Green Chemistry
Obstacle or Opportunity ?

High level drivers

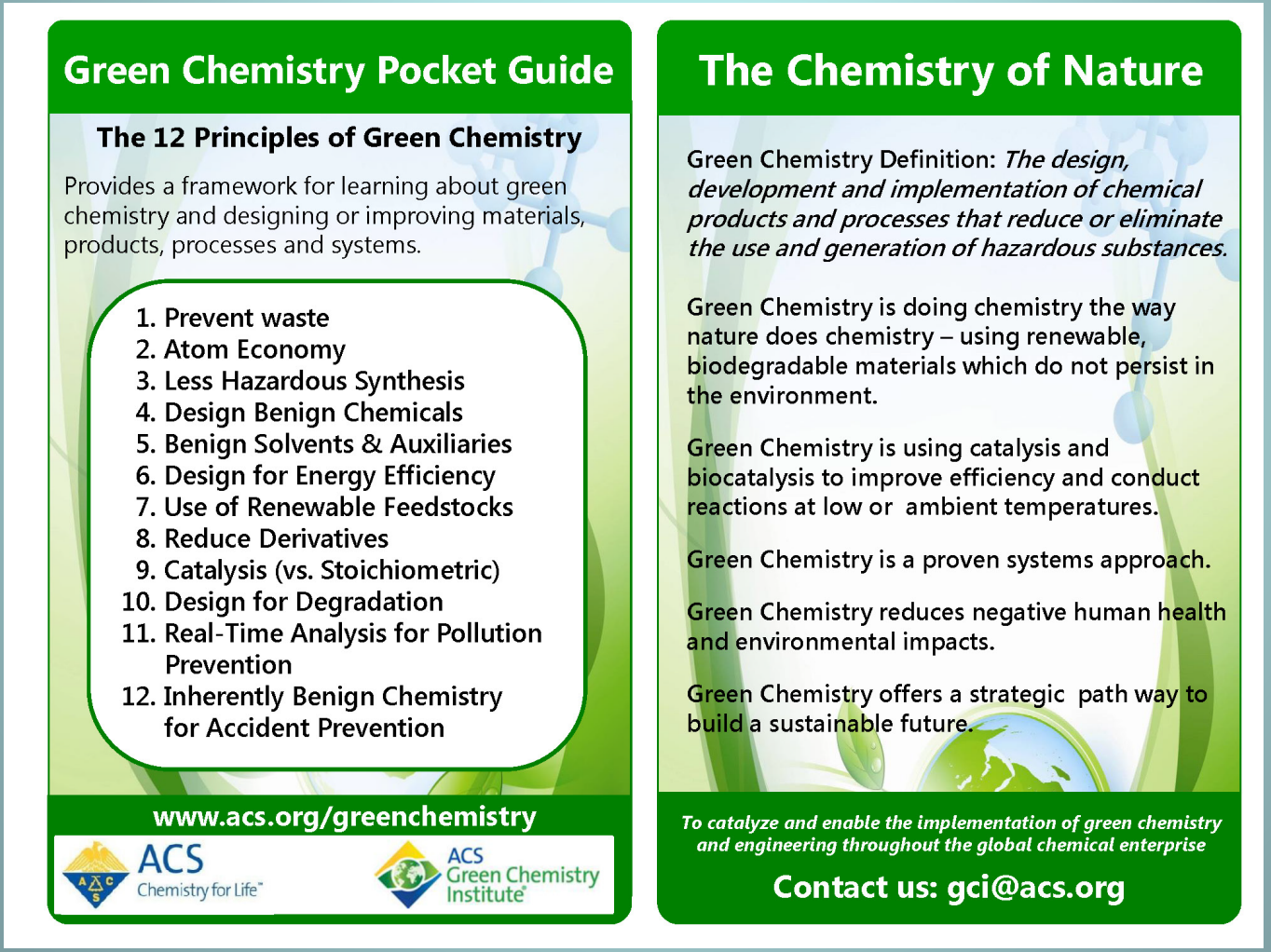
- Environmental harm
  - Energy use
  - Waste reduction
  - Water usage
  - Harmful chemicals
  - Natural resource depletion
  - Persistent chemicals
- Legislation (EU directives), REACH
- Health authorities (Sweden, UK?)
- Good social citizenship

Generally

- For small molecules >70% of R&Ds footprint is accounted for by API manufacture
- The environmental impact of our API processes are driven by route selection (Step Count)
- But this isn’t the only Criteria

Definitions

- UN sustainability



Green Chemistry Pocket Guide

The 12 Principles of Green Chemistry

Provides a framework for learning about green chemistry and designing or improving materials, products, processes and systems.

