Continuous Manufacturing – Framing a Future for Patients

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Small Molecule Design and Development

Eli Lilly and Company

Indianapolis, Indiana

April 9-11, 2019

4th FDA/PQRI Conference on Advancing Product Quality: Patient-Centric Product Design, Drug Development, and Manufacturing

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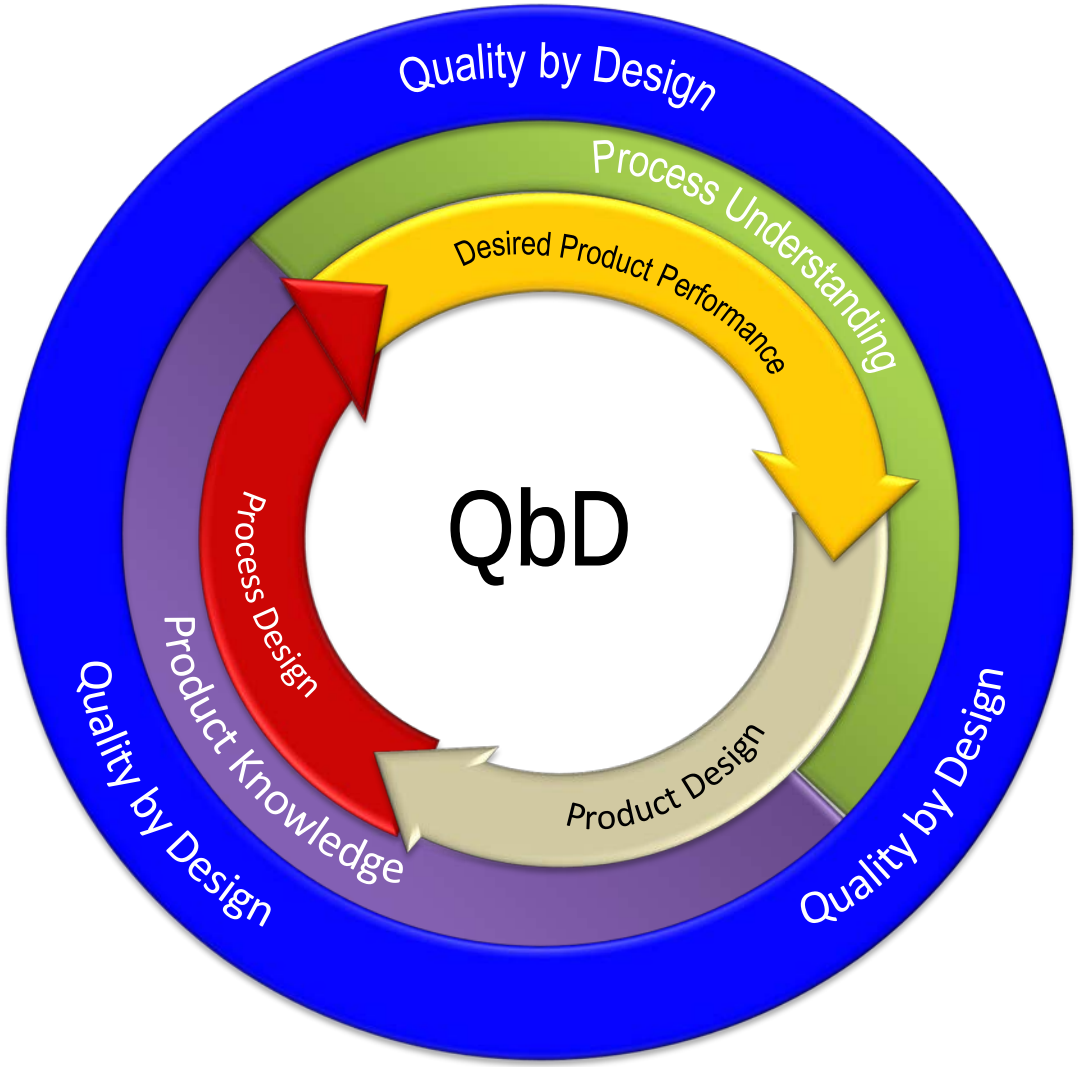
Quality by Design… In the Beginning



- **Mutual goal of industry, society, and regulators:**
  - A **maximally efficient, agile, flexible pharmaceutical manufacturing sector** that reliably produces high-quality drug products without extensive regulatory oversight.

    Dr. Janet Woodcock

    Deputy Commissioner for Operations

    Oct 2005

- **QbD raises interesting questions for us today**
  - **What does it mean to be agile?**
  - **What does it mean to be flexible?**
  - **Are we entering the time in pharma where this finally matters?**

Is the dream of tailored/precision/personalized medicine finally here?

- What are the “new” things we are starting to see?
  - Peptides
  - Oligonucleotides
  - siRNA
  - Other nucleic acid therapeutics
  - Cell therapies
  - Associated delivery mechanisms

And are we ready to meet this challenge?

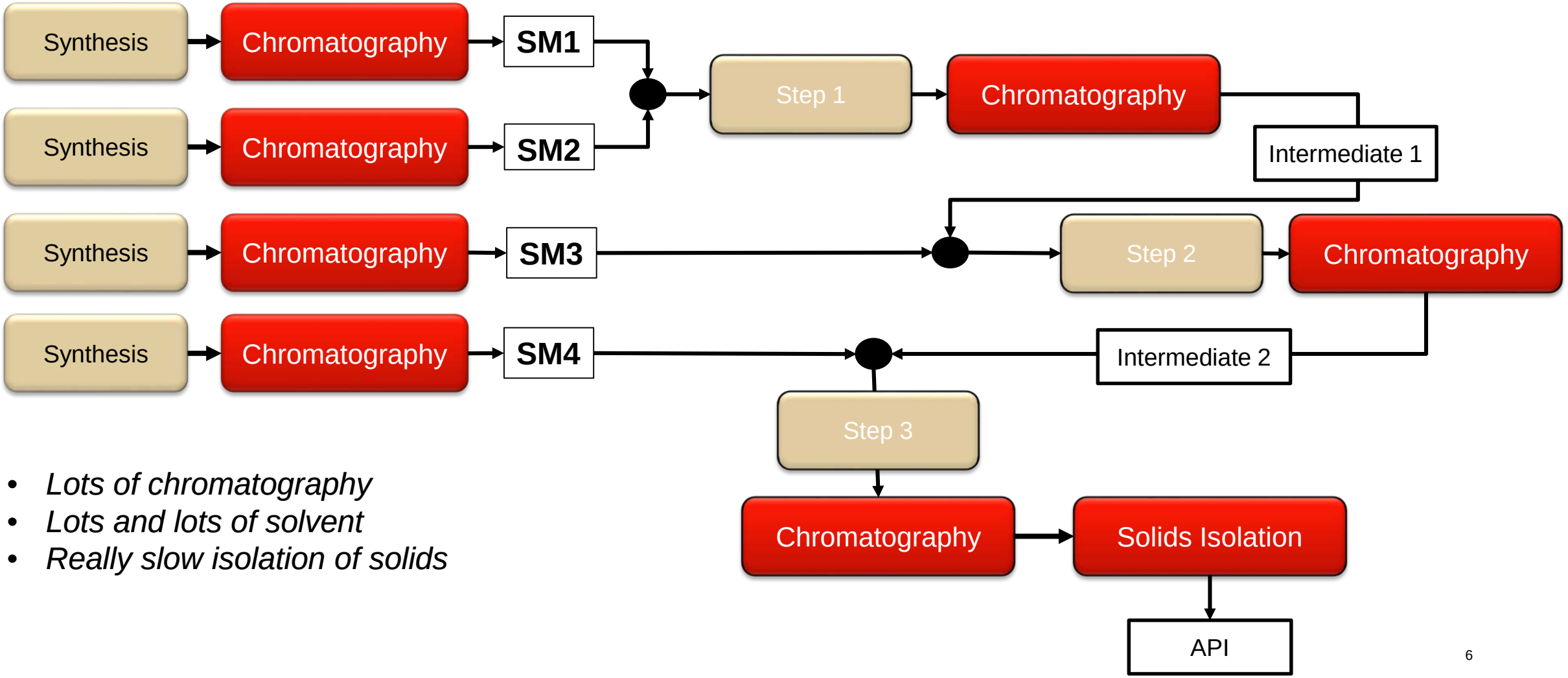
- Many are low volume
- Most can appear niche from a material generation perspective
- Current unit operations have some problems:
  - Will lead to high costs
  - Will cause control strategy challenges
- Evolution of unit operations is needed for the future of patients

A simple example scenario created by new treatment approaches

- First question – for molecules made by chemical synthesis techniques, what is the “go to” method by which impurities are controlled?
- What would you do if every molecule you made was not crystalline?
- How should we handle this challenge?

