Build A Biotech Facility: A Town Hall Discussion with Peter Cramer, AIA and Jeff Odum, CPIP

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Connecting a World of Pharmaceutical Knowledge

Can you answer the question "Why?"

- We woke up, Industry changed
  - Number of new and existing companies that got in to the disposable arena seemed to explode overnight.
- The future is here today
  - The global agencies have embraced SUS which helps streamline the approval process.
- Get on board…or get left behind
  - Most CMOs are going this way so if you don't your options will be limited.

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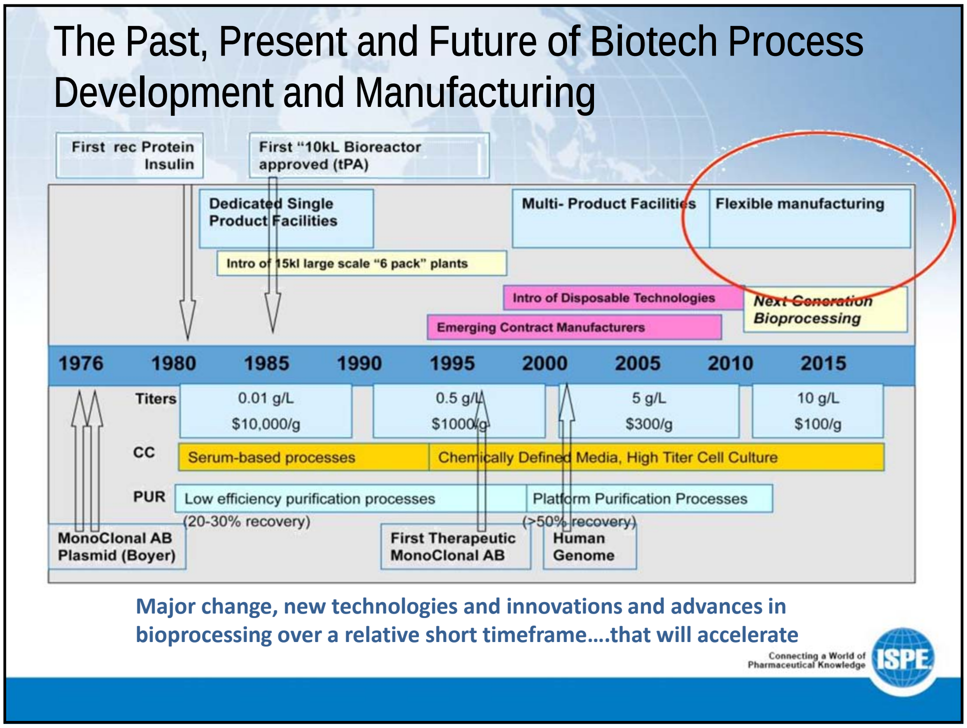
The Past, Present and Future of Biotech Process Development and Manufacturing
First rec Protein Insulin
First "10kL Bioreactor approved (tPA)
Dedicated Single Product Facilities
Multi- Product Facilities
Flexible manufacturing
Intro of 15kl large scale "6 pack" plants
Intro of Disposable Technologies
Next Generation Bioprocessing
Emerging Contract Manufacturers
1976
1980
1985
1990
1995
2000
2005
2010
2015
Titers
0.01 g/L
$10,000/g
0.5 g/L
$1000/g
5 g/L
$300/g
10 g/L
$100/g
CC
Serum-based processes
Chemically Defined Media, High Titer Cell Culture
PUR
Low efficiency purification processes
(20-30% recovery)
Platform Purification Processes
(>50% recovery)
MonoClonal AB Plasmid (Boyer)
First Therapeutic MonoClonal AB
Human Genome
Major change, new technologies and innovations and advances in bioprocessing over a relative short timeframe....that will accelerate
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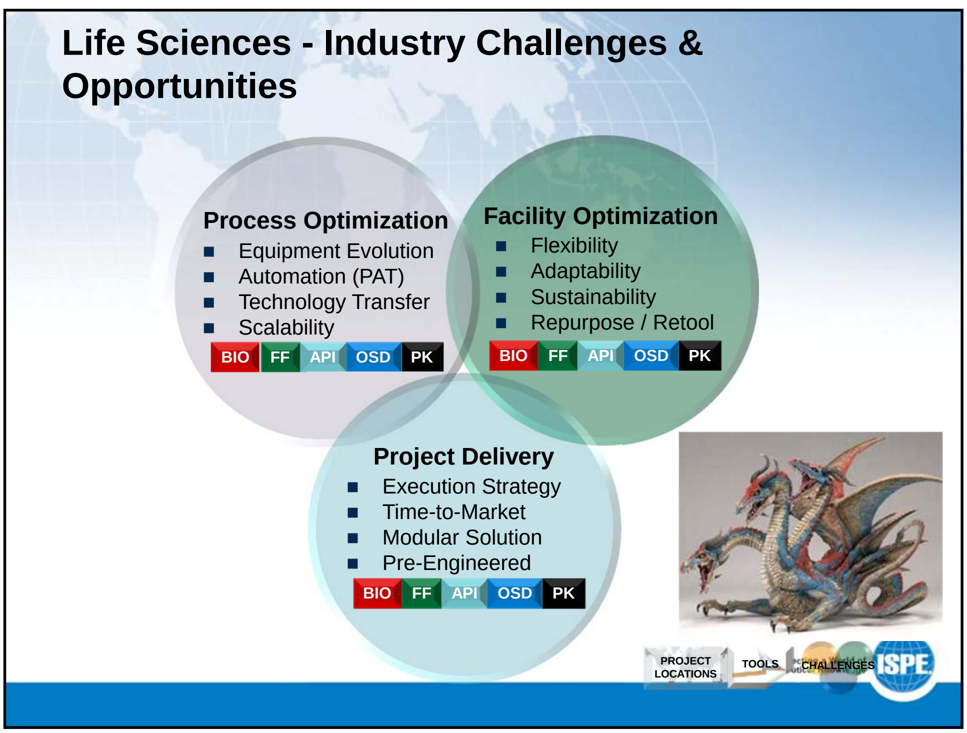
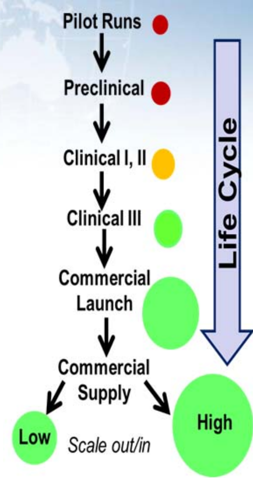

