



Flexible, Fast and Future Production Processes

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ISPE®

Small Molecule - “The Silent Majority”

Small molecules:

- Account for ~82% of new drug applications (2014)
- ~60% of new molecular entities (2014)
- Highly potent API's is a particularly strong sector



Current Industry Trends



Fewer 'Blockbuster' drugs in Pipeline

- Focus on Speciality Pharma / Patient Needs e.g. Oncology
- Smaller Volumes / Higher Potency Drugs (*'Nichebusters'*)



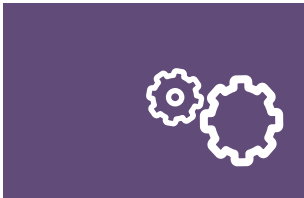
Need to get to Market Sooner

- Reduced Development Time
- Faster Production of Kilo Quantities



Rebalancing of Manufacturing Assets

- Large Scale API hardest hit
- Evolution & Repurposing of Manufacturing Sites



Lab Scale to Batch Scale

- Scale Up Efficiency
- Reduced Turnaround Times

Small Scale Project Drivers

- ▶ Small Volume “Niche” Drug Products
- ▶ Fast & Flexible Production of (Early Phase) Pharma Materials
- ▶ Sustainable Production Technology
- ▶ Reduced Capital Investment for NPI (New Product Introductions)
- ▶ Bulk API Plant Operating Efficiencies



- Existing Reactor Capacities not suitable for low volumes
- Product introductions slow & costly

Capability Gap' Identified
Primarily a Bulk API Facility

Small Scale Production Facility
(0-5kg / 5-25kg Scale)

- Production Suites
- Manufacturing & Isolation Capability

Options Within Existing
Infrastructure

- Make best use of existing real estate
- Reuse existing utility services

"Fast - Flexible - Future"
(F3 Factory Concept)

- European Initiative
- Future proof Investment

Capability Gap

Legacy manufacturing sites

- Typical production reactor volumes 6000 – 8000L
- Old style product introduction reactor volumes 1000 – 2500L
- More potent drugs – significant infrastructural gap exists



Small Scale Manufacturing Suites

New facilities

- New capacity requirements – reactor volumes 80 to 300L
- Close containment gap – facility design and containment approach
- Facilities infrastructure
- GMP considerations