1. Prevent waste
2. Atom Economy
3. Less Hazardous Synthesis
4. Design Benign Chemicals
5. Benign Solvents & Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis (vs. Stoichiometric)
10. Design for Degradation
11. Real-Time Analysis for Pollution Prevention
12. Inherently Benign Chemistry for Accident Prevention

www.acs.org/greenchemistry

ACS Chemistry for Life™

ACS Green Chemistry Institute®

The Chemistry of Nature

Green Chemistry Definition: *The design, development and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.*

Green Chemistry is doing chemistry the way nature does chemistry – using renewable, biodegradable materials which do not persist in the environment.

Green Chemistry is using catalysis and biocatalysis to improve efficiency and conduct reactions at low or ambient temperatures.

Green Chemistry is a proven systems approach.

Green Chemistry reduces negative human health and environmental impacts.

Green Chemistry offers a strategic path way to build a sustainable future.

To catalyze and enable the implementation of green chemistry and engineering throughout the global chemical enterprise

Contact us: gci@acs.org

Outline

- What does this mean for R&D and Operations?
- Implications for academia?
- What does this mean for supply chain?
- What does this mean for generics?
- What should this mean for regulators?

Relative Harm

- Industry vs Environmental Performance

Sector	Tons per Annum Product	E Factor (Kg waste/Kg
Oil and Gas	$10^6 – 10^8$	<0.1
Bulk Chemicals	$10^4 – 10^6$	1-5
Fine Chemicals	10^2 -10^4	5-50
Pharmaceuticals	10-10^3	25- > 100

- Pharma waste performance looks poor but that's for good reasons

Implications for PR&D

- Do we need more detailed environmental assessments?
- How far back do you go?
- If timelines are to remain the same ..
  - Increases the amount of work required per compound? (resource, external vs Internal)?
  - Post approval change could become the norm for complex APIs?
- Better predictive tools (comp Chem)
- New technologies ?
- Increase use of Bio-transformations?

Chemical Development

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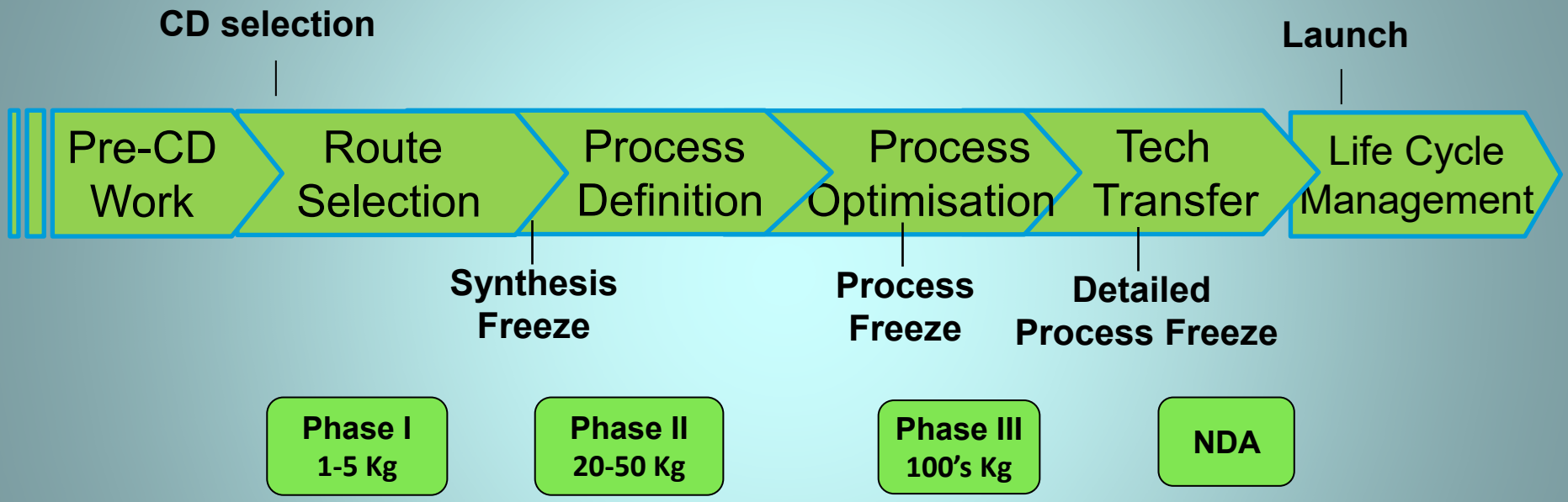
Phases of Chemical Development