The future without crystallization?

Small Molecule – 3 registered steps, 4 Starting Materials

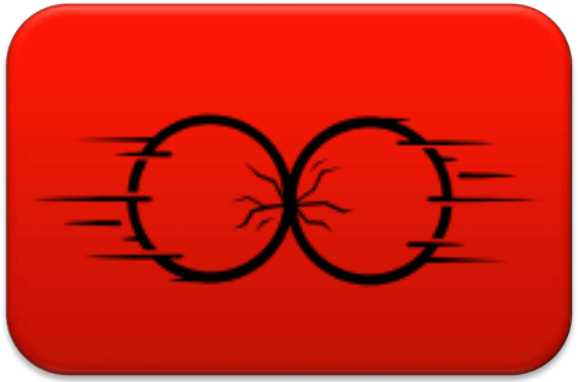


- *Lots of chromatography*
- *Lots and lots of solvent*
- *Really slow isolation of solids*

Or should we choose this instead?

- Can we develop membranes to purify streams at a molecular level?
- Can we develop multipurpose membranes?
- Can we implement very selective recycle loops?
- Can we replace purification approaches of today with something like this?

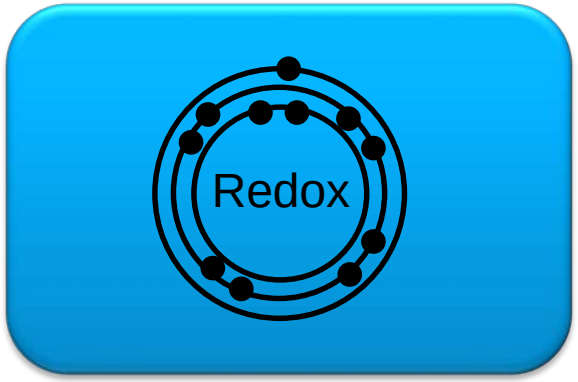
Or do we avoid the problem by producing extremely pure materials?



Mechanochemistry

Photochemistry

Sonochemistry



Electrochemistry

Size does matter

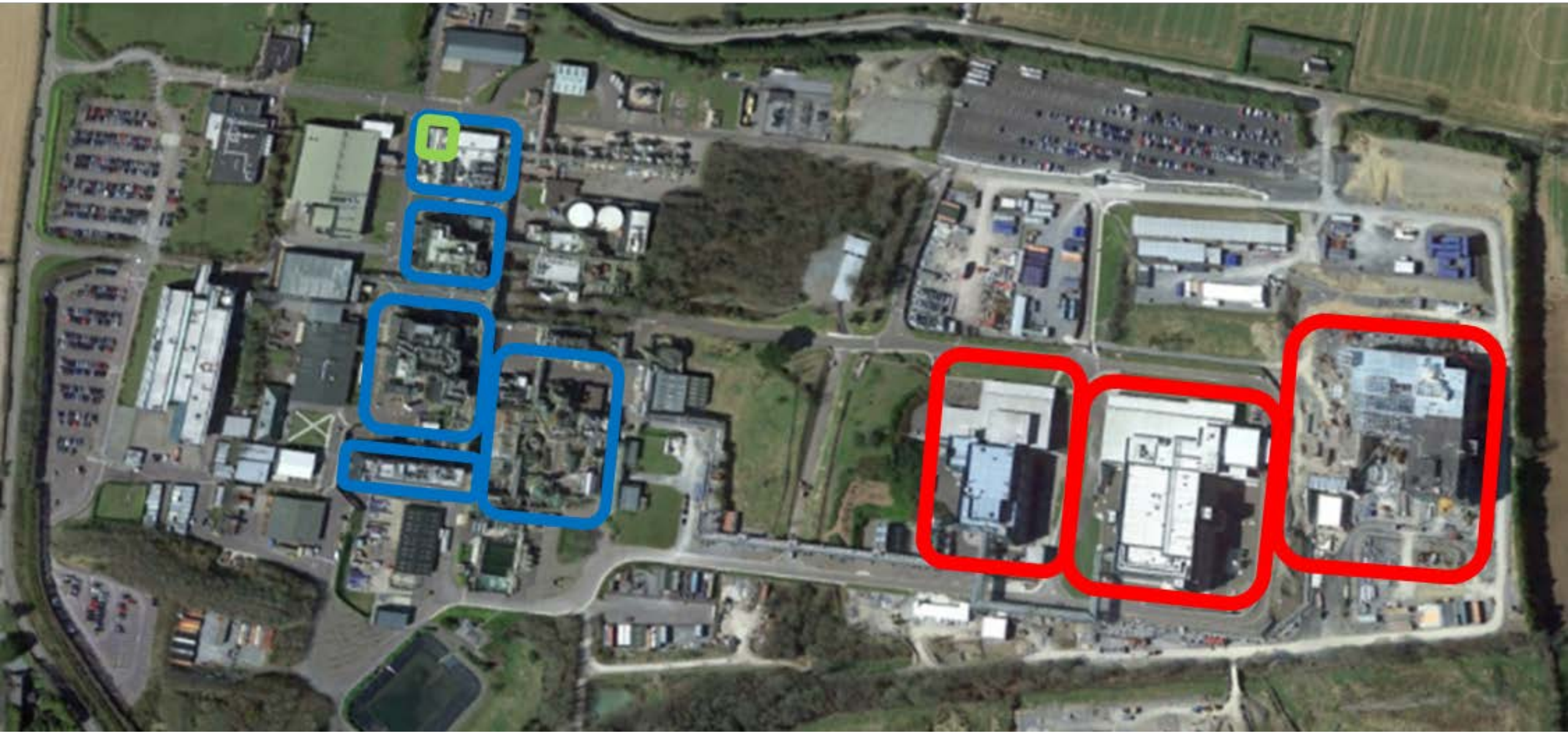
- Many different therapeutic options
- None will be large volume – less than 1 MT API
- External network unlikely to be ready to handle these for commercial purposes
- Cannot spend large $$ on any one limited use medicine
- Need a shift in pharmaceutical manufacturing infrastructure
- All new approaches will require investment to achieve

- How might we fit and control all new treatment modalities into same framework that is small in size and investment?

