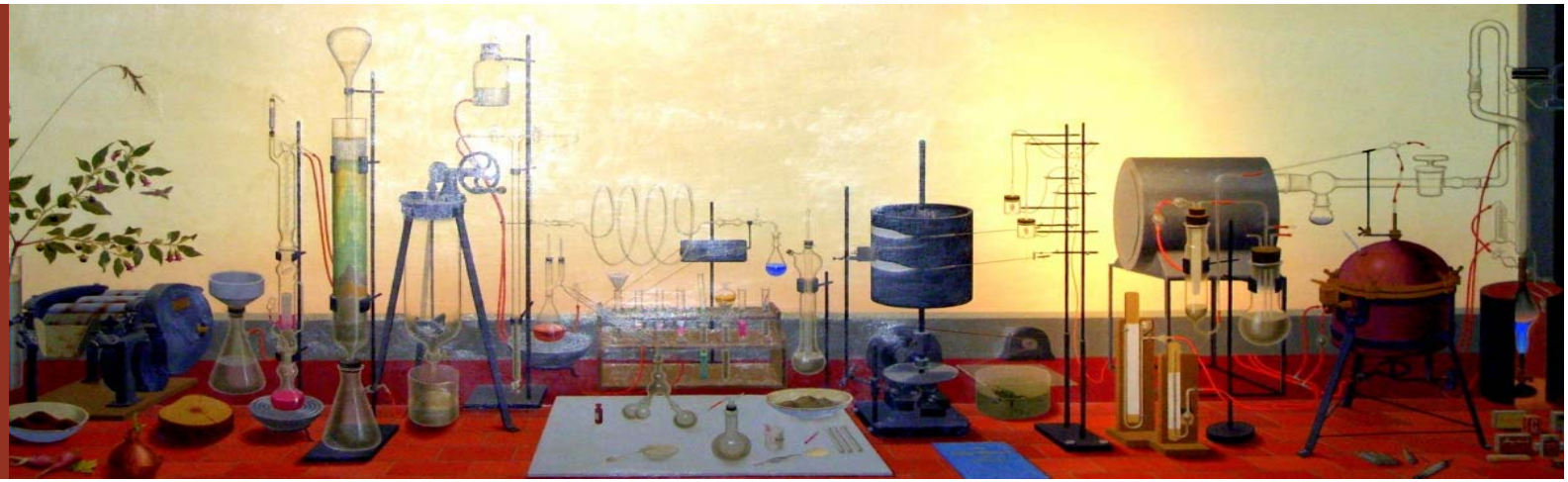

Flow Chemistry

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