Final Route Selection

- Best route may not always be the cheapest

- Many other criteria need to be met
- Time is limited

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

Green Chemistry vs SELECT

- In general terms, the shorter, more convergent, higher yielding the overall synthesis, the more likely Economic, Environmental, Throughput improvements will be made
- Also, if done rapidly should increase resource available to better optimise the final process
- Route selection is similar to candidate selection
- Safety and Legal are a given,..
- So that leaves Control

Assessment

- PMI. (kg waste/Kg of API) See Sheldon *et al*. Green Chem, 2017,**19**,18-43
- iGAL. Roshanger *et al.* Green Chem,2018, **20**,2206-2211
- These are a good start but retrospective
- However, work by AZ gives some hope of prediction. Howells *et al.* Green Chemistry. 2023,**25**,2243-2256

Route Criteria

- Agencies are predominately interested in control (impurity management)
- Not cost
- Not process safety
- Although an environmental assessment is carried out, it's not currently viewed as the key driver
- Should this change?

Optimisation

- Example: Below are the measured environmental impacts of 1 m2 of a wood sheet cladding product made in Norway:

- Global warming potential (kg CO2 equivalent): 0.44 kg
- Ozone layer depletion potential (kg R11 equivalent): 1.1 kg
- Acidification potential (kg SO2 equivalent): 0.005 kg
- Eutrophication potential (kg PO4 equivalent): 0.001 kg
- Photochemical ozone creation potential (kg C2H4 equivalent): 0.0004 kg
- How close are we in Pharma? How close could we get?