Small Scale Manufacturing Suites – Case Study 1



Small Scale Manufacturing Suites – Case Study 2



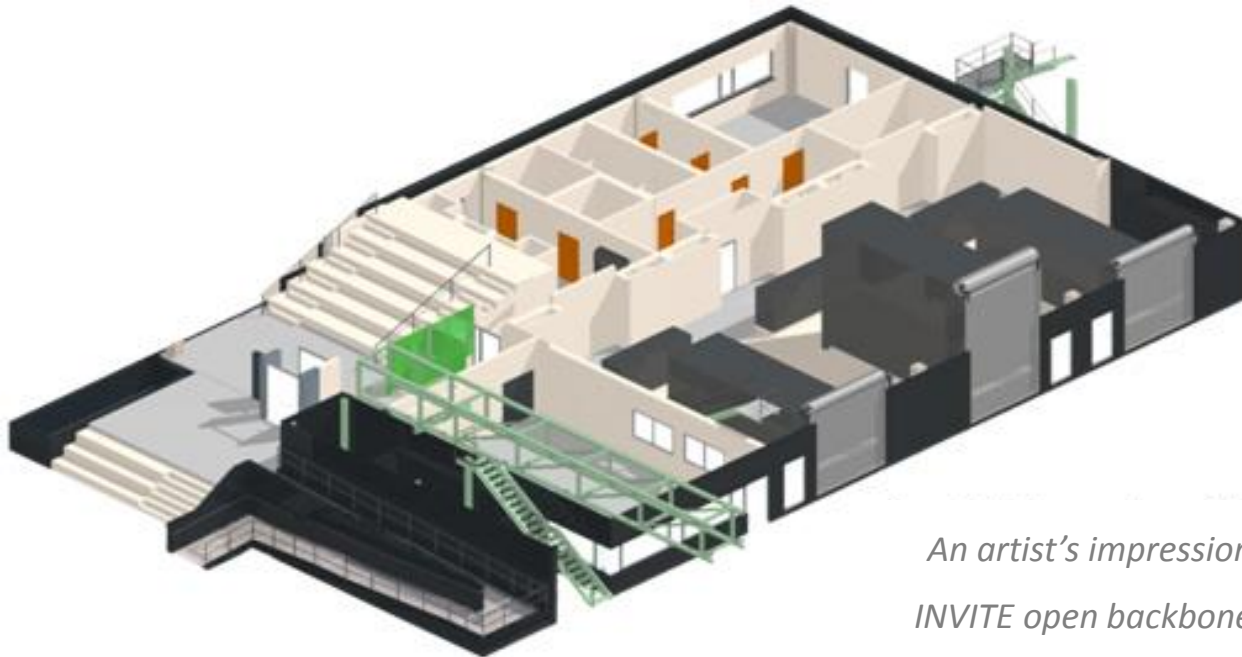
Flexibility Modules

- Trickle bed hydrogenation
- Plug flow reactors (static mixers)
- Continuous crystallization (CSTR)
- Continuous liquid-liquid extraction
- Vapour-liquid separation
- Chromatography purification technology
- Continuous filter drying

Learn from F3 concept

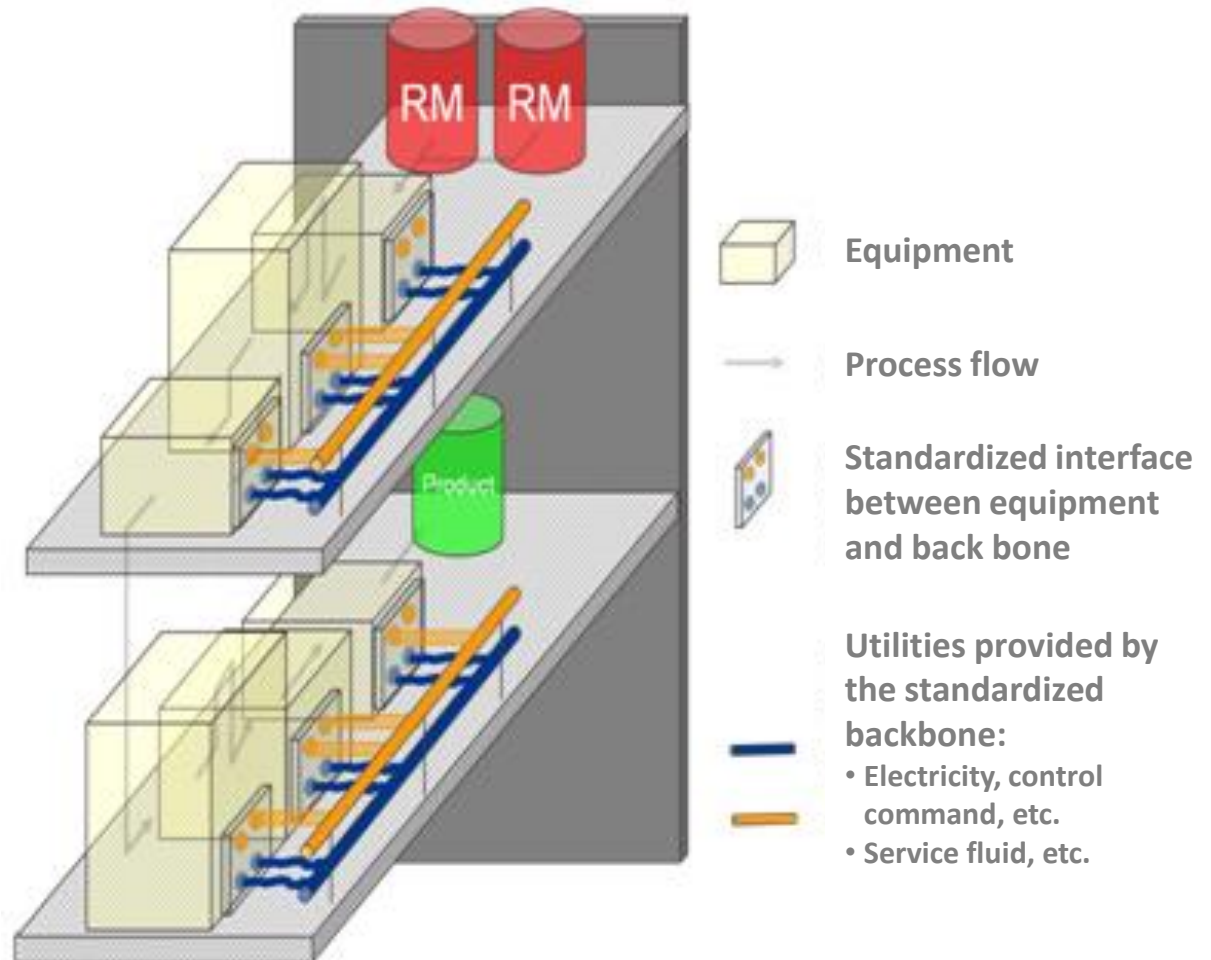
- Public/private sector initiative launched in 2009
- Develop modularised process operations
- Design and utilisation of a common large scale ‘back bone’ facility
- GMP considerations