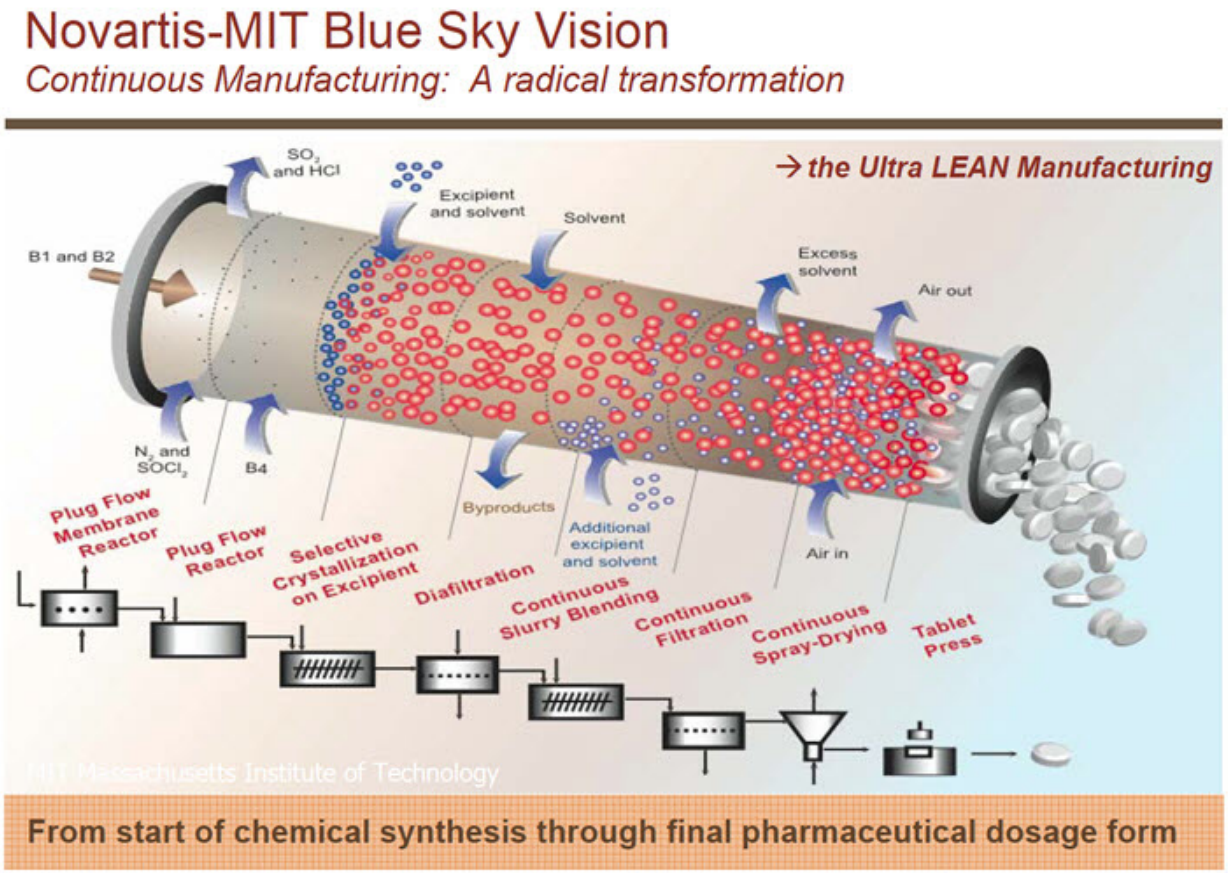
Overview

- What is flow chemistry?
- Introduction to flow platforms
- Scaling-up
- Conclusion

