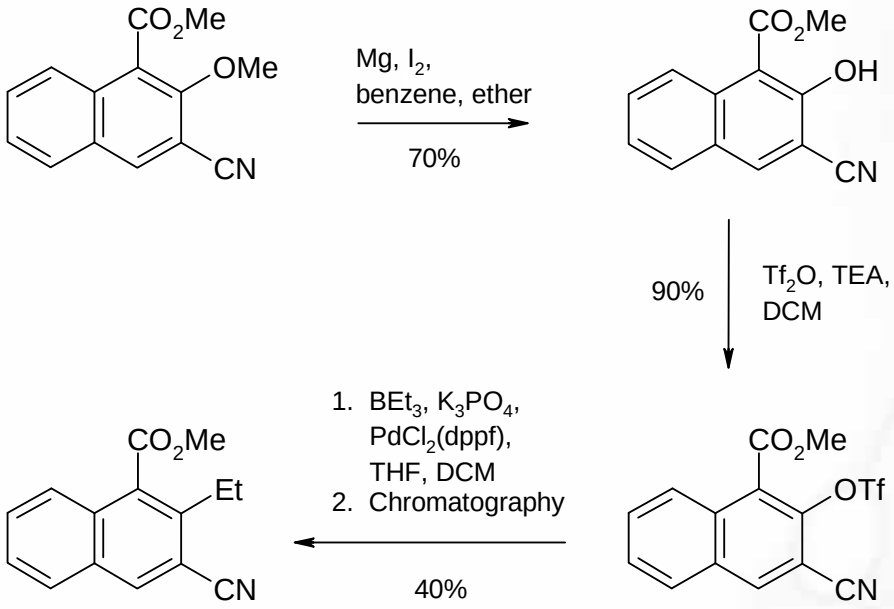
What Creates most Value? Which is Cheaper?

Route	Steps	Manufacture of 5kg in LSL.
Med. Chem. Route	**7**	**18 wks**
New Route	**4**	**6 wks**

- Medicinal Chemistry Route

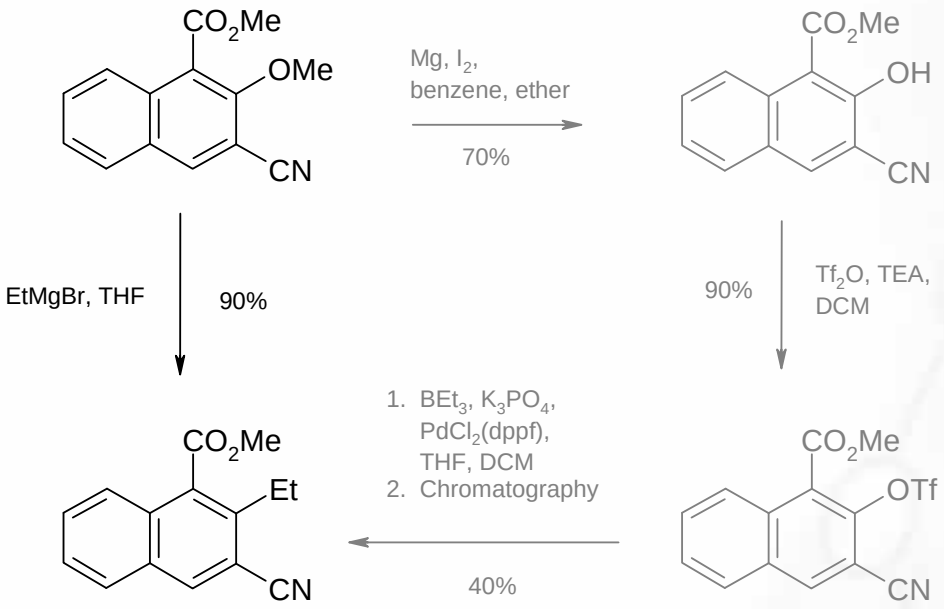
- New Route

Speeding up LO and C2 Deliveries



- Original Med Chem. synthesis used to deliver 200g of intermediate
  - Approx 2 months to manufacture in Med Chem scale-up lab
- Synthesis “problematic” for further scale-up
  - Opportunity for early investment of PR&D effort to speed-up C2 delivery