Why continuous manufacturing matters for patients

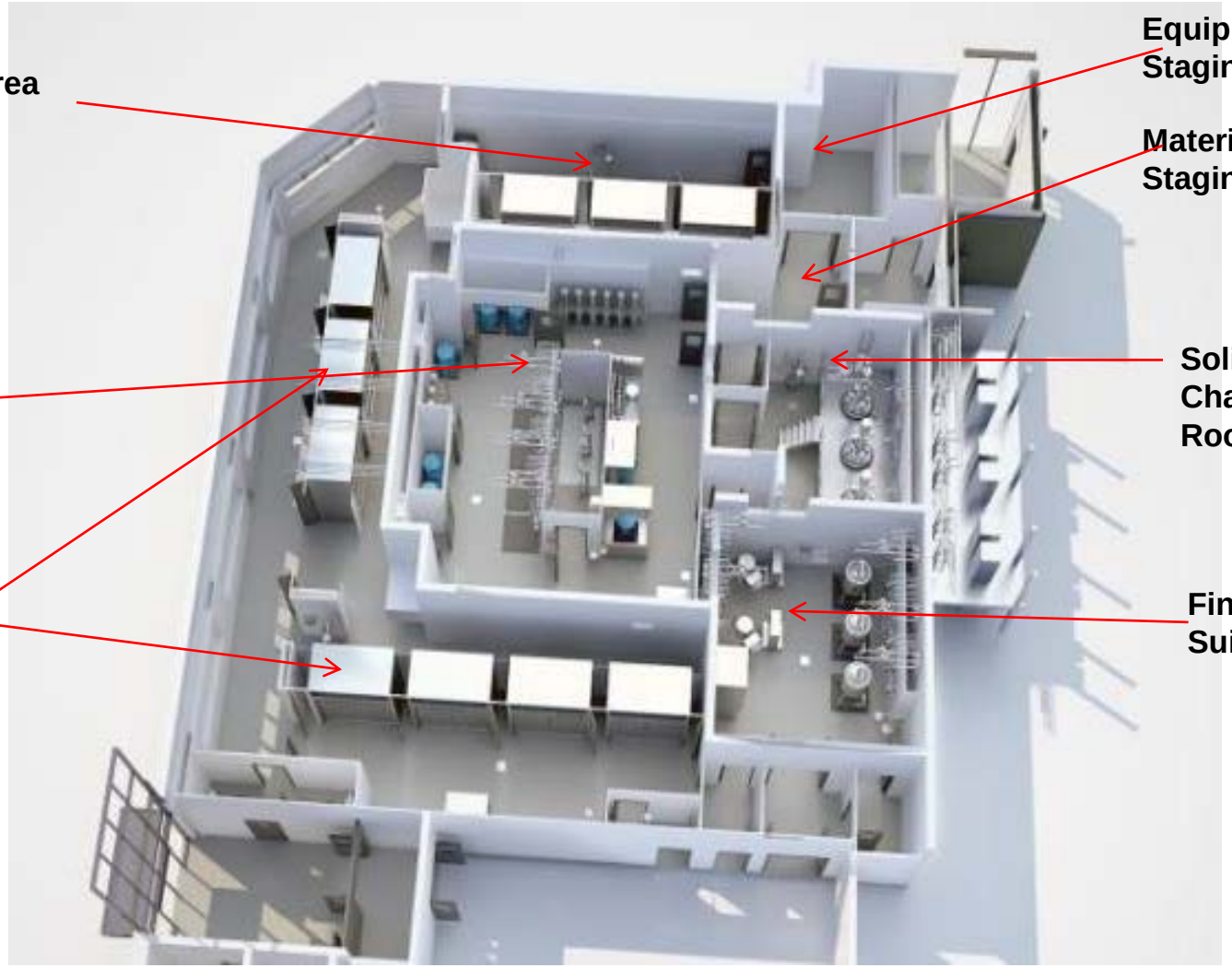
- It is NOT the solution, but without, there may be no solution
- It allows processing at a smaller scale
  - Cost issues are alleviated
  - New unit operations can be designed for purpose
- It removes/reduces mixing/scale up as the traditional most important process development variable
  - With appropriate regulatory connection, site flexibility, startup speed are possible
  - Quickly mobilizing facilities is important for personalized approaches
- It represents the mindset shift that is needed to actually move

How continuous can transform manufacturing



FOYA 2019
Facility of the Year Awards
CATEGORY WINNER
Process Innovation

SVC API Facility



- $35M Investment (Facility & Equipment)
- 18 months for construction and qualification
- Facility designed with a unique 'wheel and spoke' approach, with raw materials feeding out from a central charge room
- Production contained in dual-access fume hoods
- Facility designed for throughput of 10 kg/day

Lilly

SVC Facility: Fume Hood View

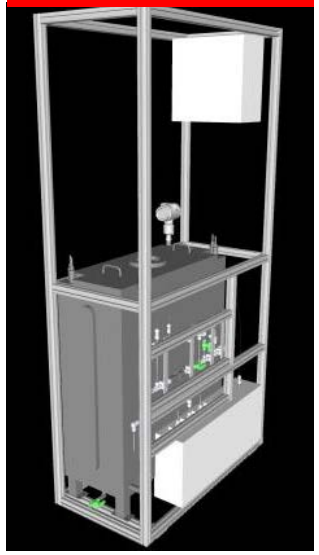
- **Modular skids** to support a wide range of unit operations
- **Flexible and adaptable**; whenever possible, use of standard dimensions / components

- **PAT** is a key component of the manufacturing control system
- **Automated systems** for sampling, analysis, and transfer of results.

SVC Facility for GMP API Manufacture

CSTR Skid

Plug Flow Reactor Skid



Feed System Skid

Skids are part of a platform to support chemical unit operations in any product

- Modular to be combined into unit operations (e.g. CSTR/mixer skids combined for a counter-current extraction).
- Flexible and adaptable – simple skids with standard components (where possible)
- Plug into Distributed Control System (DCS)
- Working with high end equipment e.g. gear pumps & data management system. CM