Flow Synthesis

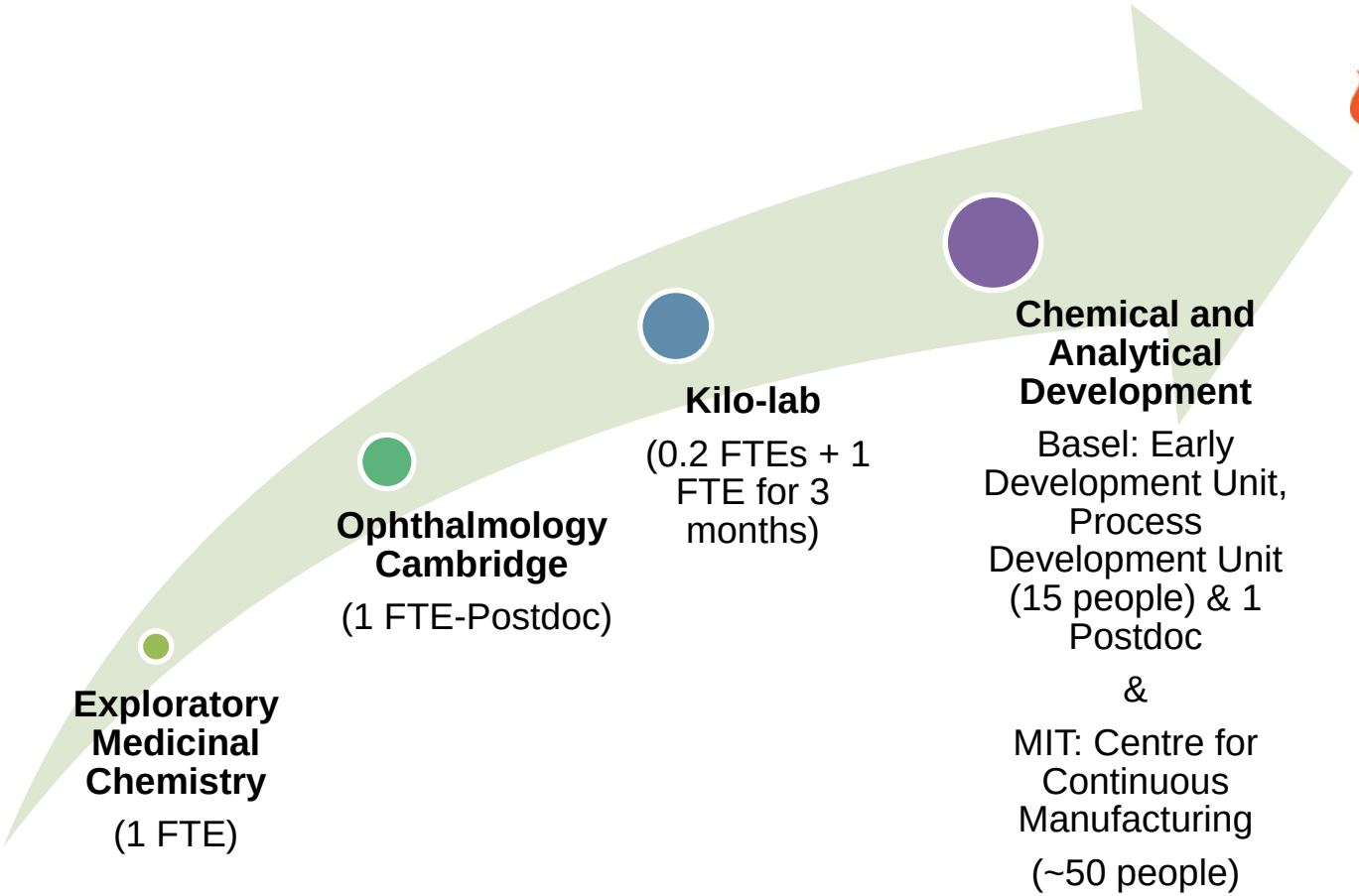
Late 2007, Novartis and MIT launched a ten-year collaboration: the Centre for Continuous Manufacturing

Aim: to replace batch process from start to finish.



