Opening the Door to the Future – Why Continuous Manufacturing was the Key

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Small Molecule Design and Development

Eli Lilly and Company

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NAS WORKSHOP ON TECHNICAL AND REGULATORY BARRIERS TO INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

The promise of the human genome

- Modalities now commonly found in pharmaceutical development
  - Peptides
  - siRNA
  - miRNA
  - LNA
  - Other nucleic acid therapeutics
  - Cell therapies
  - Associated delivery mechanisms
- Awesome, right?

Are CM&C areas ready to meet this challenge?

- Many (but not all) are low volume compared to SM facility capacity
- Most can appear niche from a material generation perspective
  - So why invest?
- Most can appear niche from a “how often will we use it” perspective
  - So why invest?
- Current unit operations have some problems:
  - Will lead to high costs
  - Will cause control strategy challenges
  - So why invest?
- Tendency may be to avoid internal investment
- Evolution of pharmaceutical processing unit operations is needed for the future of patients

A few of the unit operation challenges ahead

- Dealing with undesirable solvents
- Purification and isolation operations that are inefficient
- Sustainable starting materials
- New chemistry needed
- Scalability of delivery vehicles

Where the challenge of new modalities and rapid response to global health needs intersect

- The pharmaceutical manufacturing facility as we know it today, built largely on a batch infrastructure…

Pharmaceutical Manufacturing Site

100 acres

40 hectares

Pharmaceutical Manufacturing Site

170 acres

69 hectares

Contract Manufacturing Site

215 acres 87 hectares

What do they all have in common?

- They are big
- They are expensive
- They are designed for multi-use, but within the confines of 20th century chemistry and unit operations

- This is the problem – existing scale - that hinders us from both new modalities AND rapid response to global events. It's hard to mobilize things at this scale, and you certainly can't distribute manufacturing easily in multiple locations

Size does matter

- Many different therapeutic options
- Depending on therapeutic area – 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
- 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?