Life Sciences - Industry Challenges & Opportunities
Process Optimization
Equipment Evolution
Automation (PAT)
Technology Transfer
Scalability
BIO FF API OSD PK
Facility Optimization
Flexibility
Adaptability
Sustainability
Repurpose / Retool
BIO FF API OSD PK
Project Delivery
Execution Strategy
Time-to-Market
Modular Solution
Pre-Engineered
BIO FF API OSD PK
PROJECT LOCATIONS
TOOLS
CHALLENGES
ISPE

Manufacturing Challenges/ Opportunities

- Multiphase Opportunities
  - ❖ More Products
    - Biosimilars
    - Therapeutic Families
    - ADM Business Models
  - ❖ Faster, Faster
    - Faster Product Lifecycles
    - Advances in Clinical Designs
    - Less "Tech Transfer"



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What are the big decisions that need to be made when designing a biotech facility: Do you know?

- Capacity Requirements:
  - What products do you need to make today and in 5 – 10 years.
  - How diverse is the range of products that will need to be made, Will different equipment be needed for different products
  - Are you willing to reduce the number of products that can be made to reduce cost, schedule etc.
- Traditional vs. Hybrid vs. All Single Use
  - Adaptability - Having the ability to adopt new strategies (medicines, modalities and technologies)
  - Responsive - Adjusting and responding quickly to changing conditions and market shifts
- Schedule: How long do you have to get the facility on line.
  - This will impact project delivery model
- Budget: How much can you spend
  - Cost effective - Maintaining cost-effectiveness and the ability to adapt to cost pressures
- Do you have a Site in Mind
  - Greenfield, Brownfield or Renovation

Decisions Lead to

What you will get for results:

- Manufacturing Output
- Capital investment
- Facility buildout time
- Cycle time
- Flexibility
- Environmental impact
- COGS

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Single Use 6

What are the big decisions that need to be made when designing a biotech facility

First things first: Do you know?