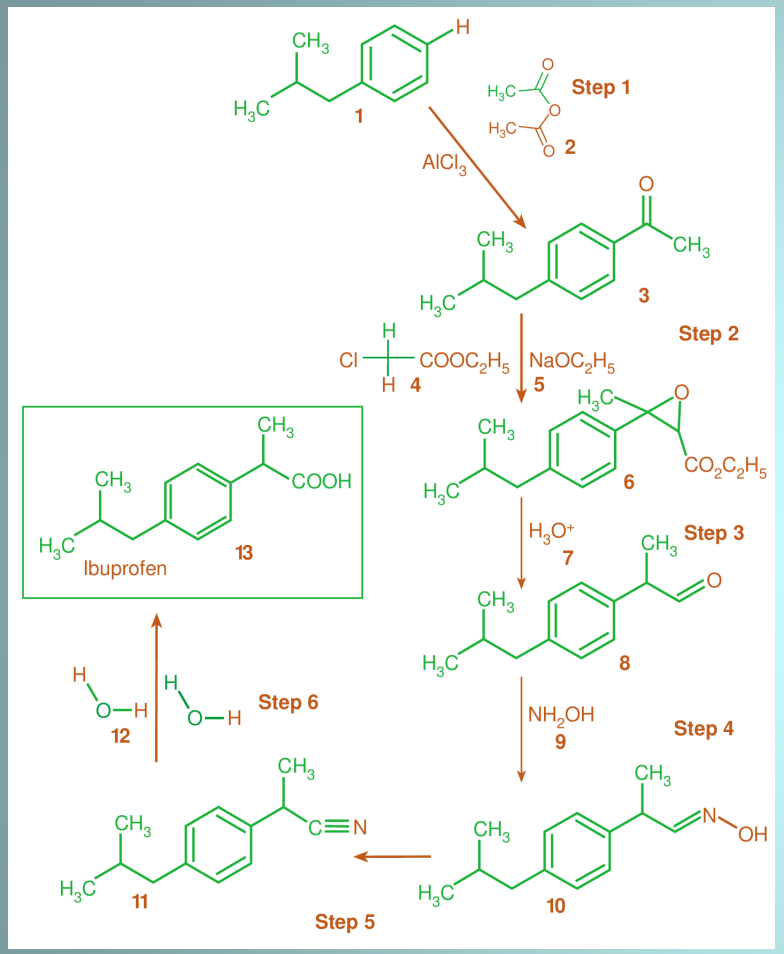
Optimisation

- Focus predominately on process robustness/reproducibility
- Key activity is solvent selection. See Dorazio *et al,* Org.Process. Res.Dev. 2016,20, 260-273
- Solvent accounts for around 70% of waste
- Solvent recovery is a key issue

Post approval Change

- If we don’t have enough time during the pre-approval stage, then this the logical approach
- How far do we take it ?
- This also has implications for operations?

ibuprophen



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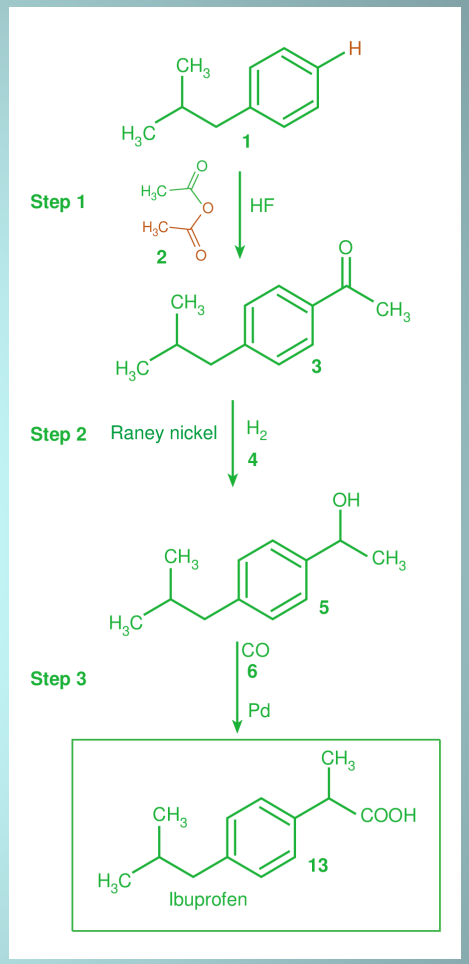

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http://www.scheikundeinbedrijf.nl/content/Modules/Modulenaam/Files/case.pdf

Post approval change

- So, we done this for ibuprophen…..
- Can we do this for other older medicines?
- Dutch Gvt proposal
  - https://www.agro-chemistry.com/news/greening-chemistry-gets-broad-support-from-political-parties-in-the-netherlands/

Regulatory

- API risk should be viewed relatively e.g vs Food industry in the area of impurity management
- Current focus on low level impurities make us nervous about route change
- PGIs, N-Nitrosamines
  - Soak up vast amounts of resource with little or no patient safety benefit
  - Make companies wary of recycling solvents even though this is the biggest source of waste
- Tightening of specifications post approval

- If we are really serious about green chemistry, we need green regulations
- Make post approval improvements the norm or even mandatory ?

Regulatory

- Progress has been made
  - BACPAC
  - QbD
  - ICH Q12
- But we need to encourage this as much as we can