Learn from F3 concept



*An artist's impression of the
INVITE open backbone facility*

Learn
from
F3
concept



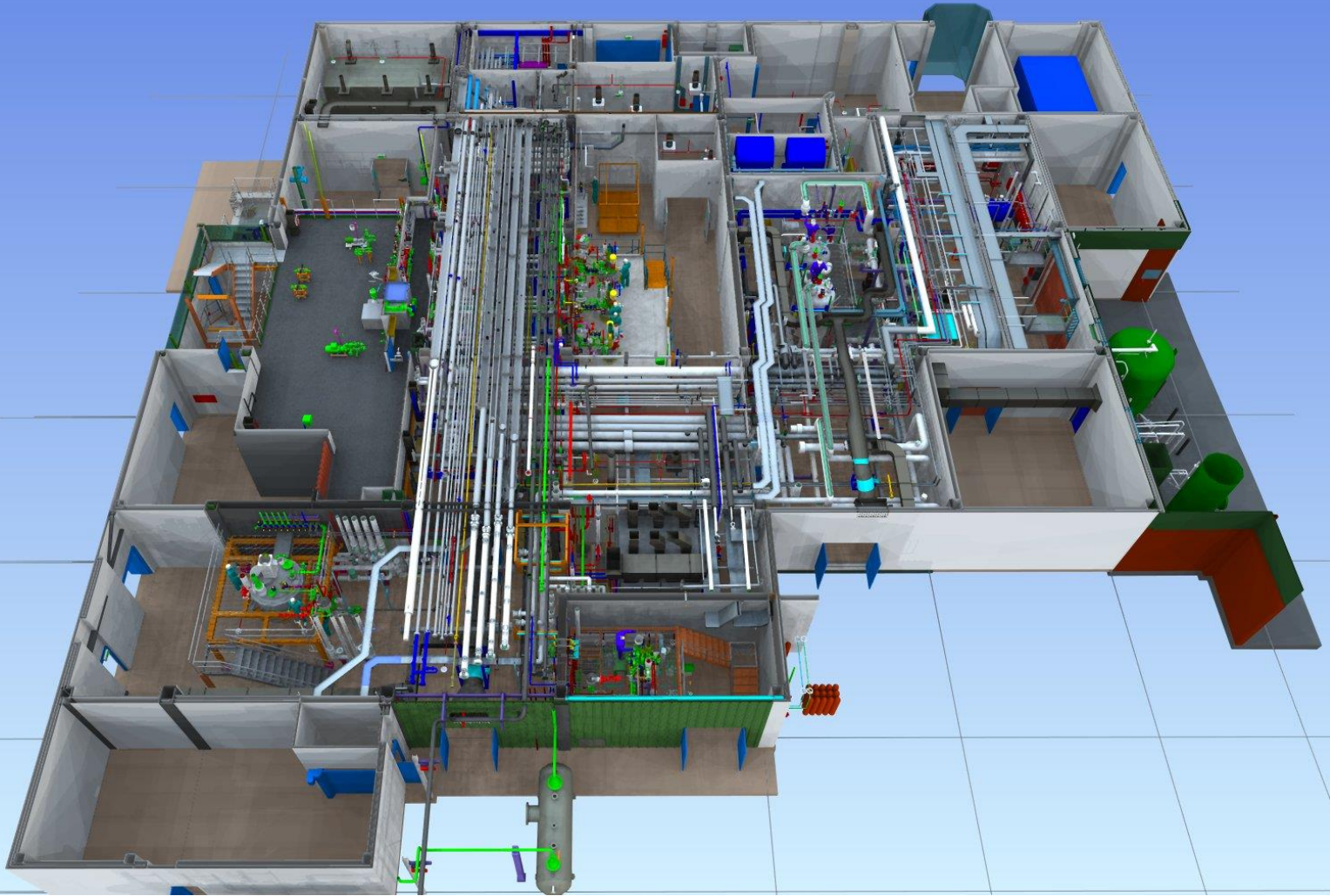
Implement concept

- Backbone amended to suit available real estate and infrastructure
- Allow for interaction with modularised units
- Key is utility provision, supply and receiver vessel provision