- Independent, Central or Shared Utilities
- Space Constraints, Labor Constraints, Existing Space
- Stick built interior wall or modular panels, available of suppliers and installers.
- Built to meet existing company standard to define a new benchmark.
- Risk levels,: Completely Closed Process
  - Room Classification
  - Separation of areas
- Automation approach: Vendor Supplied, Company Standards

Decisions Lead to

What you will get for results:

- Manufacturing quality
- Capital investment
- Facility buildout time
- Cycle time
- Flexibility
- Environmental impact
- COGS

Single Use 7

Advances in Bioprocessing – *Upstream* Process Optimization

- **Companies continue their strategy of process intensification, getting more DS out of their bioreactors' to achieve higher cell densities, increased titers and yields**
- **New monitoring and control systems for bioreactor processes enhance process definition and reduce variability**
- **Focus on media (e.g. animal free and defined)**
- **Further advances in process scale-up capabilities going from bench top to production**

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Advances in Bioprocessing – *Downstream* Process Optimization

- **Purification is the most common process constraint**
- **It has been further exacerbated by higher and higher upstream titers**
- **There are growing cost considerations (e.g. Protein A is an expensive resin)**
- **Development of alternative technologies (e.g. membranes)**
- **New downstream platforms will be needed for new product types**
- **New requirements due to the growth of vaccines**

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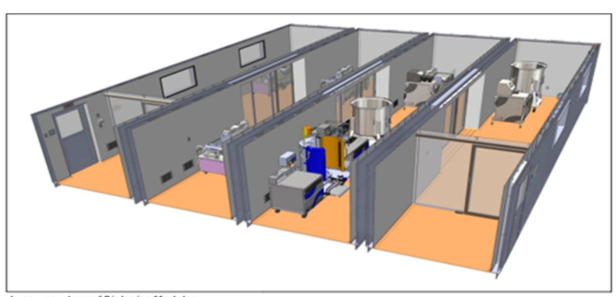

Image courtesy of Biologics Modular

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Pro's & Con's of Single Use
The things Mom didn't tell you…

- *Do you really know the drivers/goals of Innovation?*

Pluses	Neutral	Minuses
Low capital investment		Rely on vendors
No cleaning validation		Higher consumables cost
	Leachables/Extractables	Inventory storage
Decreased process times		Lot /material tracking
Fewer FTE's		Vendor initiated change controls
Easier to transfer/move process		

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SUS Implementation…

- …need not be "all or nothing" (where it makes sense)
- …cost drivers are more than capital costs
- …risks include both schedule and logistics
- …may be outside of the QA Group's box
- ……Vendor selection/partnership becomes critical

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Project Delivery Tools (Toolbox) that define your companies "Best Value"

- The challenged to deliver truly flexible biopharmaceutical manufacturing facilities with significant reductions in schedule, cost, and client operating resources.
- A flexible "platform" approach can provide advantages to achieving reductions in schedule, cost and internal resources and at the same time deliver production flexibility where it really matters.
- Analysis tools can highlight the advantages and disadvantages of the different project delivery methods on production flexibility and provide a method to quickly gain insight into which platform approach is best suited to a specific project's needs.
- "Platform" and standardized project delivery approaches can help establish project requirements at the start of a project in a efficient way.
- Decision trees can be built to guide the decision making process given real world project conditions and constraints.

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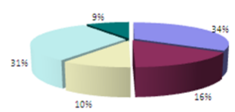
Business Case Analysis: TCO Approach to Compare Technology Cost

Case Study – Summary Cost Breakdown

	Gram	Batch	Campaign	Year	%
Capital	68.1	140,166	14,156,788	14,156,788	34%
Materials	32.2	66,231	6,689,296	6,689,296	16%
Consumables	19.3	39,695	4,009,187	4,009,187	10%
Labour	63.5	130,638	13,194,430	13,194,430	31%
Other	18.7	38,432	3,881,667	3,881,667	9%
TOTAL	201.8	415,162	41,931,368	41,931,368	100%

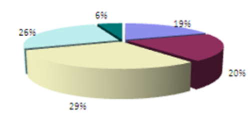


MAb Typical 201.8 US$/g

Total Capital (US$ M)	Batches per Year	Campaign Batches	Throughput (kg/yr)	Batch Size (kg)	DSP Yield (%)
67.6	101	101	207.7	2.1	51%

Stainless steel (base case)