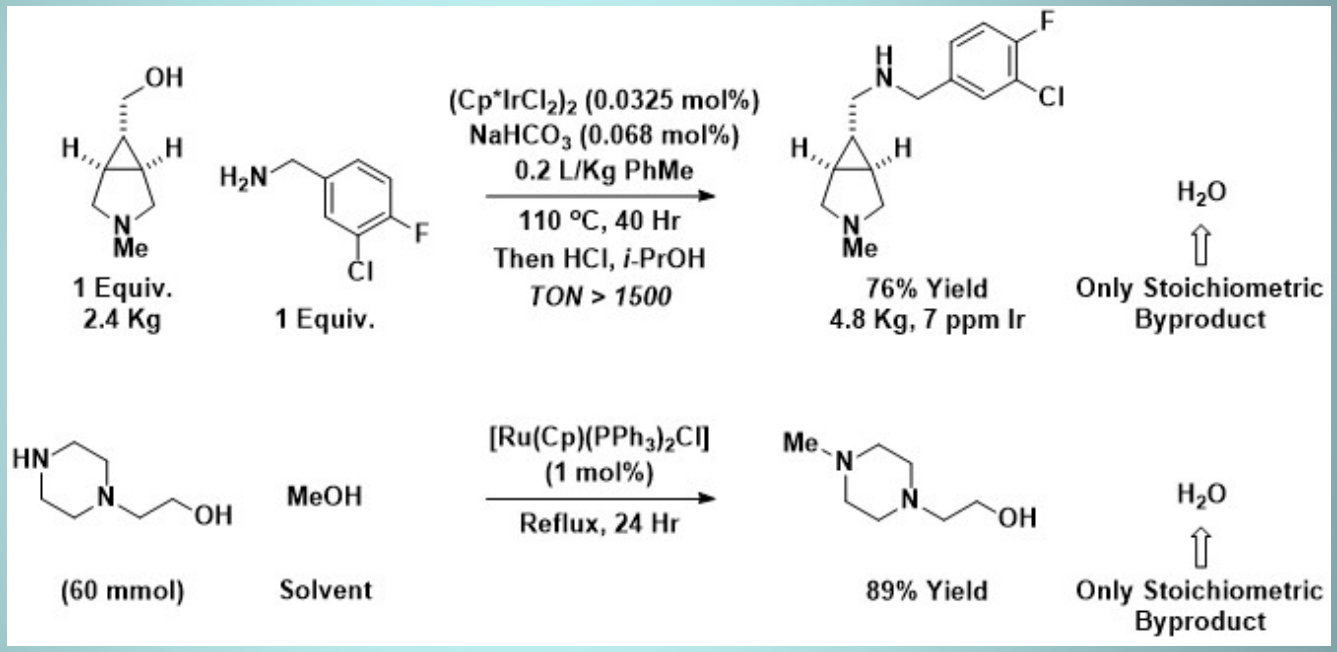
Academia

- Are we solving real problems?
- Asymmetric methods (chem 21 substrates)
- What about work up?
- Solvent recovery. Green Chem., 2012, 14, 2197
- Waste treatment (API in the environment)

Examples

- Catalytic reduction
- C-C Bond formation??
- Bio-catalysis (cascade reactions)

Good methodology



Williams *et al* Chem Commun, 2004, 90-91

Supply Chain

- Greater focus on Asia (especially RMs)
- This increasingly going to generate issues on capability and capacity
- CRO margins haven’t increased in almost 30 years

Generics

- At some stage the focus is going to move from Pharma to the generic sector who have a much greater footprint
- The solution is the same
  - Shorter more effective API processes (Step count)
- But margins are shrinking
- Capability ? (visibility)