SVC Flexible Equipment Platform

Feed Make-up Vessel

Feed Canisters

Plug Flow Reactor Skid

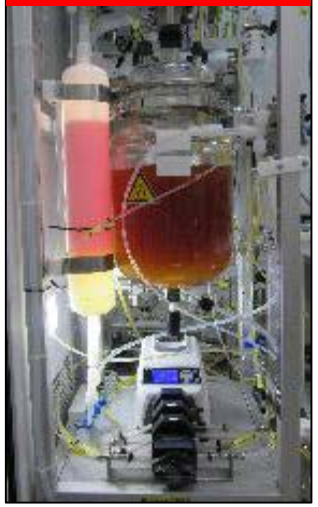
Feed Pump Skid

Interconnect Tubing

Surge Collection Vessels

Plug Flow Reactor Skid

CSTR Skid



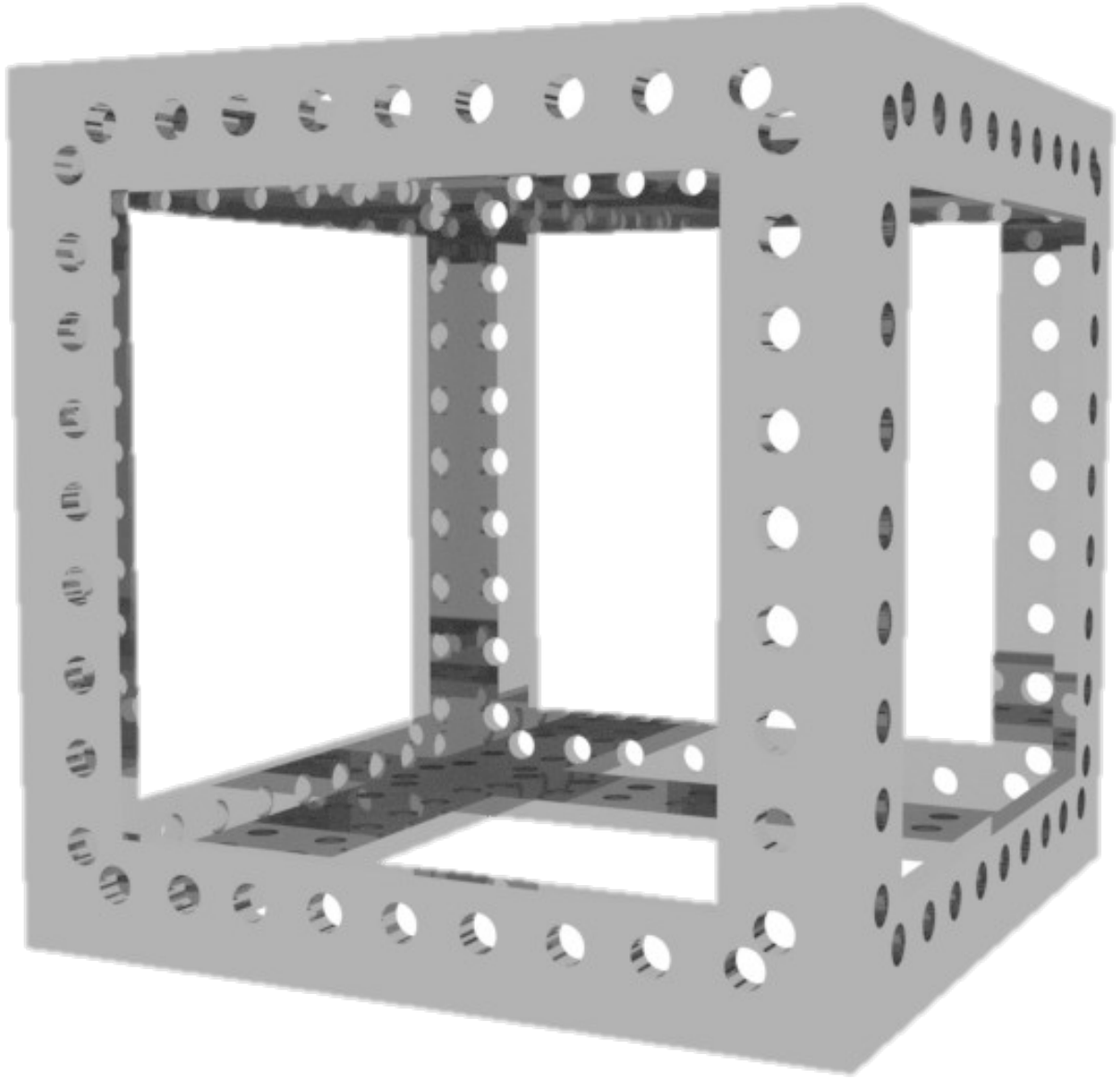
Filtration Skid

Batch Isolation

Modularity

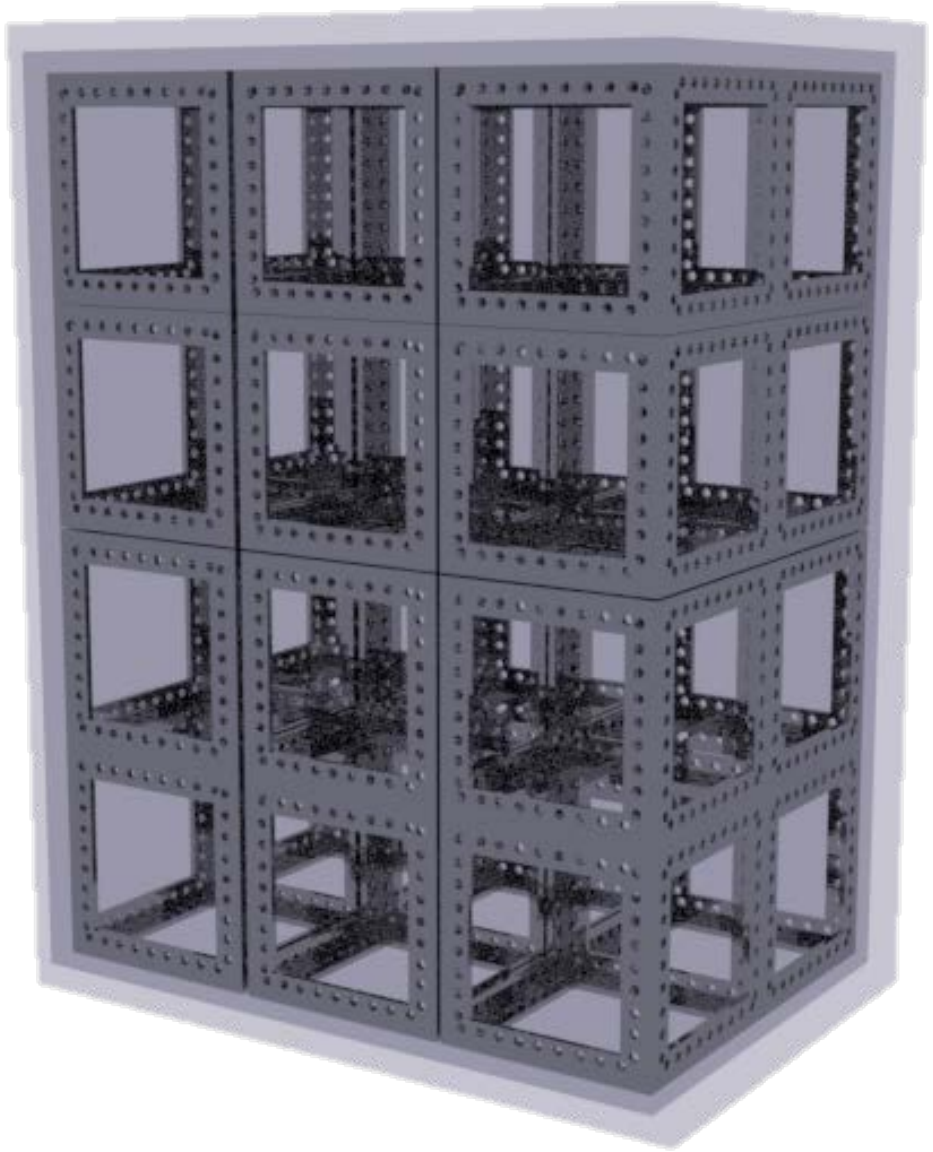
Brick level

1 brick



Modularity
Fume hood level

Fume hood = 24 bricks



Modularity
Facility level