	Gram	Batch	Campaign	Year	%
Capital	29.4	60,567	6,420,101	6,420,101	19%
Materials	30.9	63,509	6,731,920	6,731,920	20%
Consumables	44.4	91,334	9,681,412	9,681,412	29%
Labour	39.2	80,711	8,555,313	8,555,313	26%
Other	8.2	16,793	1,780,042	1,780,042	5%
TOTAL	152.1	312,913	33,168,789	33,168,789	100%



MAb Typical 152.1 US$/g

Total Capital (US$ M)	Batches per Year	Campaign Batches	Throughput (kg/yr)	Batch Size (kg)	DSP Yield (%)
30.7	106	106	218.0	2.1	51%

Disposables for all options

Direct outputs from bioSolve

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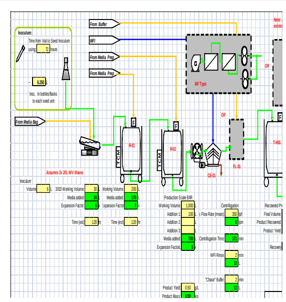
Capacity Modeling

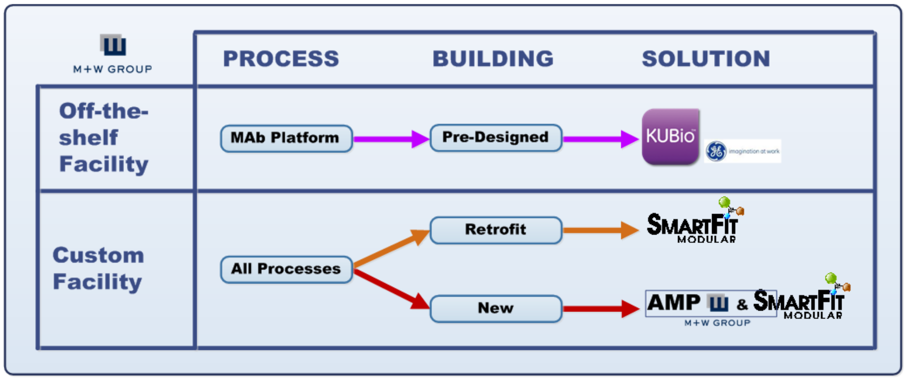
- Capacity analysis
- Utilizing basic parameters and this simple model, we can determine:
  - Optimal Bioreactor size
  - Number of runs/year
  - The number of bioreactors required
- Other considerations:
  - Custom equipment or off-the-shelf?
  - Redundancy philosophy
  - Process flexibility



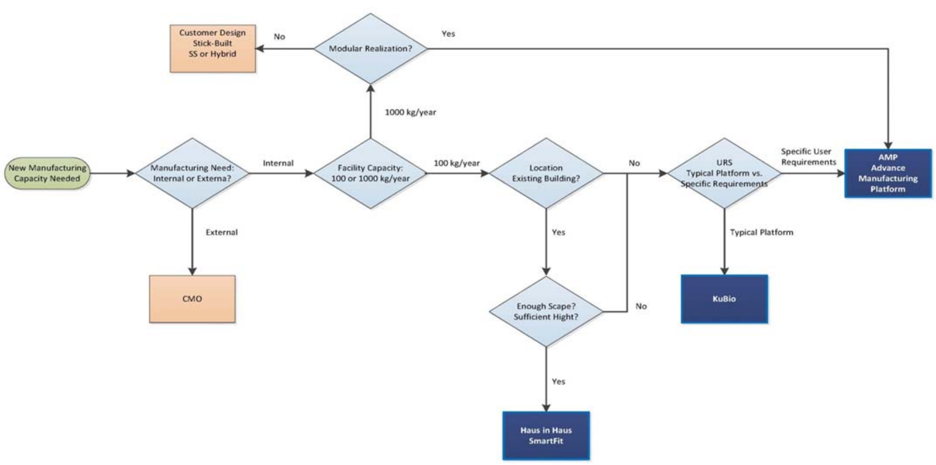
Annual Capacity Model	
KG required	100
Bioreactor Working Volume	2,000
Productivity (g/L)	3.0
Yield	70%
BRX Run Length	14
BRX Turnaround Time	4
Number of Days/Year	365
Facility Shut Down Days/Year	15
Bioreactor Utilization	90%
Number BRX Days/Year	315
Yield/Bioreactor (grams)	4,200
Number of runs required	24
Total grams required (grams)	100,000
Total grams produced	100,800
Total BRX Days	216
Bioreactor Utilization	69%
Number of Bioreactors Required	2
DSP:USP WFI Usage Ratio	9
Water Usage (L)	480,000