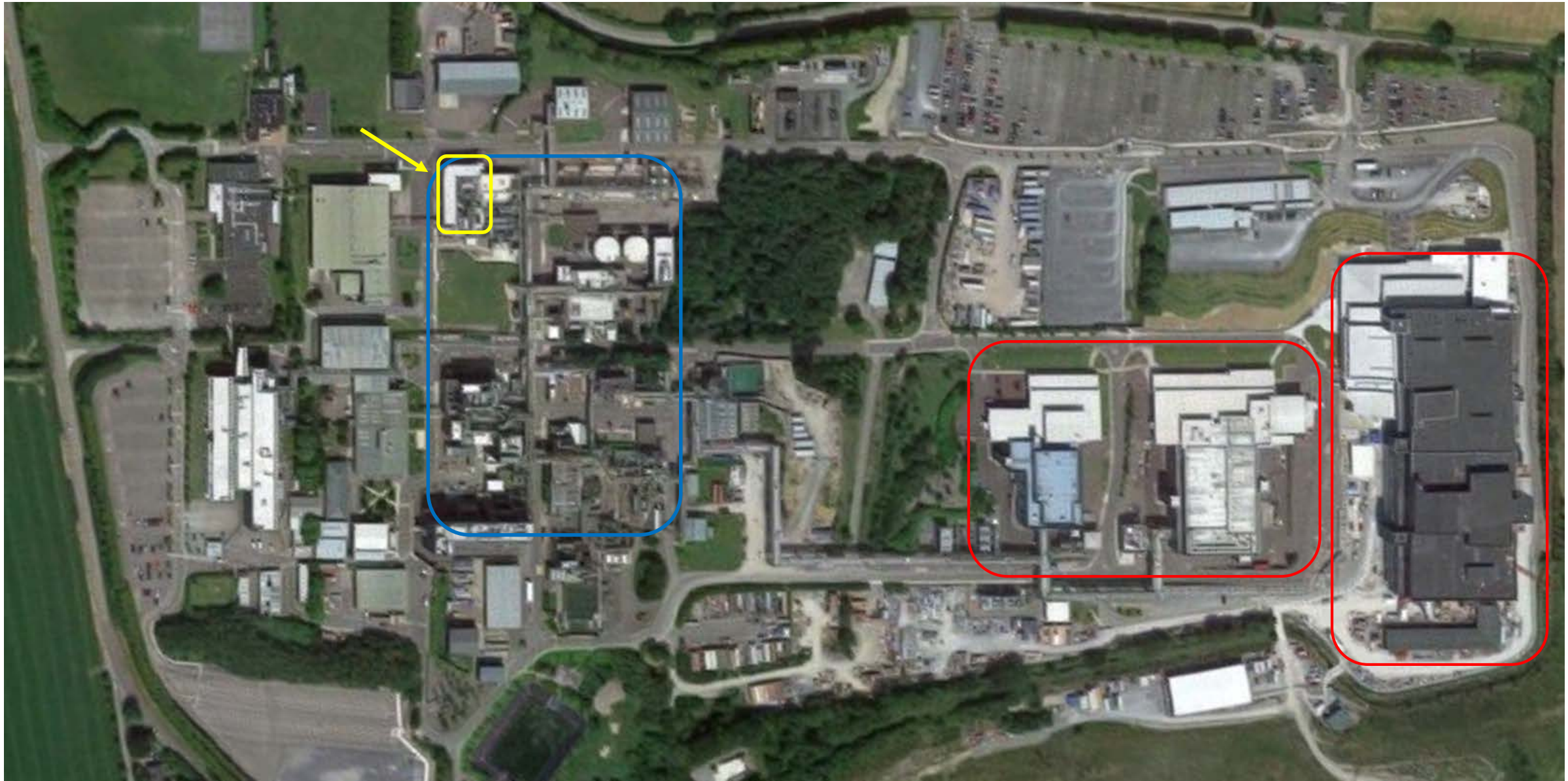
Why continuous manufacturing is the key

- 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 most important process development variable
  - With appropriate regulatory connection, site flexibility, rapid startup speed are possible
  - Quickly mobilizing facilities is important for multi-use, personalized approaches, as well as responding to world needs

Facility of the Future

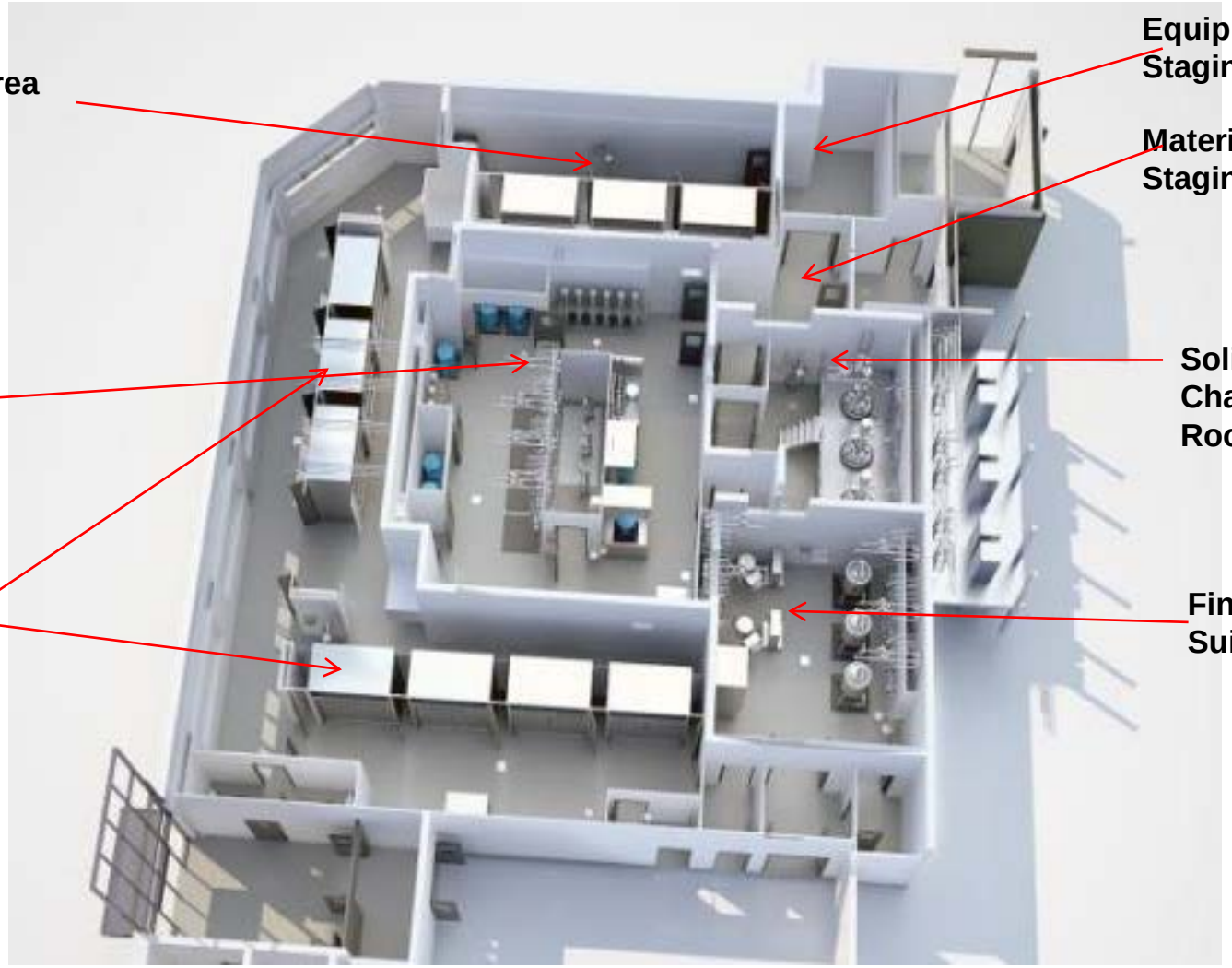
- CM should be thought of as the approach to miniaturizing to “module” level
- Facility design becomes about allowing modules to move in and out as needed
- Multiple groups can design modules that can fit into an accommodating facility
- If desired, modules could be standardized for better understanding and common use
- New modalities become about new technology that fits into flexible facility – not about building a new facility