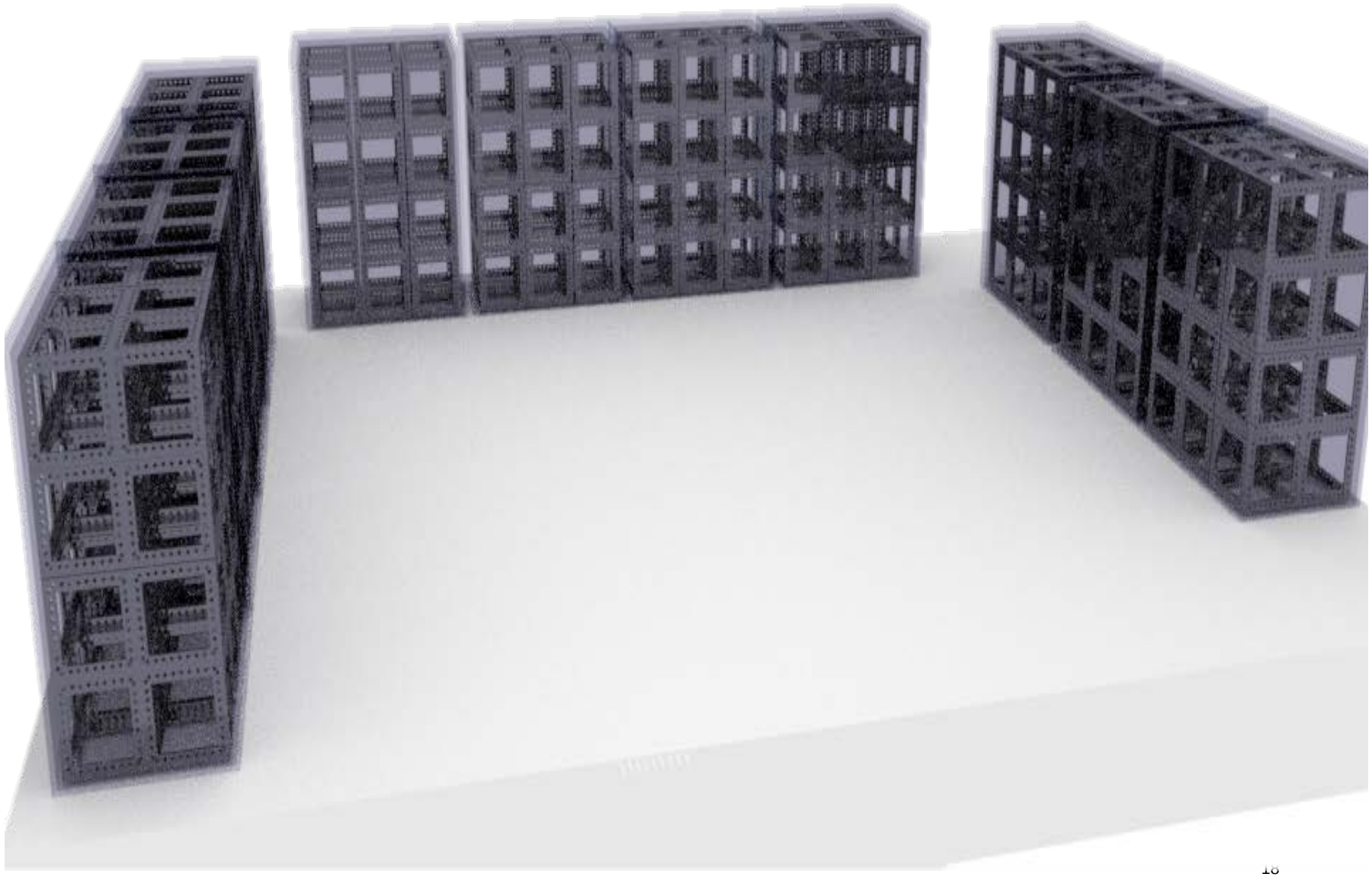
1 facility

=

11 Fume Hoods

=

264 bricks

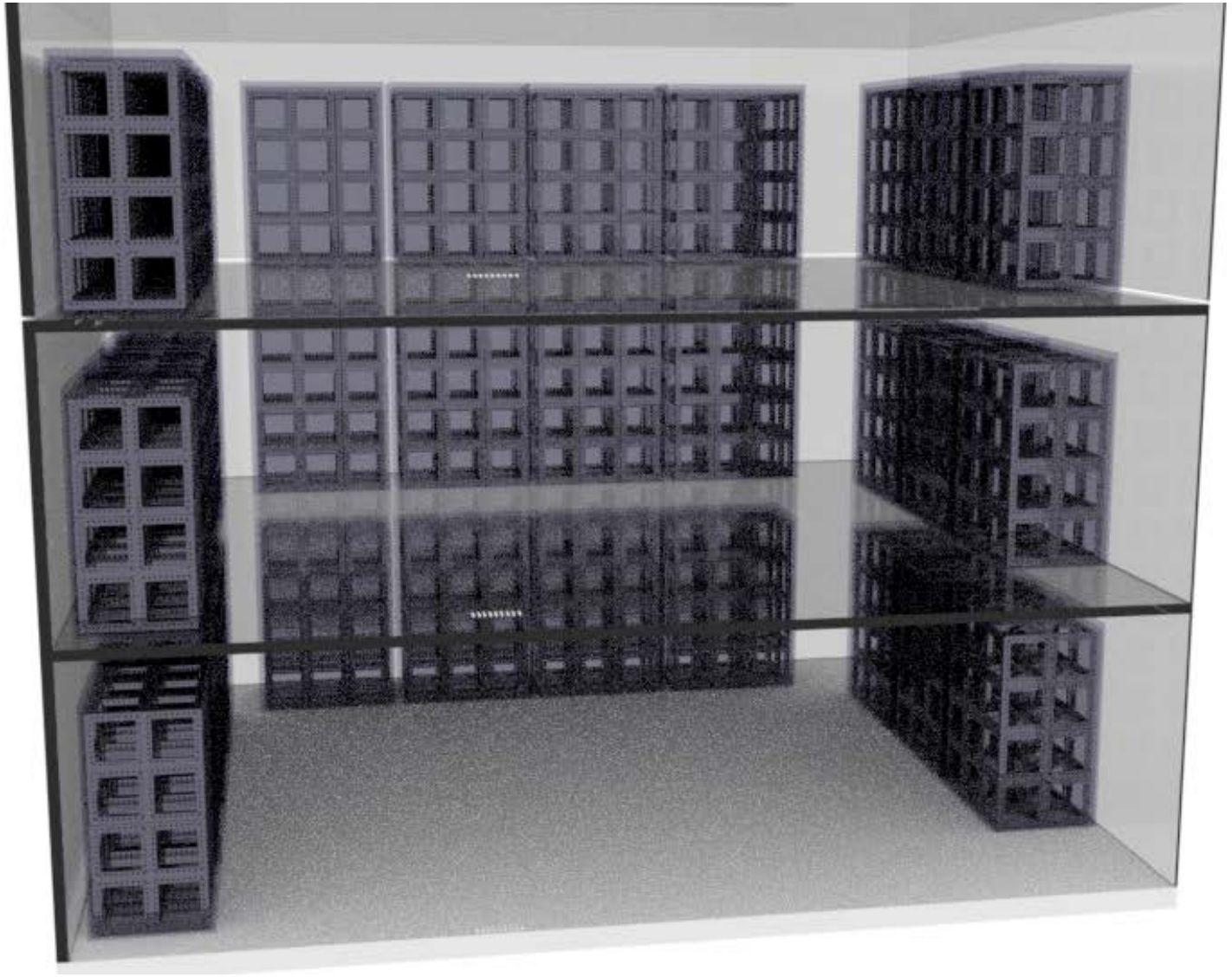


Modularity
Multi-Facility Level

New Modality 1

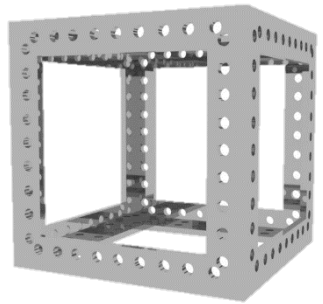
New Modality 2

Small Molecule

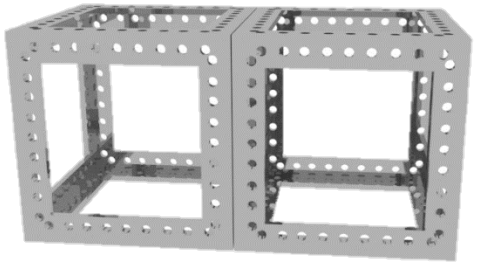


It is all about Real Estate

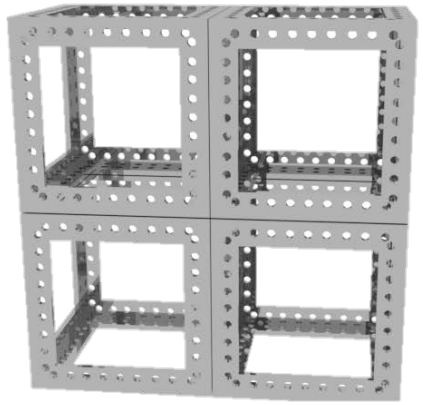
Feed skids
Divert skids (1)



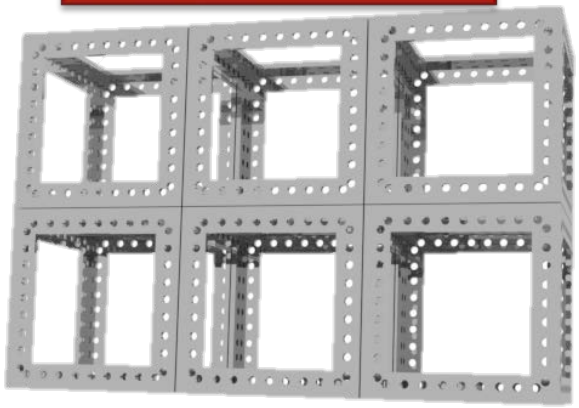
Dilution carts
AVS skids (2)