Flow Chemistry within Novartis

- Collaboration within Novartis



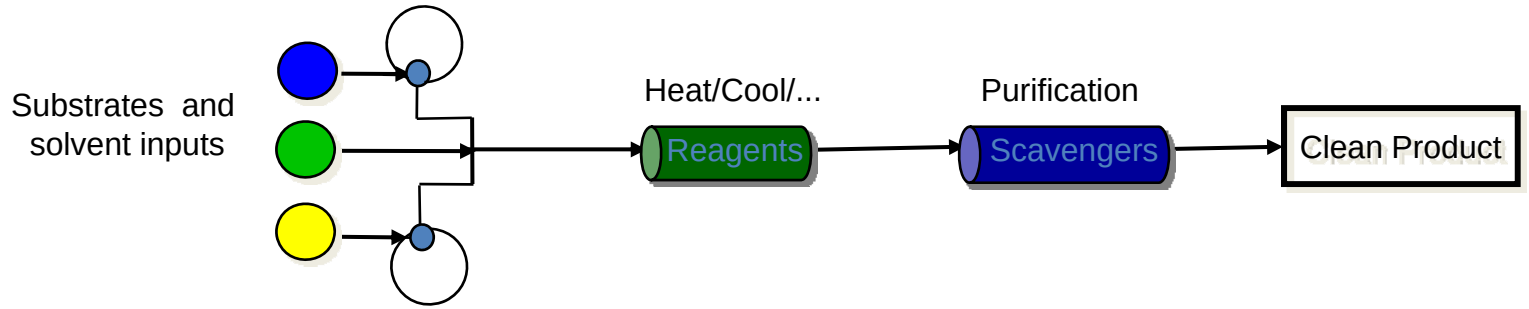
NOVARTIS

By 2015: First production step in continuous flow

Aim of the Project

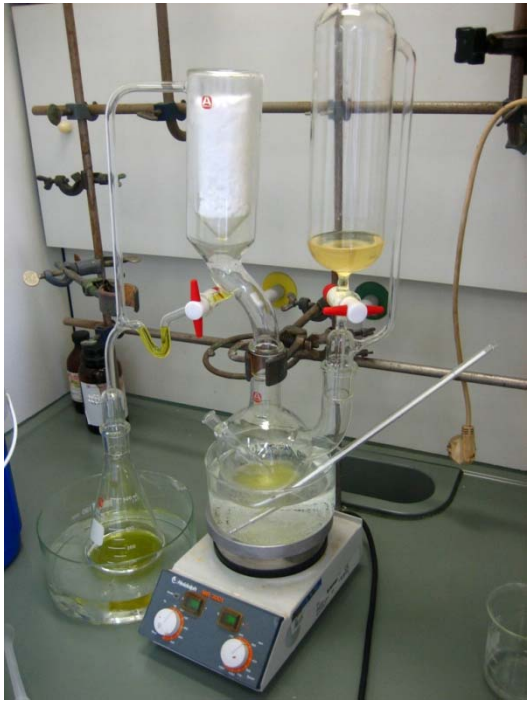
- Evaluate this new technology for Discovery Chemistry.
- Provide medicinal chemists with safe access to important reactions/scaffolds, that would normally be avoided due to their hazardous nature:
  - Fluorination (toxic, corrosive compounds).
  - Diazomethane and diazoketone chemistry (toxic, carcinogenic, volatile, explosive compounds)

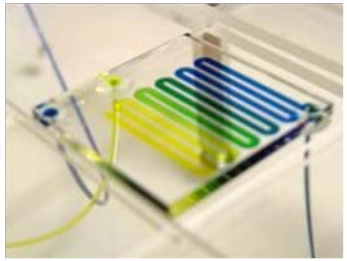
- Investigate the use of polymer-supported catalysts/reagents/scavengers to obtain pure products without resorting to off-line purification.

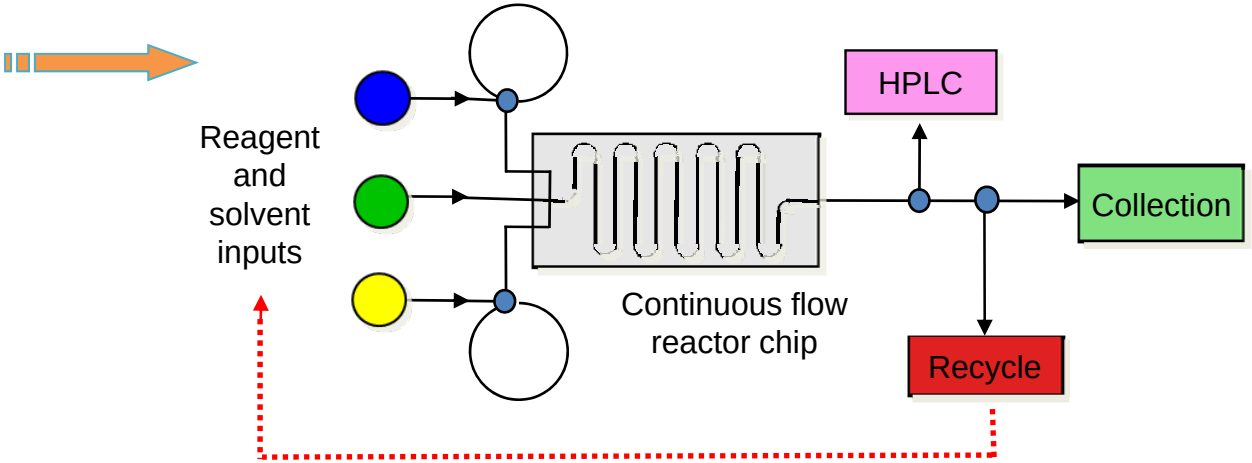


Flow Synthesis

- What is flow chemistry?