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

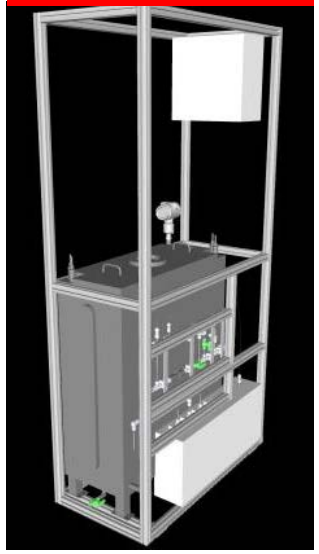
- **Modular skids** to support a wide range of unit operations
- **Flexible and adaptable**; whenever possible, use of standard dimensions / components

- **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 (ie, mix and match as needed).
- Flexible and adaptable – simple skids with standard components (where possible)
- Plug into Distributed Control System (DCS)

SVC Flexible Equipment Platform

Feed Make-up Vessel

Feed Canisters

Plug Flow Reactor Skid

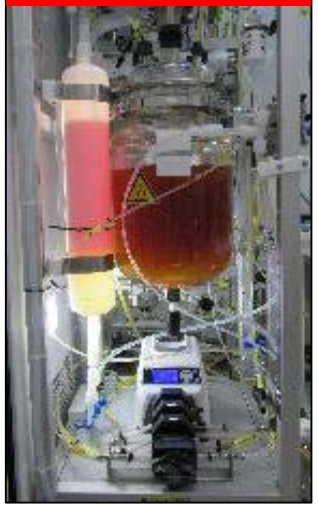
Feed Pump Skid

Interconnect Tubing

Surge Collection Vessels

Plug Flow Reactor Skid

CSTR Skid