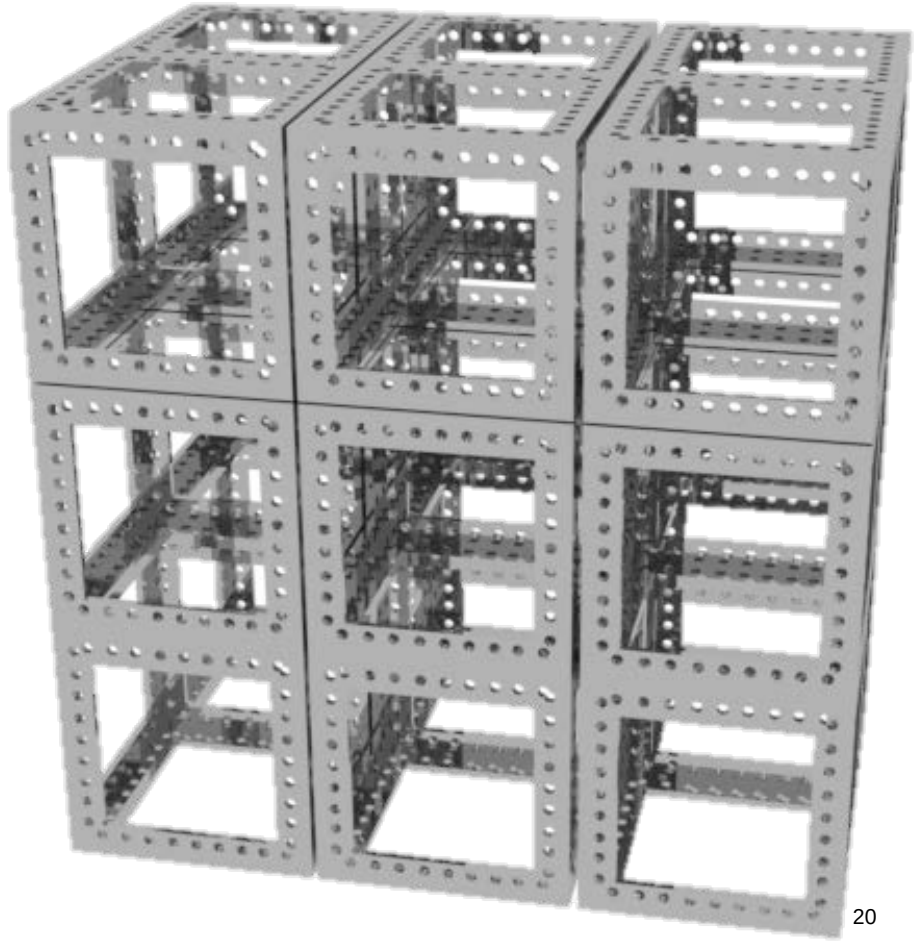
CSTRs, Evaporator,
MSMPRs (4)



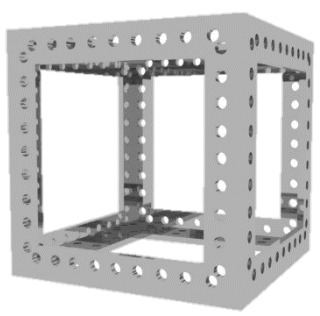
FTIR probe
(6)



PFR
(16)



Example 1 – Small Molecule (4 steps)