Real World Flexible Facilities Approaches

- **Why?** limit the risk - time and budget
- **Target?** Single-use and hybrid facilities



Decision Trees:



Create and Analyze Multiple Options using a "Option Evaluation Matrix"-

- Identify the *key goals and drivers* for the project:
- "Develop alternatives that highlight the advantages and disadvantage associate with the use of different single use technologies"

Description	Weight	Scheme A		Scheme B		Scheme C	
		Raw	Wt.	Raw	Wt.	Raw	Wt.
SITE AND MASTER PLAN OPTIMIZATION							
Ease of expansion: Ability to Support Future MFG. Requirements							
Impact on existing site usage: Roads, Wetlands, Underground Utilities							
Serviceability: Access to Utility areas, Yard, Tank Farms, Warehouse Docks							
Minimizes disruption to Existing Operations during Construction							
Minimal Impact to existing Fill/Finish Activities							
Ideal location for Personnel Entry Points							
PROCESS AREA OPTIMIZATION							
Ease of Expansion (Additional Cell Culture or Purification Suites)							
Layout support use of Disposable Technologies							
Close proximity of Inoculation Laboratories, Seed and Production Bioreactors							
Buffer Hold adjacent to Purification, Media Hold Bags directly adjacent to Reactors							

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- "Develop alternatives that highlight the advantages and disadvantage associate with the use of different single use technologies"

Description	Weight	Scheme A		Scheme B		Scheme C	
		Raw	Wt.	Raw	Wt.	Raw	Wt.
SUPPORT AREA OPTIMIZATION							
Dispensing directly adjacent to Media and Buffer Prep							
Wash area directly adjacent to Purification and Cell Culture							
Locker Rooms adjacent to Supply Corridor							
Optimize use of existing space above ceiling (Interstitial), i.e., walkable ceilings							
Chases for Piping, Electrical and HVAC distribution							
High Bay "Narrow Isle" Warehouse (Optimize Existing S.F.)							
Ease of Early Occupancy for Offices and Labs							
ACCESS, FLOWS, AND SERVICEABILITY							
Central "Supply-Corridor" with Perimeter-"Return-Corridor"							
"One-way Flow" concept for personnel, materials and equipment							
Separate Gown & Degown Airlocks							

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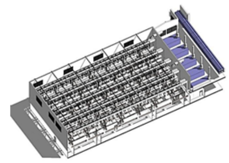
AMP Features – Value Analysis

Launch Facility Design Features

Future Flexibility	Speed to Implement	Quality	Flexibility	Cost
Design Reuse at Other Locations - Modular Engr.	+	+		-
Built in Expansion Capability, Expand w/o redesign			+	-
Separation of Process and Building Shell	+		+	$0
Minimize Reconfiguration for Product Changeover	-		+	-

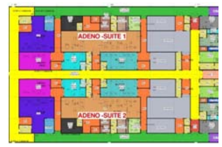


Launch Facility Design Features

Component	Speed to Implement	Quality	Flexibility	Cost
Walkable Ceiling	+	+		$175,000
Long Span Trusses	+		+	$220,000
BL-3 Design	-		+	$325,000
Added Height Limit (4.7 m) to Bottom of Truss			+	$35,000

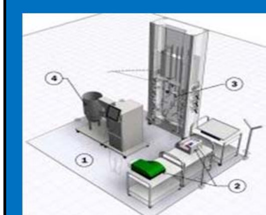
Launch Facility Design Features

Component	Speed to Implement	Quality	Flexibility	Cost
Identical Process Suite Sizes (Adeno Virus)	+		+	$720,000
Modular Construction (PAMs)	+	+	+	$40,000
Standardized Structural Frame	+	+		-
Convertible to Production Facility (Blockbuster)			+	$0

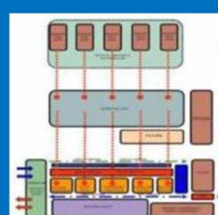


Pre- Engineered Solutions

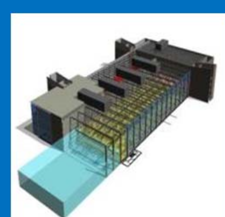
- Innovation Drives Efficiency - Reduces Cost and Schedule