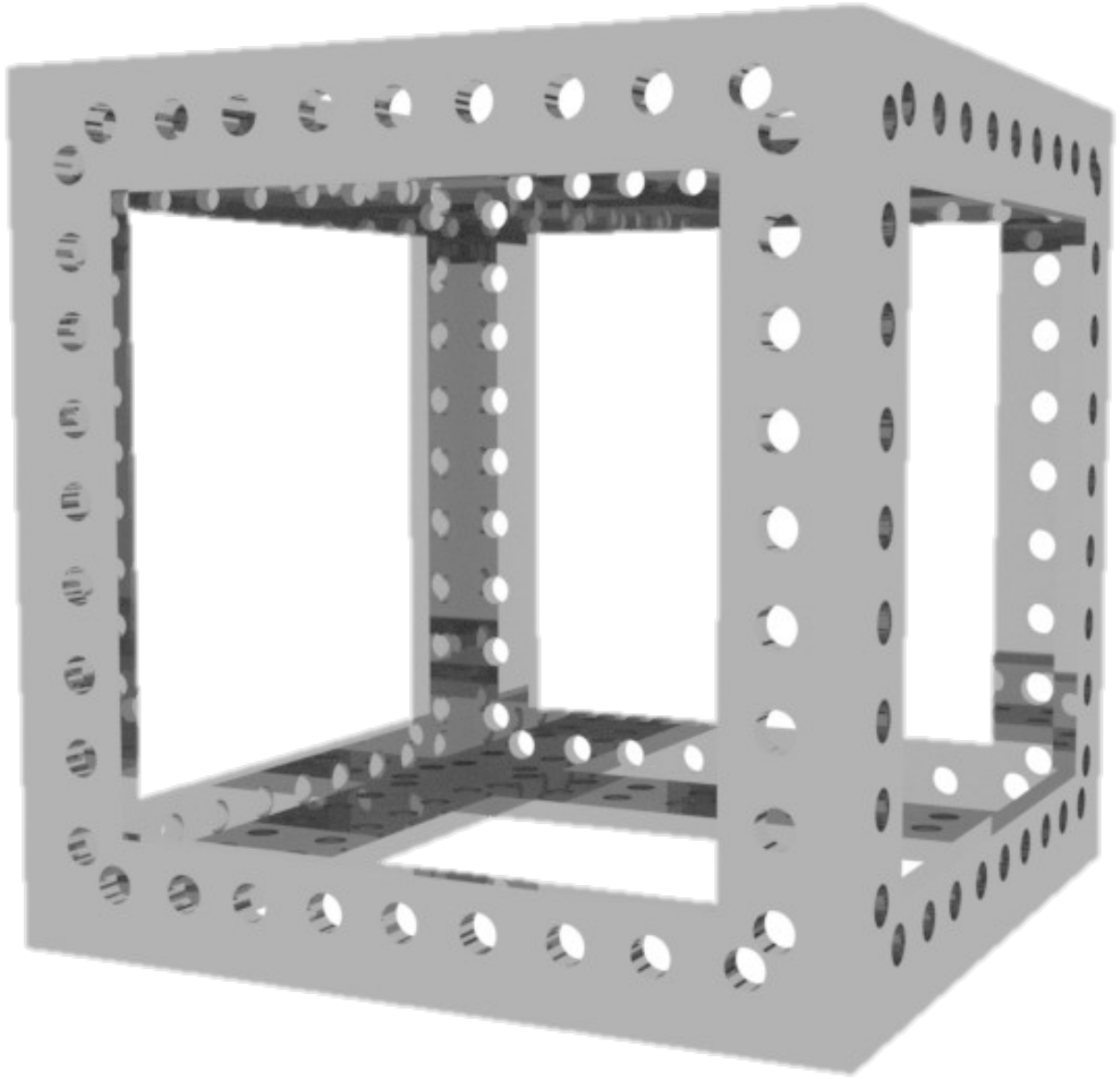
Filtration Skid

Batch Isolation

Modularity

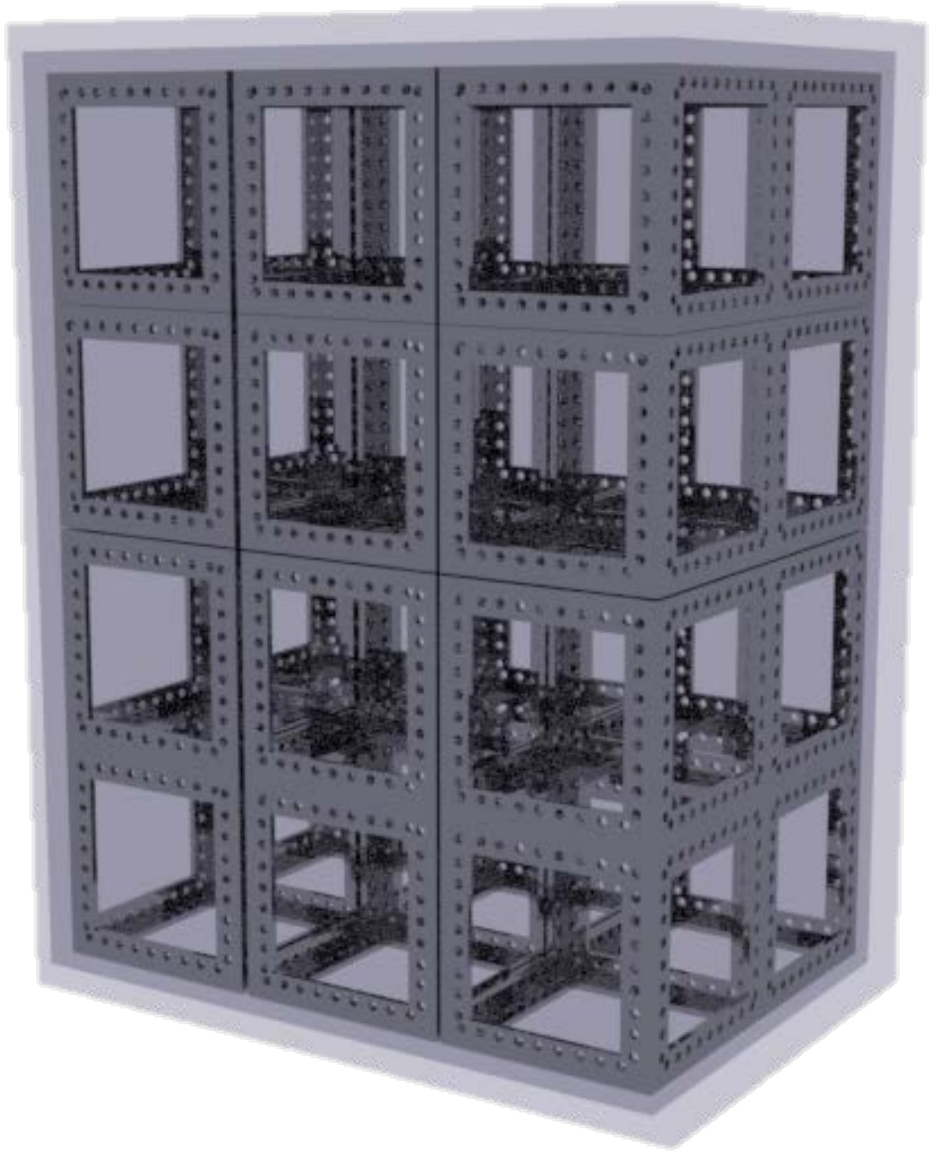
Brick level

1 brick



Modularity
Fume hood level

Fume hood = 24 bricks



Modularity
Facility level

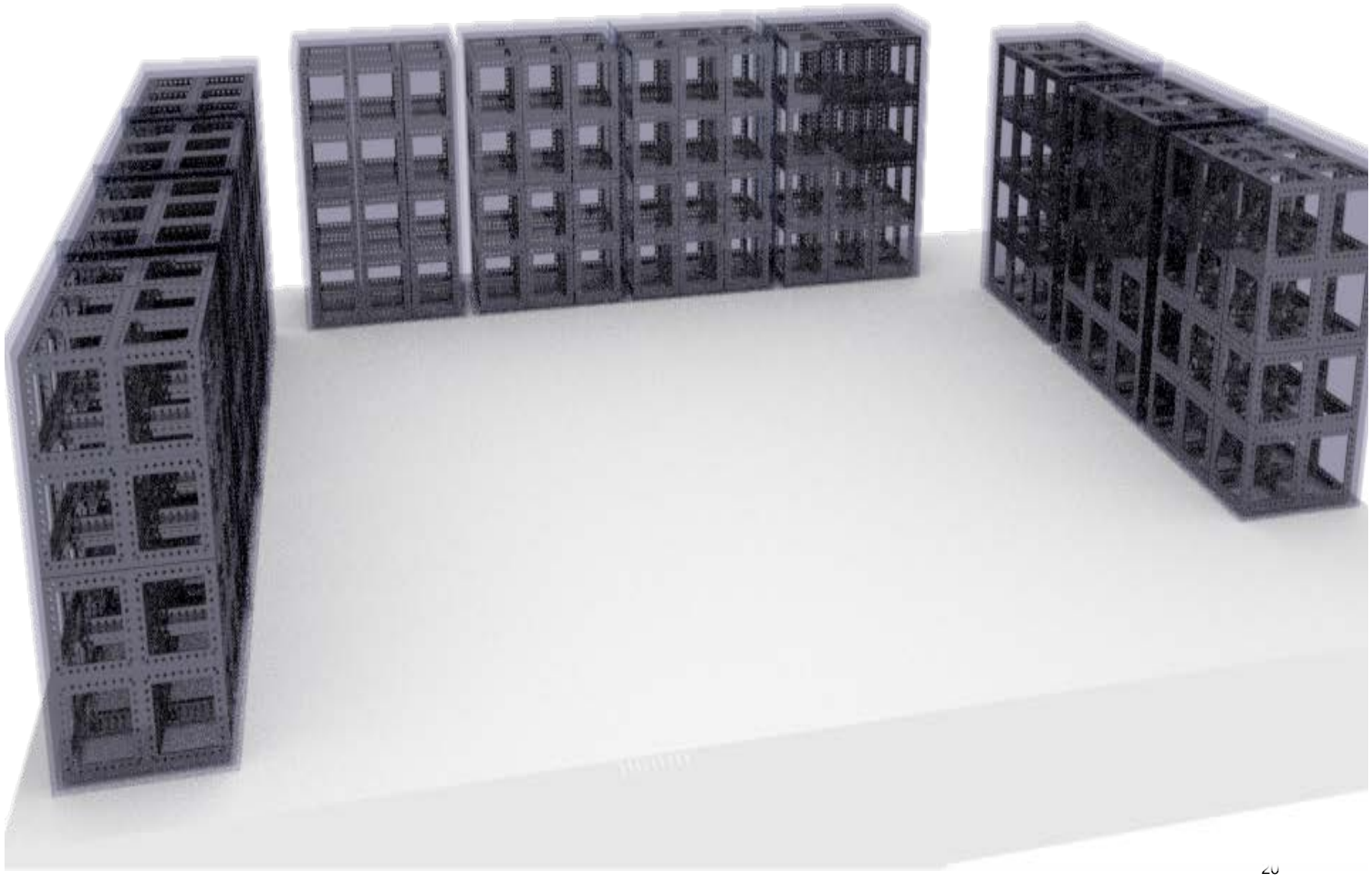
1 facility

=

11 Fume Hoods

=

264 bricks

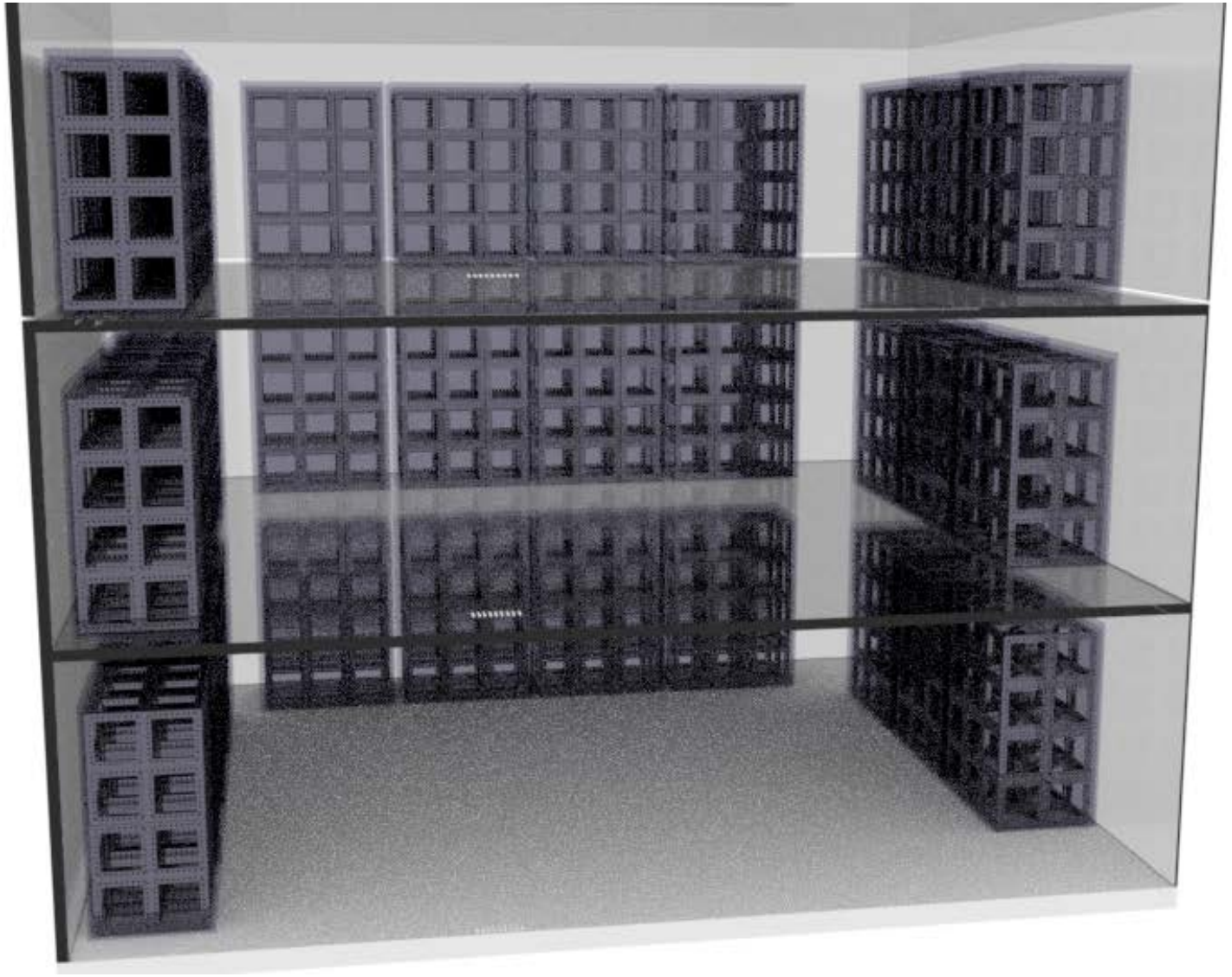