Route Change



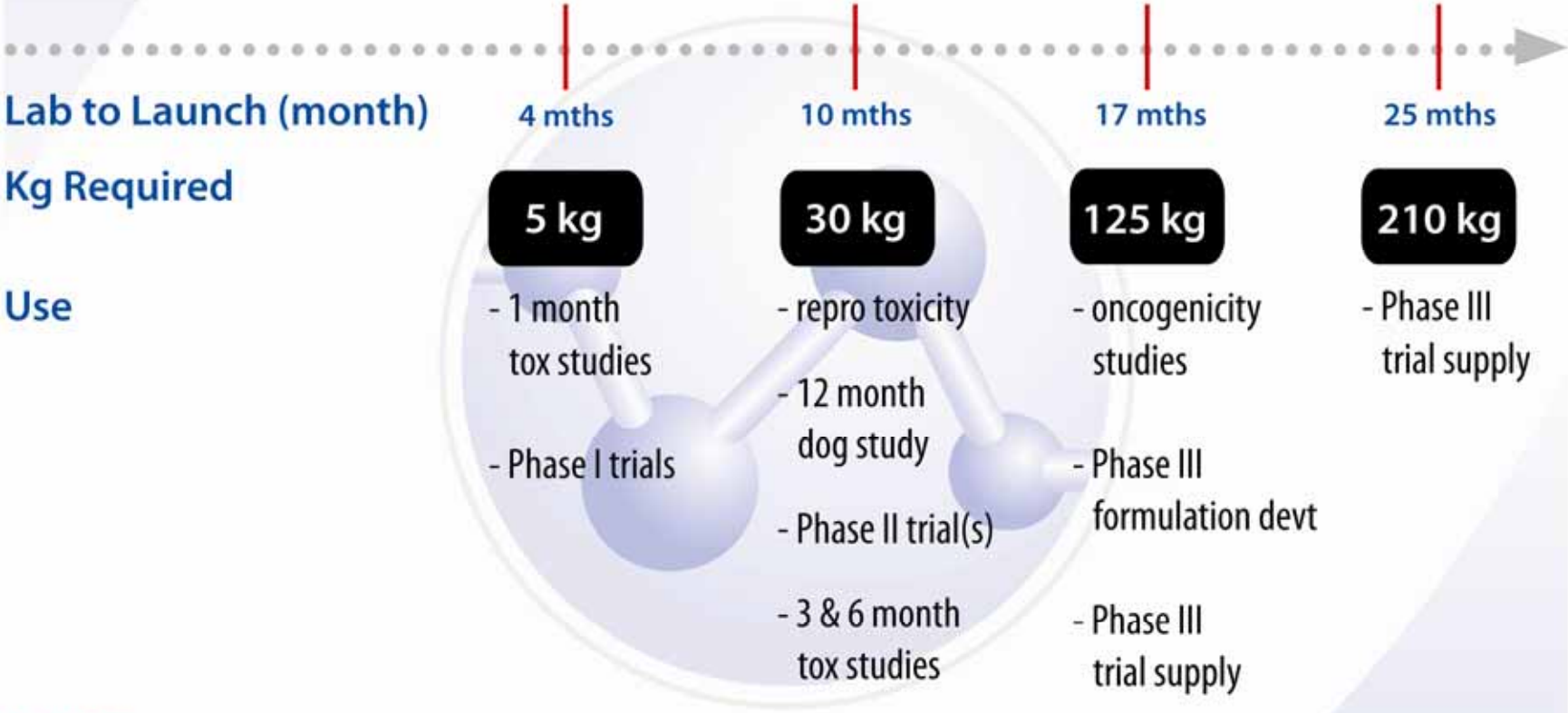
- First reaction with EtMgBr gives 90% recovery
  - <0.5% (NMR, HPLC) of nitrile and ester addition products
  - Chemistry adopted by Med Chem for further material requirements (C1)
    - Nomination occurs several months early