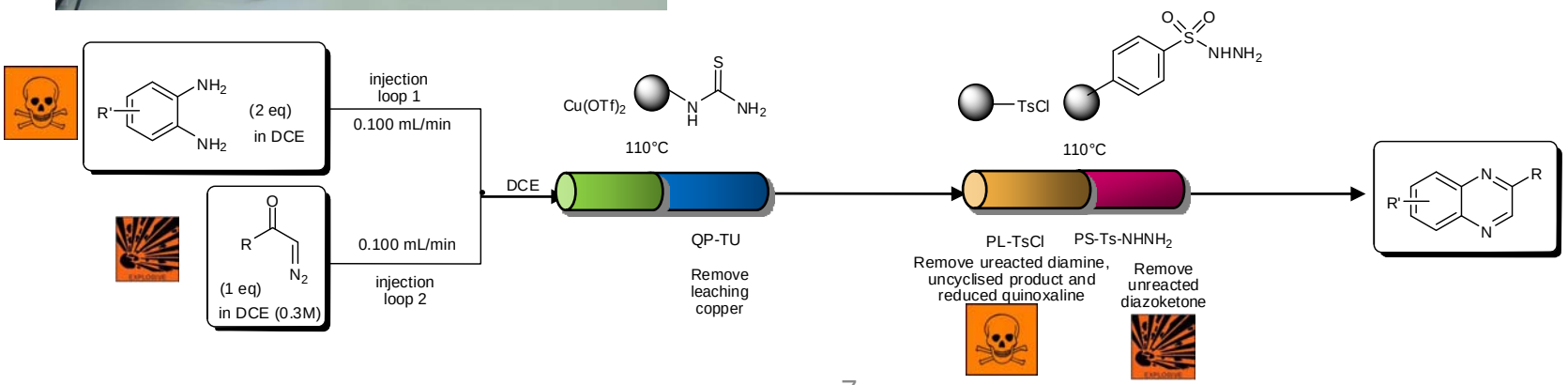


Batch

Flow

Setting up an Experiment

- **Reaction of potentially explosive diazoketone and carcinogenic, mutagenic phenylene diamine.**
- ***In-line* purification using suitable scavengers: <u>Flow:</u> reaction/purification - single process (2h) *vs*. <u>Batch</u>: reaction then extraction then purification - 3 separate steps (5h).**
- **Minimal handling of toxic material.**
- **Pure product isolated.**
- **Minimal usage of solvent: <u>Flow:</u> 24mL *vs*. <u>Batch:</u> ~100mL .**



Flow Synthesis

Research and Development Interest:

- If a reaction can be optimized on a small scale in flow, then scale-up will be rapid and low-risk.

Industrial interest:

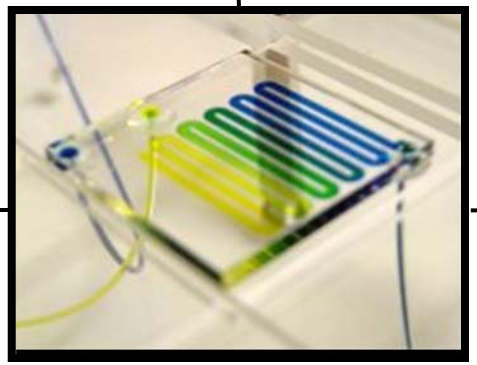
- GlaxoSmithKline: 1st continuous processing pilot plant producing active pharmaceutical ingredients on a 3.5 tons per annum scale, material cost savings 6-10%, reduction in the number of unit operations

- DSM: nitration - Naproxcinod: 150 mL reactor-13kg/hr.