Modularity
Multi-Facility Level

New Modality 1

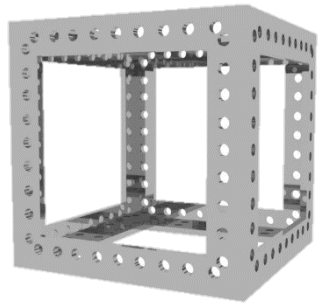
New Modality 2

Small Molecule

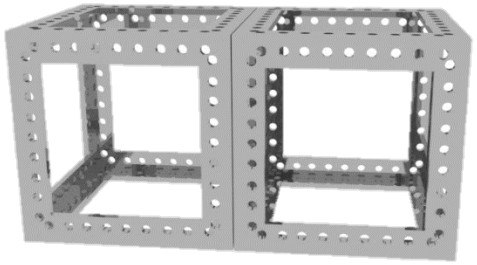


It is all about Real Estate

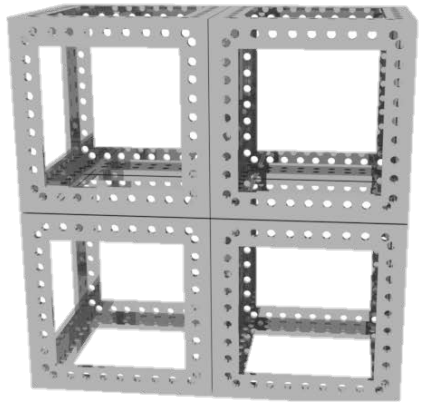
Feed skids
Divert skids (1)



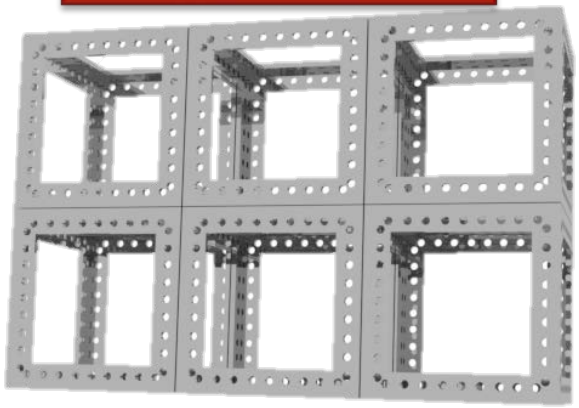
Dilution carts
AVS skids (2)