The Development Process

Key points

- Critical path will vary from CD to CD
- The faster the development plan and/or the more complex the molecule, the longer API supply will be on the critical path

Campaigns vs. Time, as Fast as it Can Go
Lab to Launch in 6 years



Key points

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Key things to keep in mind

- Need to always think of the bigger picture
  - Can act tactically but always try and think long term
  - CMC needs to be running ahead of development
- Small amounts of up front Chemical Development investment early on can pay huge dividends later on even if the candidate drug (CD) doesn't make it all the way to market
- Losing even 1-2 years of exclusivity can reduce NPV of a product by 30%
- So speed to market or key decision point needs to be considered from day one, not once you've got to Proof on Concept

Solid Form

Selecting the final solid form

- Can be a contentious area but shouldn't be
  - Chem. Dev. shouldn't supply what Formulation can't use
  - Formulation shouldn't select a form that Chem. Dev. can't make
- Early supply of representative material can be an issue
- Having made the selection if the science is telling us to change, we should change
- However, the link between the API production process and API performance is still vague

Solid Form

- When do you need the final form?
  - Depends who is carrying the greatest risk (on average mid phase 2 is probably OK)
- When do you know you have it ?
- What are the risks of the form changing?
- Science still not fully understood but risk increases as one moves from BCS class I to BSC class IV

Biopharmaceutical Classification System for Oral Drugs

- Class I High solubility, High permeability
- Class II Low solubility, High permeability
- Class III High solubility, Low permeability
- Class IV Low solubility , Low permeability

Route Selection

Final Route Selection

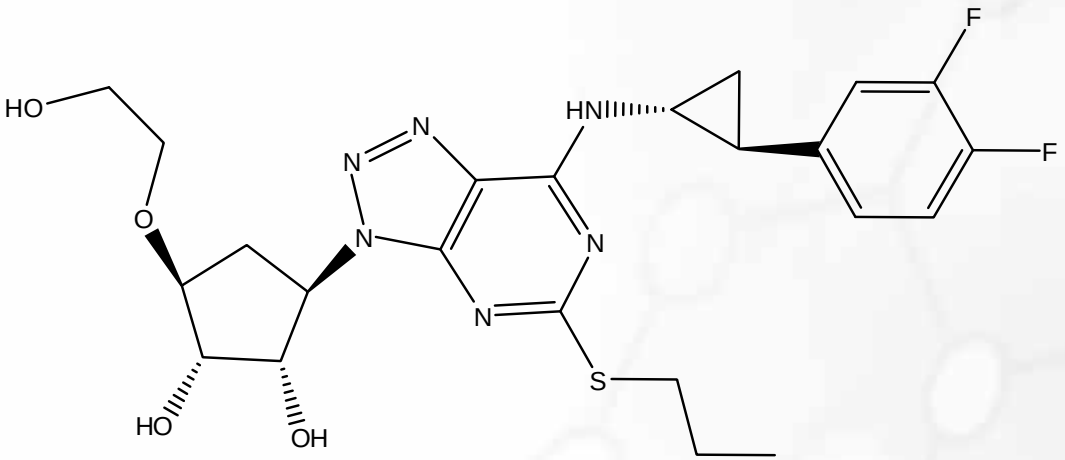
- Best route may not always be the cheapest
- Many other criteria need to be met

For full article see Butters et al Chem. Rev,(2006),3002-3027.