Standardized Process Train

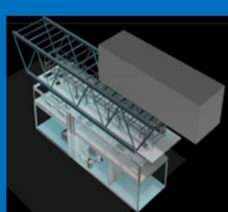


AMP: Ballroom Process Hall



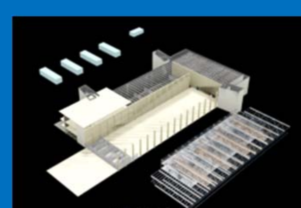
AMP: "Kit of Parts" Modular Design Approach

"House in House" Solutions (PODS)



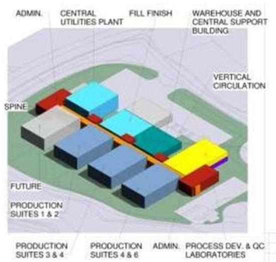
Modular Building Components

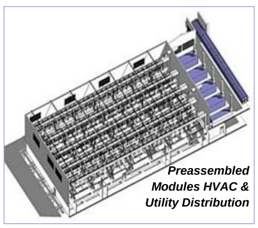
Pre-Engineered Facilities "Kit of Parts" Layouts

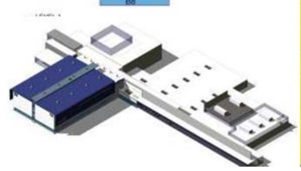


AMP: Expandable & Flexible to future process Technologies

Trends: "Flex Shell" Production Ballroom







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Design Features – Value Analysis

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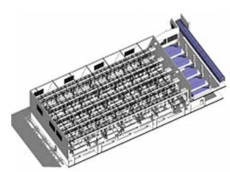

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Standardized Structural Frame	+	+		-
Convertible to Production Facility (Blockbuster)			+	$0

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Case Studies

Case Studies: Multi Product Opportunities

AMP: BSL-1

AMP: Biologics Facility

AMP: BSL-2+

AMP – BSL-3

4 Different Products Capable of being Produced in the Same Footprint

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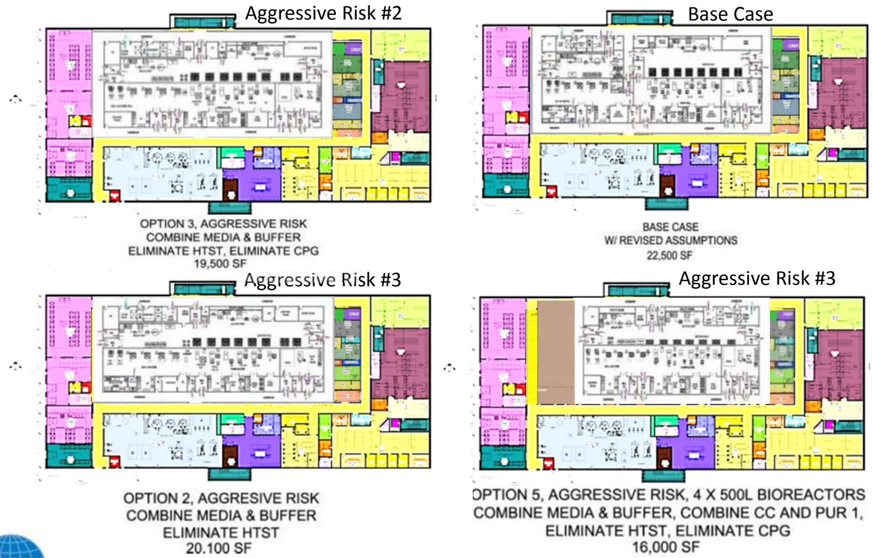
Case Study: Different Risk Profiles



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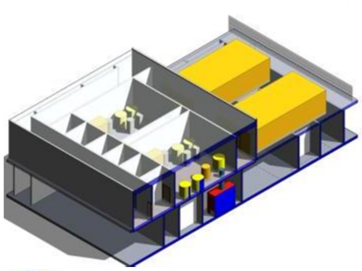
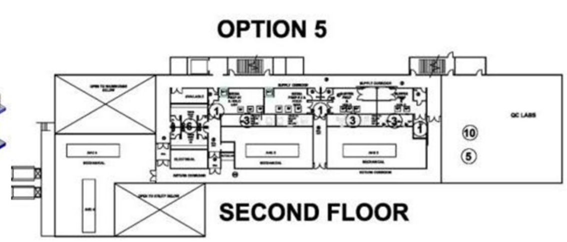
Case Study: Multi Story