Benefits of Flow Synthesis

Increased reactivity
Superheated reactions
Pressurized reactions
Use of hazardous reagents
Generation of unstable intermediates
Telescoped reaction sequences
Fast reaction optimization
Enhanced safety

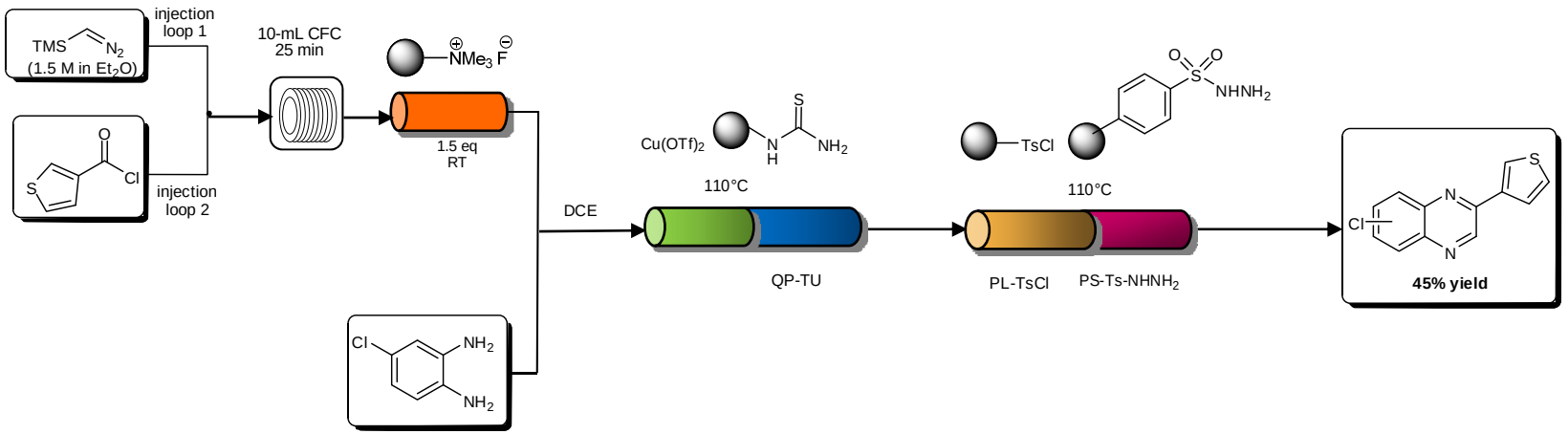
Increased efficiency
Reduction in synthesis time
Suitable for automation
Synthesis on demand



Lower solvent usage
Less waste
Recyclable components
Lean Sigma concept
24/7 operation

One-step Further: Multistep-Synthesis

No isolation of potentially explosive intermediate.

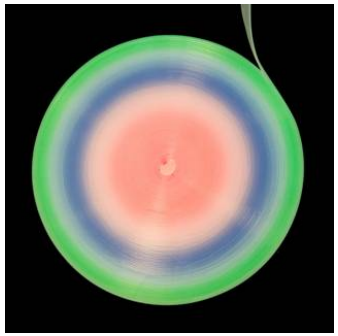


L.J. Martin, A.L. Marzinzik, S.V. Ley, I.R. Baxendale *Org. Lett.*, **2011**, *13*, 320

Scaling-up

- Issues with batch chemistry scale-up:
  - Need to re-develop syntheses (time/money consuming).

- Flow chemistry scale-up:
  - Parallel reactions: same reaction conditions as the reactions optimized on small scale.
  - Efficient mixing.
  - Efficient heat dissipation (exothermic reaction).
  - Less side-product / better selectivity.



19 pores (Diameter: 80-250µm)

OBSERVATIONS

- ***Advantages:***
  - Improved safety: **reduced personal & environmental hazard.**
  - Improved control of reaction parameters (automation, selectivity, reproducibility).
  - **Improved reactivity (*eg.* reaction time for quinoxaline 2h to 1sec).**
  - Minimized quantites of chemicals, solvents and waste products: **reduced environmental waste.**
  - Easily scaled-up: **improved efficiency, reduced cost**.
  - **Small footprint: continuous manufacturing facilities cheaper to construct (capital savings up to 50% vs. Batch).**
- ***Limitations:***
  - Handling of solids/suspensions (clogging issues).
  - Current lack of *in-line* analysis.
  - Limited literature precedents.

Future Goals

- Show impact on research & development.
- Increase collaboration/communication with KiloLab/Chemical and Analytical Development /Cambridge.
- Show economic benefit for Novartis.
- Increase awareness of flow chemistry opportunities.