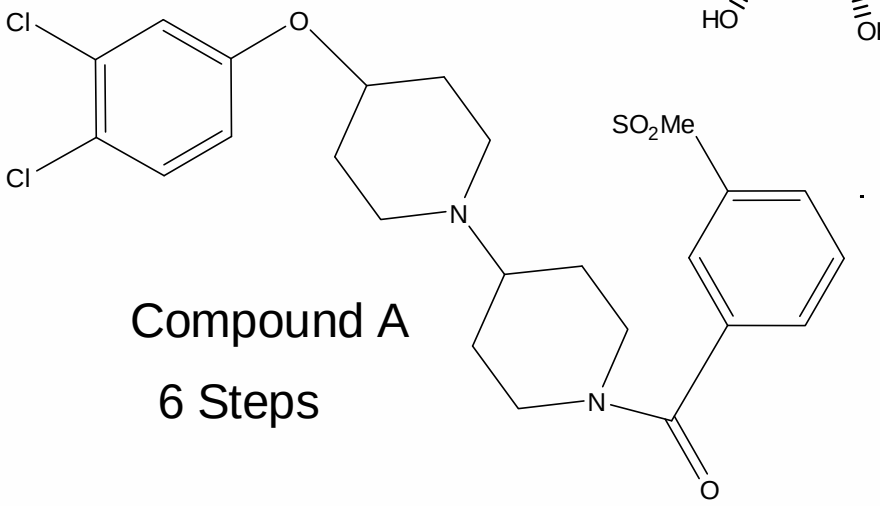
CD Complexity

- What is Chemical Developments' unit of capacity?
  - It's number of chemical stages, **not numbers of Drug Candidates**
- What is the most time-consuming aspect of Chemical Development?
  - Experimental lab and plant scale up, due to the fact that we are still very poor at making predictions (is this likely to change in the next 10 years?)

CD Complexity



Brilinta
24 steps



Compound A
6 Steps

Consequences of Step Count

1. **Delivery**
   - For Compound A (5kg) delivered at candidate nomination
   - For Brilinta, (0.85kg) delivered 6 months after candidate nomination

2. **Synthesis Freeze:**
   - Final Route in place in time for 28 day dog tox for Compound A
   - For Brilinta, Final Route in place 22 months after candidate nomination

3. **Synthesis Freeze:**
   - 2 Chemistry FTEs needed for Compound A to reach synthesis freeze
   - 24 Chemistry FTEs needed for Brilinta (12X increase in resource)

You have to select the best molecule you have, but **Step Count and API Amounts** will have a big impact on speed
.The relationship between steps and FTEs isn't linear

However, **Route Development** can often alter the delivery situation quickly and dramatically

Advantages of Efficient Chemistry

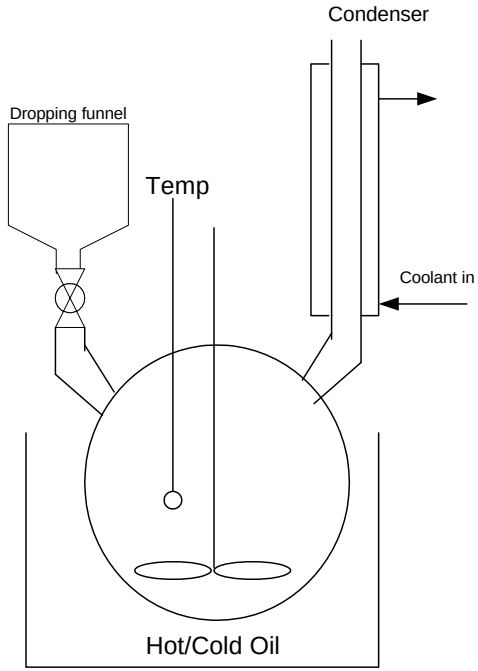
- Cost reduction
  - Lower $/Kg price
  - Campaign avoidance
- Faster to NDA
  - As development times speed up, API is on the critical path for less time
  - More activities can be done in parallel
- Overall, you have more flexibility
- This also holds true for discovery