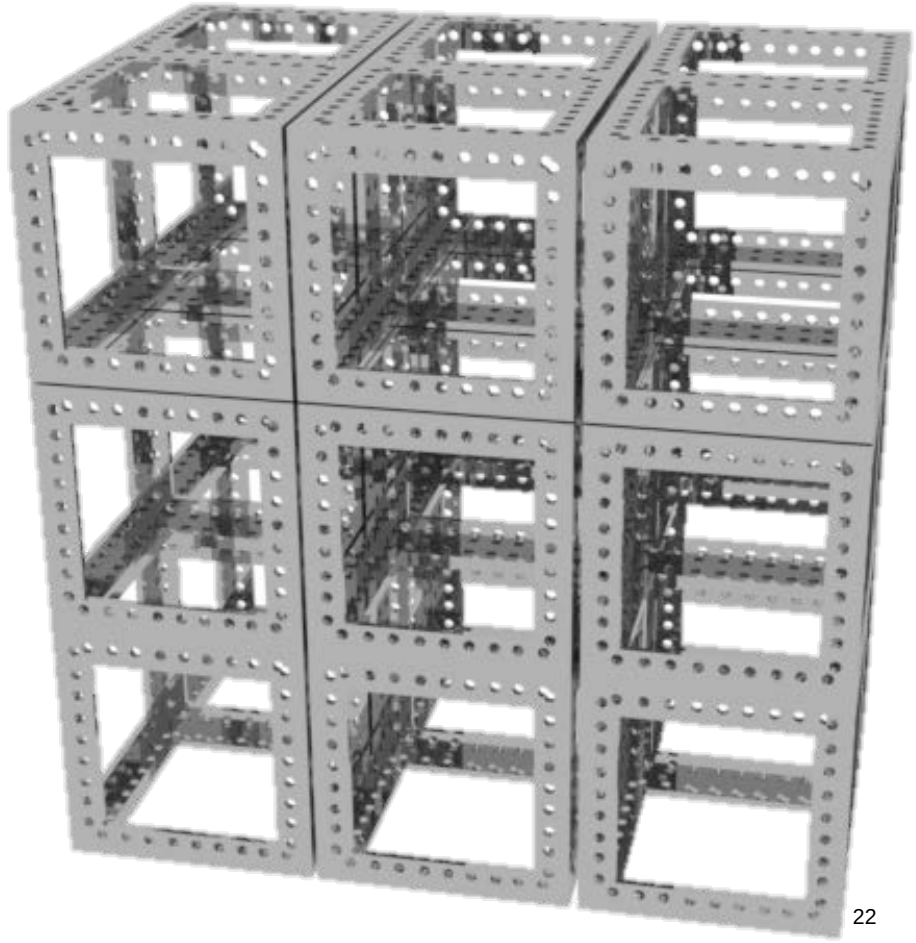
CSTRs, Evaporator, MSMPRs (4)



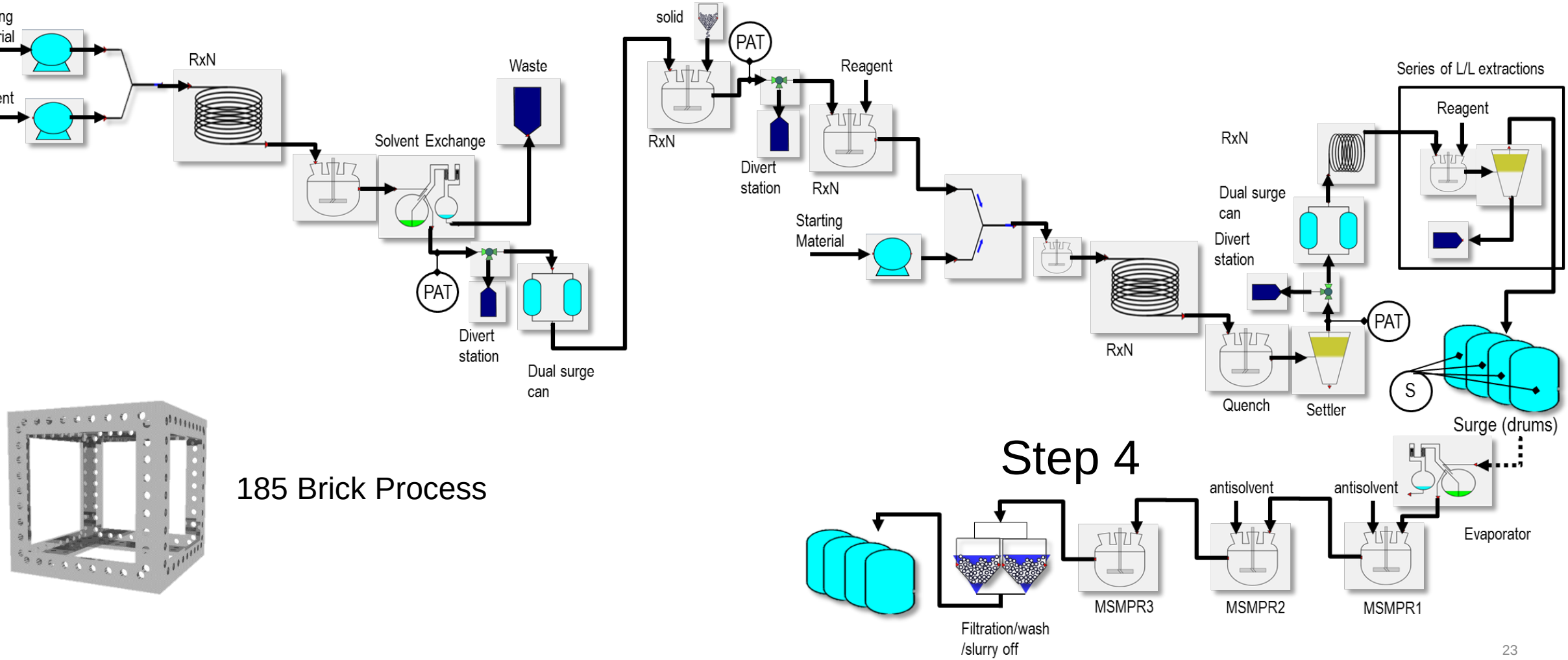
FTIR probe
(6)