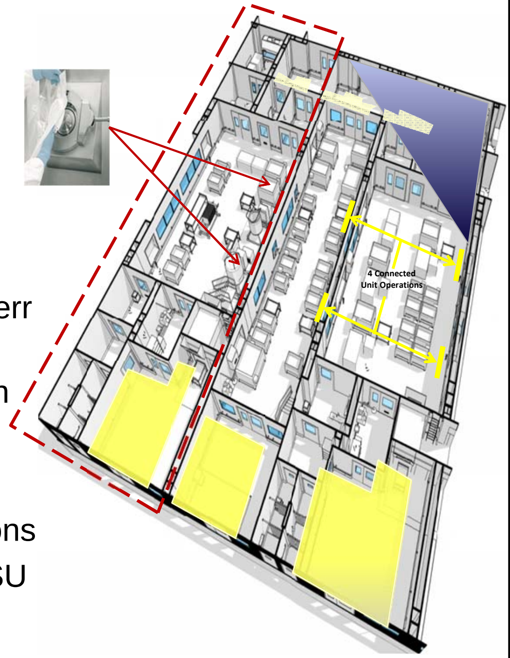


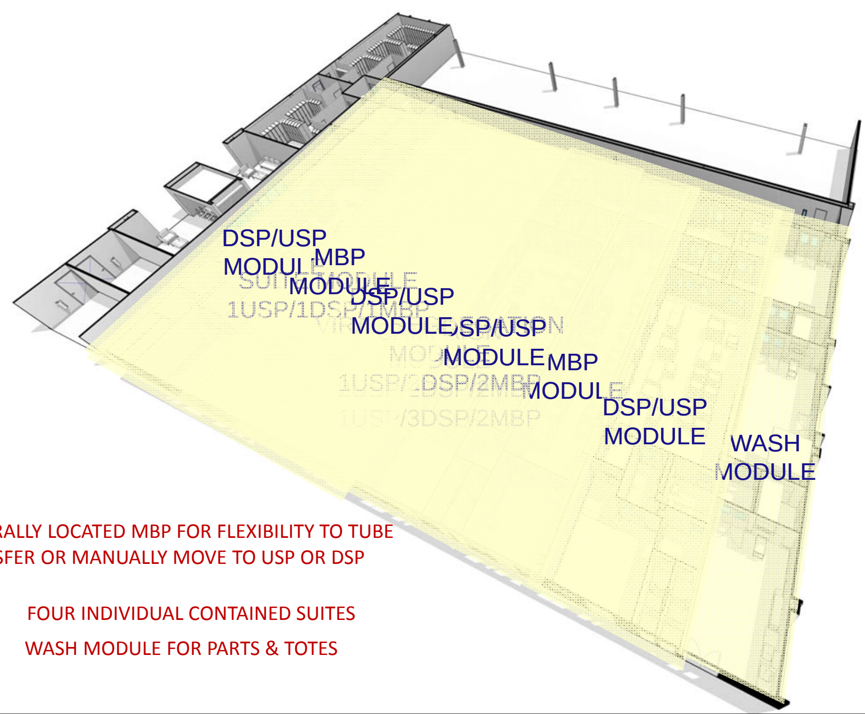


Single Use 30

Case Study

- Architecture
  - Open Suite Design
  - 100% Modular Planning
    - Reproducible/Transferrable
    - Modular Construction
    - Walkable Ceilings
    - Rapid Transfer Ports
    - Unit Operation Stations
    - Incoming/Outgoing SU Staging





Summary: Biotech Plant of the Future

- New technologies, design concepts and operating philosophy that will serve to define the biotech plant of the future
- Changes in capacity utilization is a driver
- Shift to multi-product and multi-purpose strategies to maximize flexibility and asset utilization
- Implementation of DS and DP platform technology for new and legacy products
- Growing application of single use / disposable technologies as technology and economics evolve especially with smaller batch size
- More sophisticated automation solutions enhancing process understanding and control
- Utilization of modular manufacturing concepts

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