Scale up and Optimisation

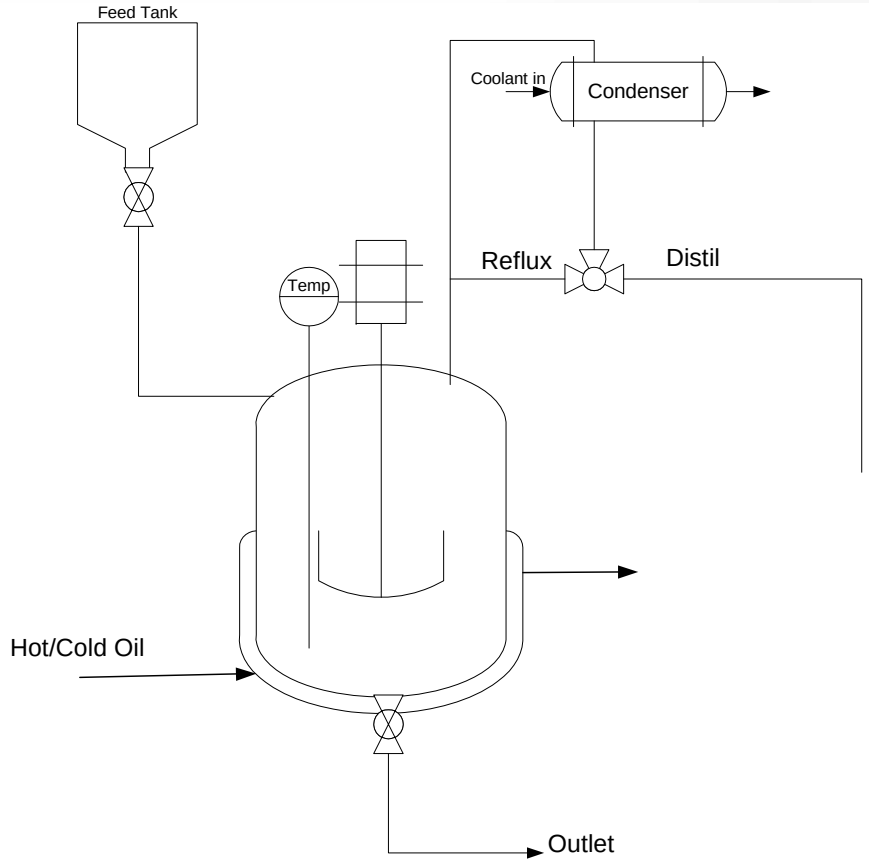
Lab to …….

…… Plant

Lab to plant



Laboratory



Plant

Kinetics/Process Hazards

- The main difference between lab and plant is that things take longer
- In some cases much longer !!!
- It’s not just addition, heat up and cool down times that change
- Work up and isolation are just as important as making the right bonds

Mixing effects

- Mixing effects are the most cause of scale up difficulties
- Timescales for bulk mixing
  - Lab, 1 Litre - 2-3 seconds
  - Plant,10 m^3 - 20 seconds
  - Large Plant, 50 m^3 - 30-60 seconds

Optimistion

- The Chemistry
  - Reagents and conditions
  - Solvents and volumes
  - Reaction times and temperatures
  - Work up and isolation, what stages?
- The Process
  - Type of vessel, continuous, batch
  - Agitation
  - Filtration, phase separations
  - Morphology of intermediates

Analytical Methodology

- Goes hand in hand with chemistry
- Also has to work closely with tox. and regulatory
- Methods are a function of the route of synthesis
- As we get towards the end we can often have more analysts on a project than chemists
- A major difference between Chemical Development and Medicinal Chemistry

Validation

Validation / Critical Process Parameters

- What aspects of the process are critical for assuring API is made to the appropriate quality ?
- What are their ranges of acceptability ?
- Are there nearby edges of failure ?
- Where is the control of quality coming from?, the chemistry ?, plant/equipment capability ?
- The better you understand the process the easier the above will be

Validation/ Critical Process Parameters

- Once you think the process is sufficiently well understood it needs to be demonstrated on the plant at an appropriate scale
- A minimum of three consecutive, successful batches have to be carried out, producing API of an acceptable quality
- Once you have approval , then the story is only just beginning

Questions?