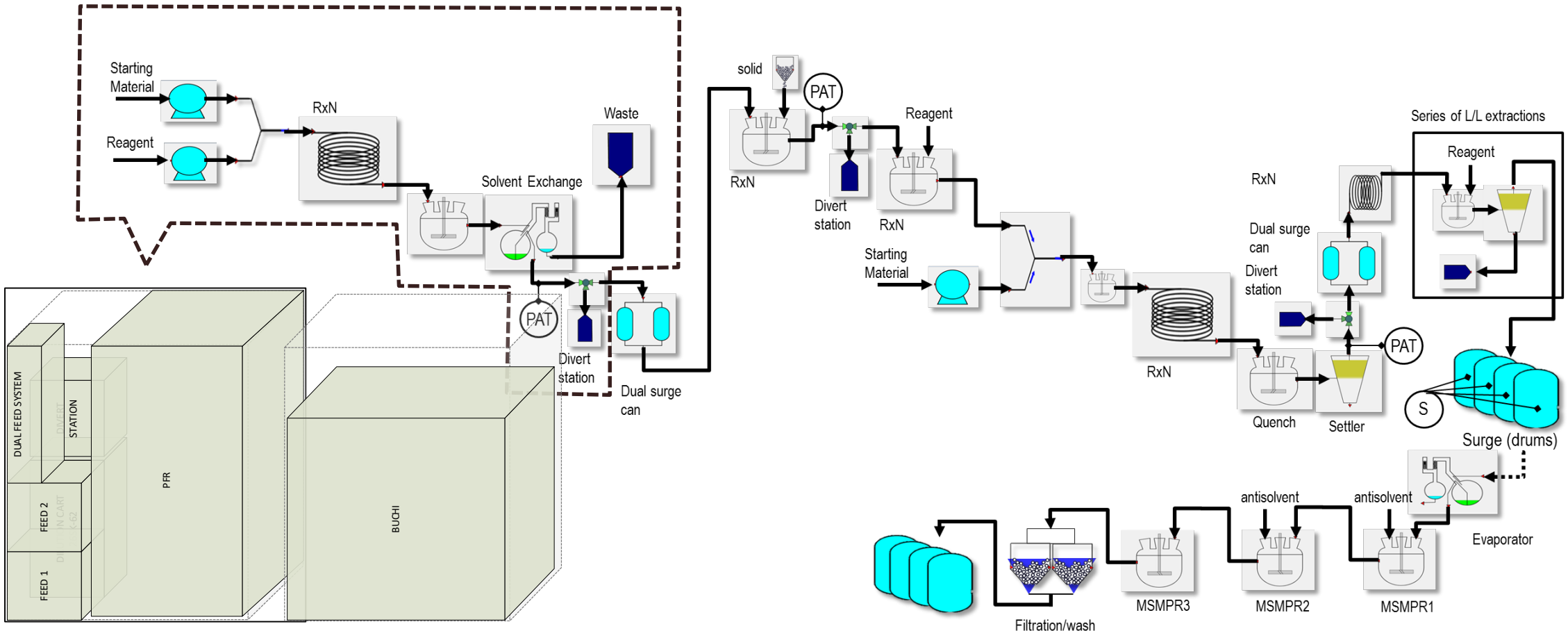


185 Brick Process

Small Molecule

Step 1

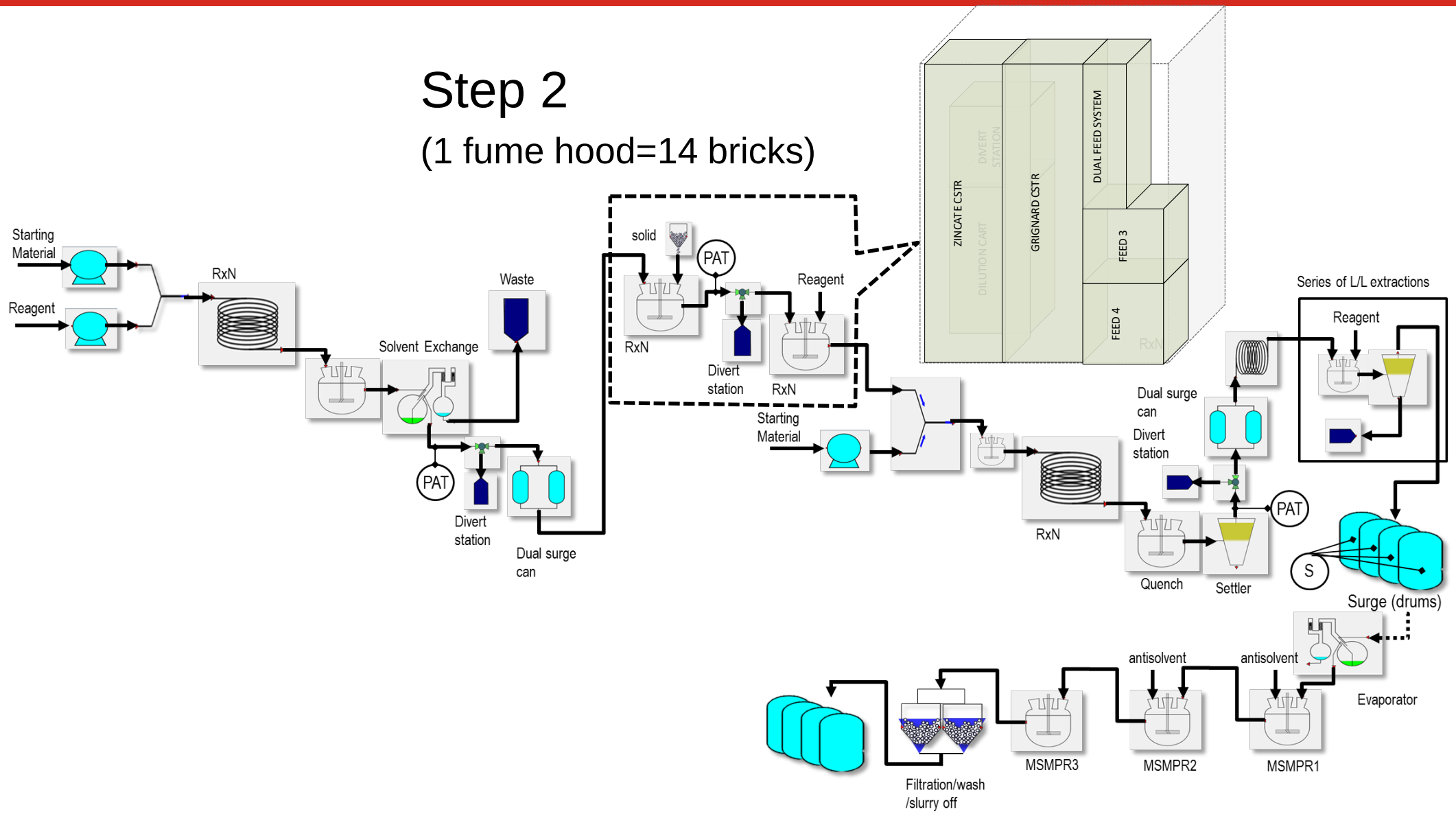
(2 fume hoods = 47 Bricks)



Small Molecule

Step 2

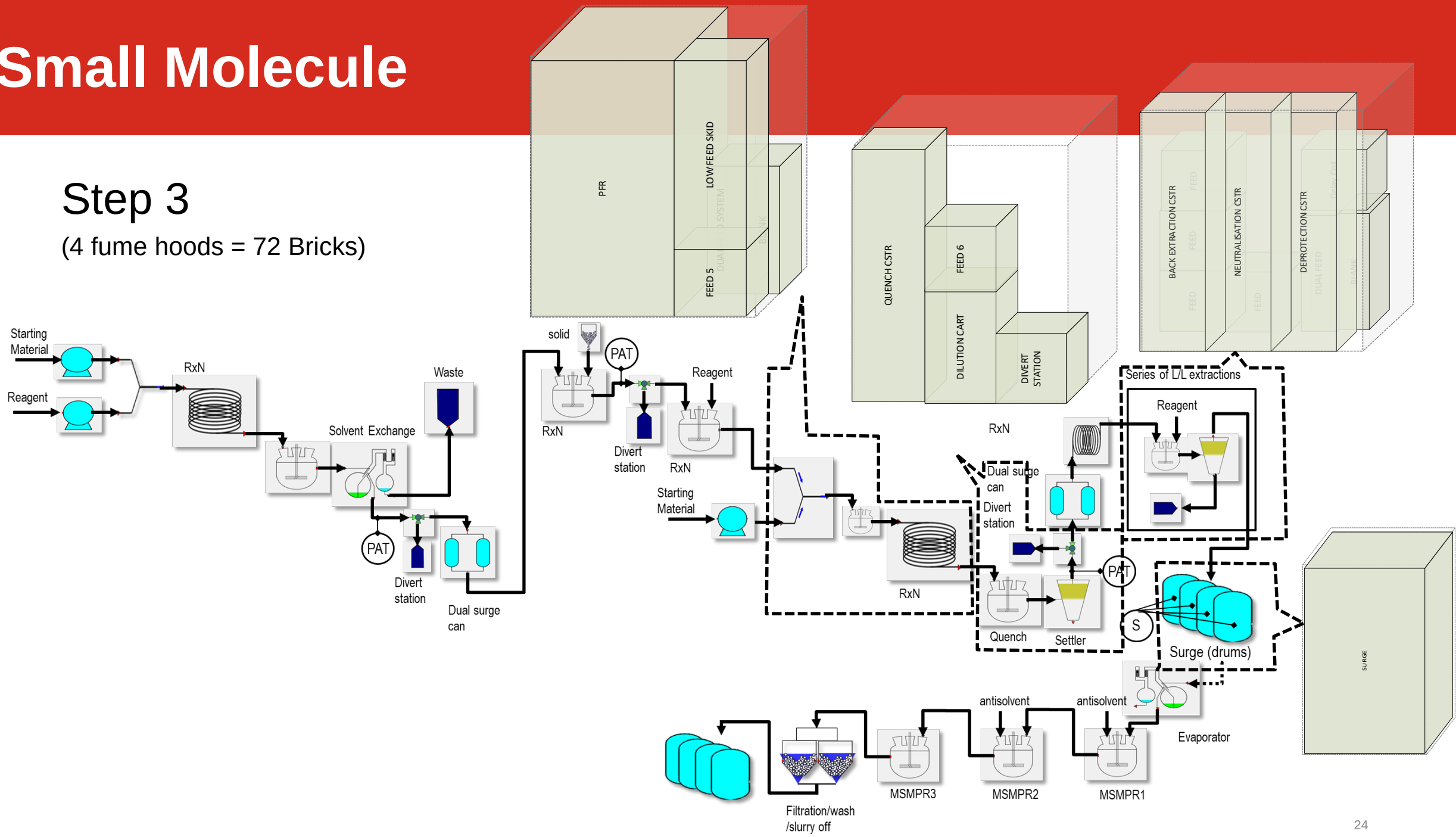
(1 fume hood=14 bricks)