PFR
(16)



Example 1 – Small Molecule (4 steps)

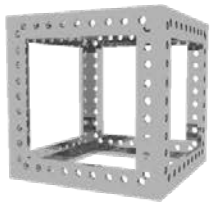


185 Brick Process

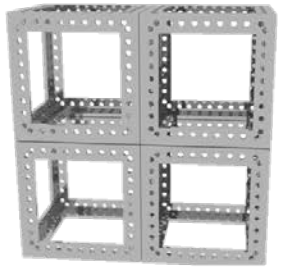
As new needs arise

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

Feed skids
Divert skids



CSTRs, Evaporator
MSMPRs



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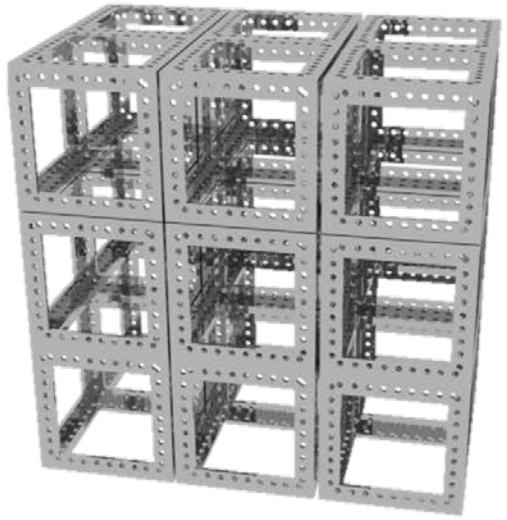
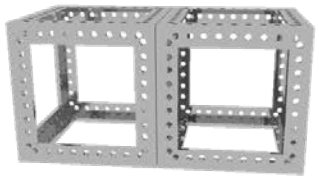
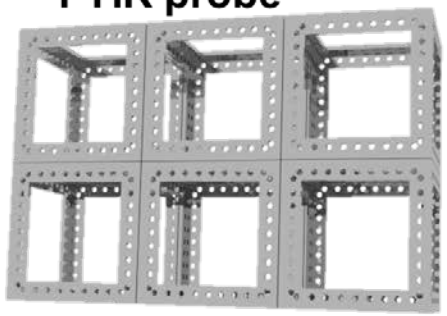


Dilution carts
AVS skids



FTIR probe



- How many bricks are needed for old operations?
- How do we replace traditional operations with new ones?
- How many bricks are needed for the new?
- Design can be contributed to by all within a common facility framework

How to accelerate the FotF

- Filing advanced technology feels a bit like punishment currently
  - Extra questions on filings are viewed as bad
  - Extra questions = extra effort = lots of debate as to whether or not any of this is worth it
  - Models are definitely viewed as a bad idea – maintenance
  - PAT is viewed as a bad idea - maintenance

  - *Could the educational piece be divorced from the review?*
  - *Could we agree on what is needed to prove certain arguments?*

How to accelerate the FotF

- If science and technology exist to replace procedural expectations, procedures should be replaced
  - New sites will be needed to respond quickly to world needs - hard to do if you have to “prove” new site equivalency
  - Quit defining everything new within the boundaries and terminology of the old, e.g., process validation

- The best of all – a filing incentive would be most obvious to business units of companies

Conclusions, and challenges

- Next wave of medicines requires us to change
- Rapidly addressing world health crises 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 be rebranded to focus on design. The future requires it

Acknowledgments

- Carla Luciani – for always thinking big thoughts
- Marty Johnson – for his infinite creativity in designing the future