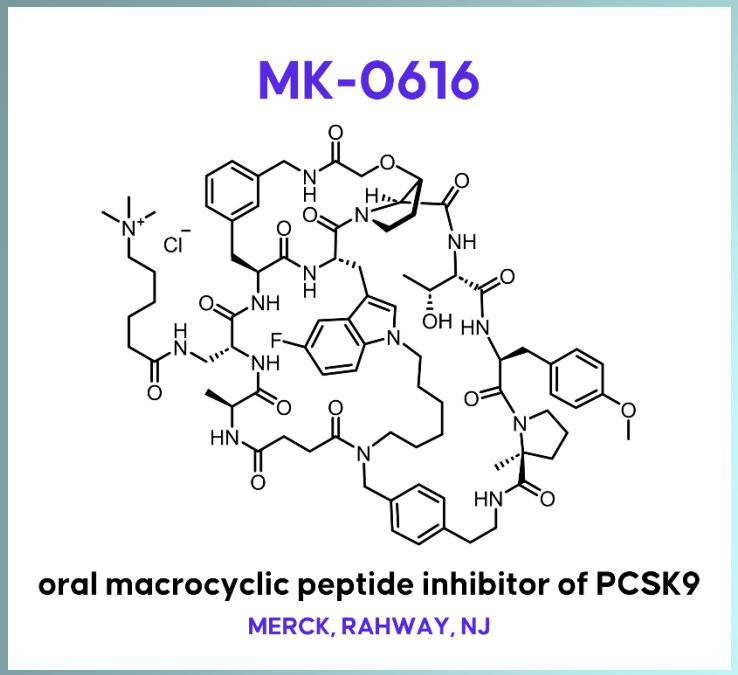
Additional issues

- Scientific Collaboration
- How do we increase publication, especially small and generic companies and CROs?
- ACS Green Chemistry round table is a good forum but we could do more?
- Much of this is or should be precompetitive?
- J.Med.Chem vs OPR&D ?

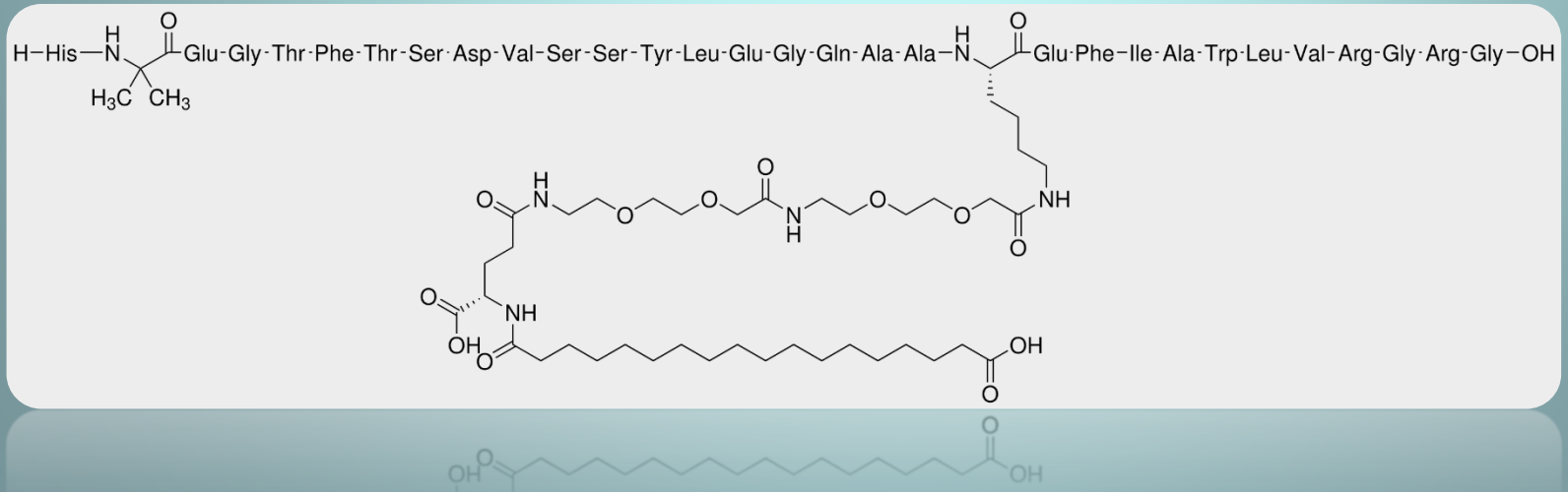
Conclusions

- We have the ability to significantly green the pharma supply chain but…
- There looks to be a disconnect between the innovator companies and the longer term (generic suppliers)
- Are the regulations up to the challenge?
- Do thye fully understand the scientific and commercial issues?
- Route selection sets the stage for everything else

Future



Is complexity increasing?



Future

- Comp chem/Automation
- E.g Univ Liverpool automation centre
- https://www.liverpool.ac.uk/cooper-group/research/digital-chemistry/
- Flow automation

Opportunity or Obstacle ?

- Anything that reduces environmental harm has to be good
- If we do this right, in theory, API supply could be cheaper, more profitable and more sustainable
- But, this has to be an opportunity !!

Thanks for listening

Happy to answer questions