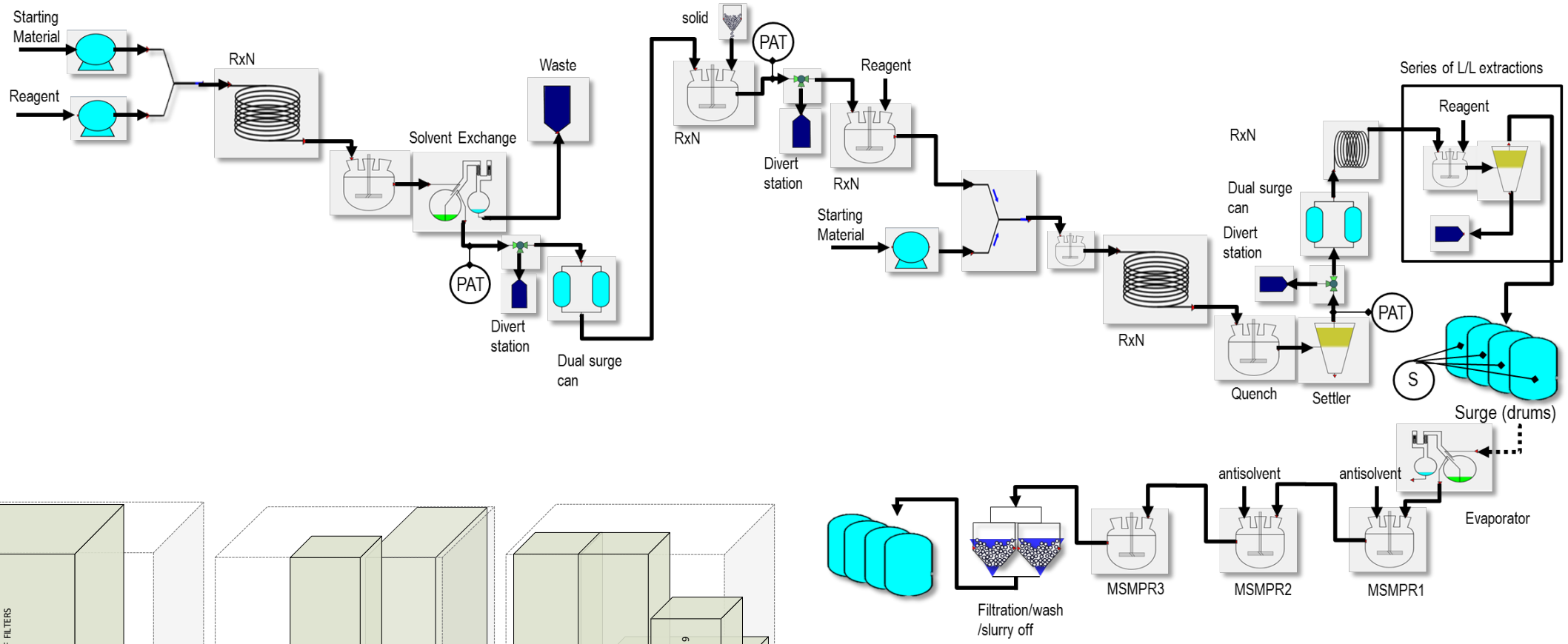
Small Molecule

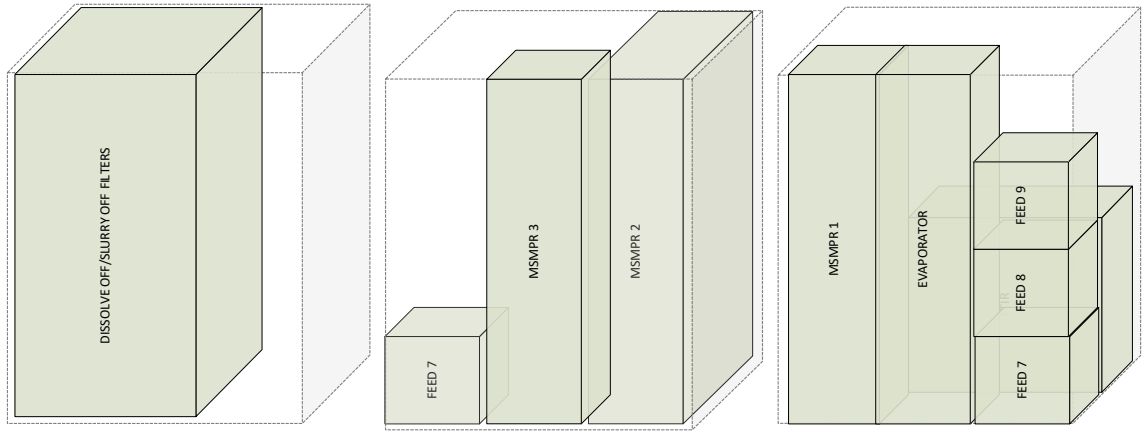
Step 3

(4 fume hoods = 72 Bricks)



Small molecule





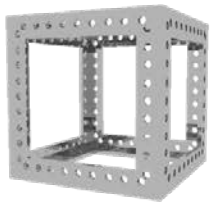
Step 4

(3 fume hoods= 52 bricks)

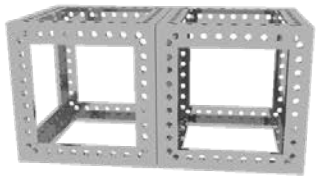
Nucleic acid therapeutics

Don’t view as “new” approach.
View as types and number of bricks…

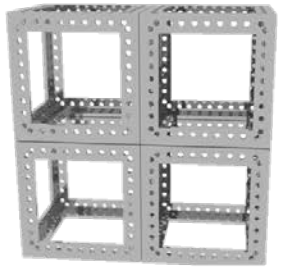
Feed skids
Divert skids



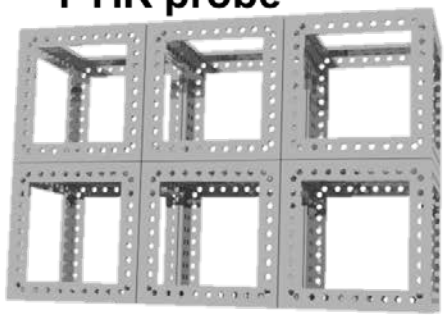
Dilution carts
AVS skids



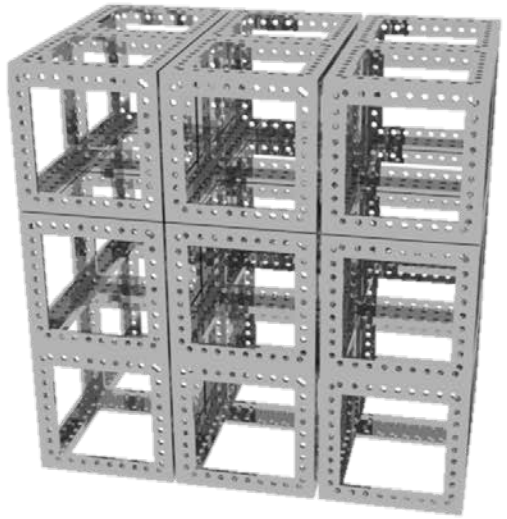
CSTRs, Evaporator
MSMPRs



FTIR probe



PFR



- How many bricks are needed for chromatography?
- How do we replace traditional chromatography by SMB?
- How many bricks are needed for nanofiltration?
- How does a solid phase synthesizer for SVC should look like?

Unit Operation by Bricks – Today and Tomorrow

Unit Operation	# of Bricks
Standard Prep. Chrom.	>24
Amorphous Filtration	>24
Nanofiltration	24
Surge (full decoupling)	24
Solvent exchanger (Buchi)	24
SMB	16
Dissolve off/Slurry off filter	16
PFR	16
MSMPR (large)	8
FTIR Probe	6
Evaporator	4
CSTR, MSMPR small	4
Dilution Cart	2
Divert Skid	1
Feed Skid	1

← 4000 L Feed + 60 cm Columns + ~100L fraction collection

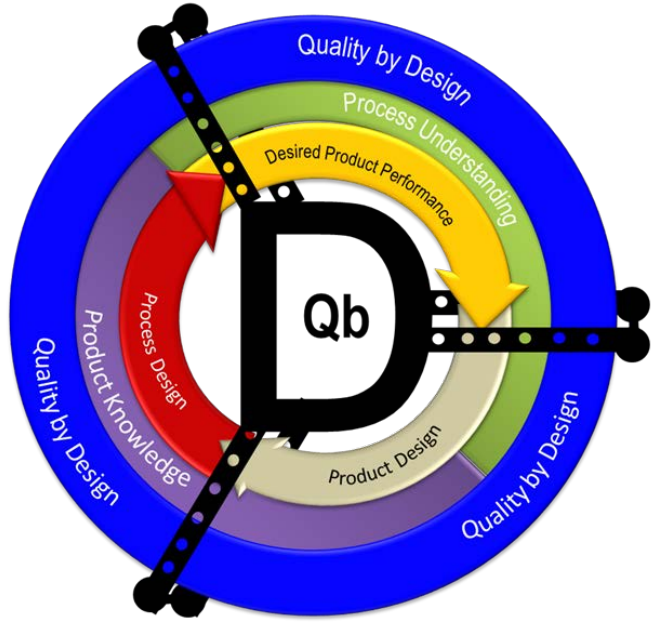
← Standard AFD ~0.5 m^2

← Independent of the area

← 400 L Feed, 10 L fractions, 5 cm columns

Conclusions, and challenges

- Next wave of medicines requires us to change
- Continuous manufacturing is the framework that allows us to address these needs
- SVC-style facilities gives flexibility already
- New unit operations are needed
  - Separations are key
  - Novel reaction platforms could reduce burden



- QbD should never have been about multivariate PARs, risk and control strategies – it's about *design*

Acknowledgments

- Marty Johnson
- Jen Groh
- Chris Polster
- Shujauddin Changi
- Nick Klitzing
- Sarah O’Keeffe
- Ray Boyce
- Rob Moylan
- Bret Huff