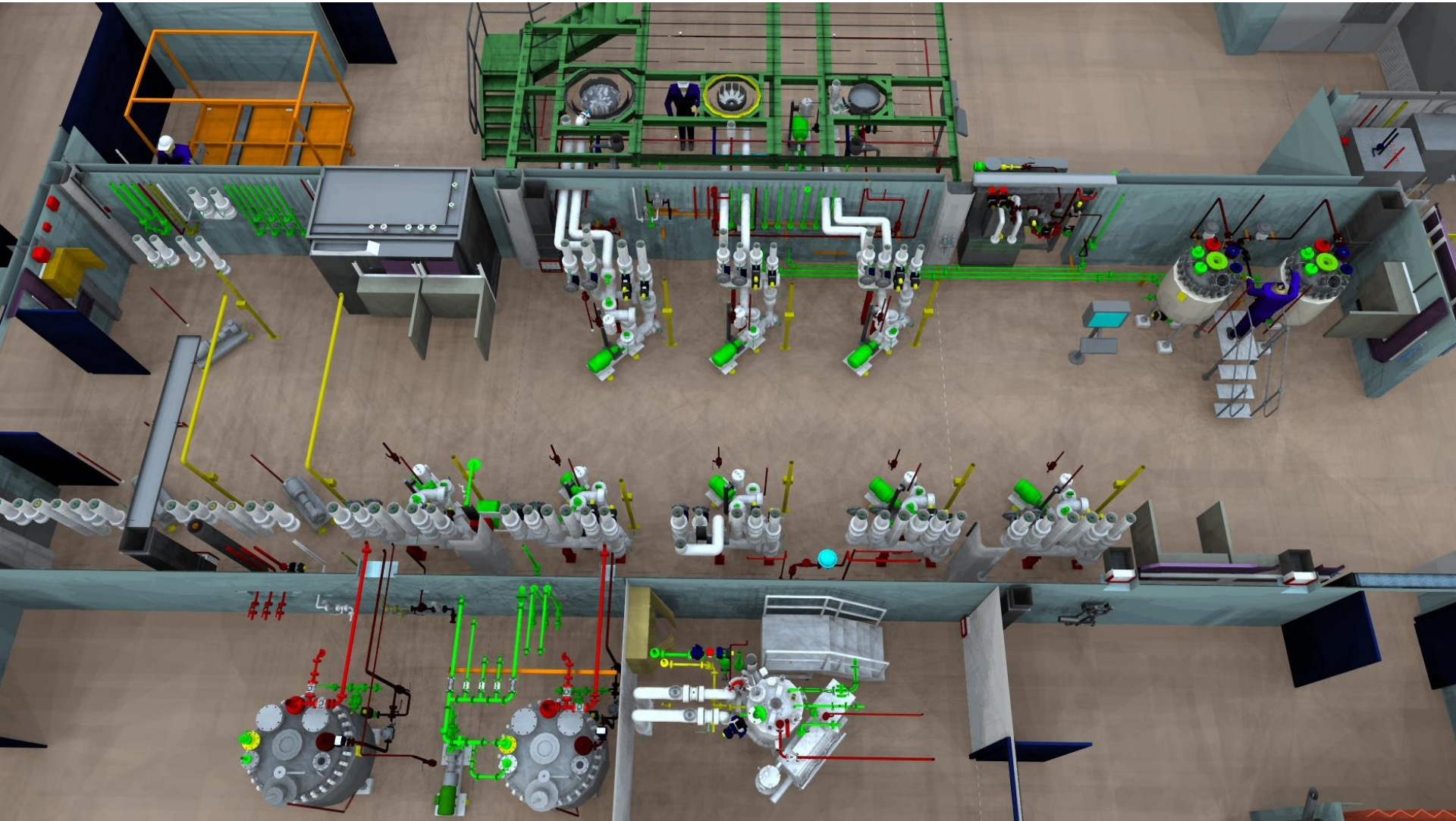
Backbone utilities



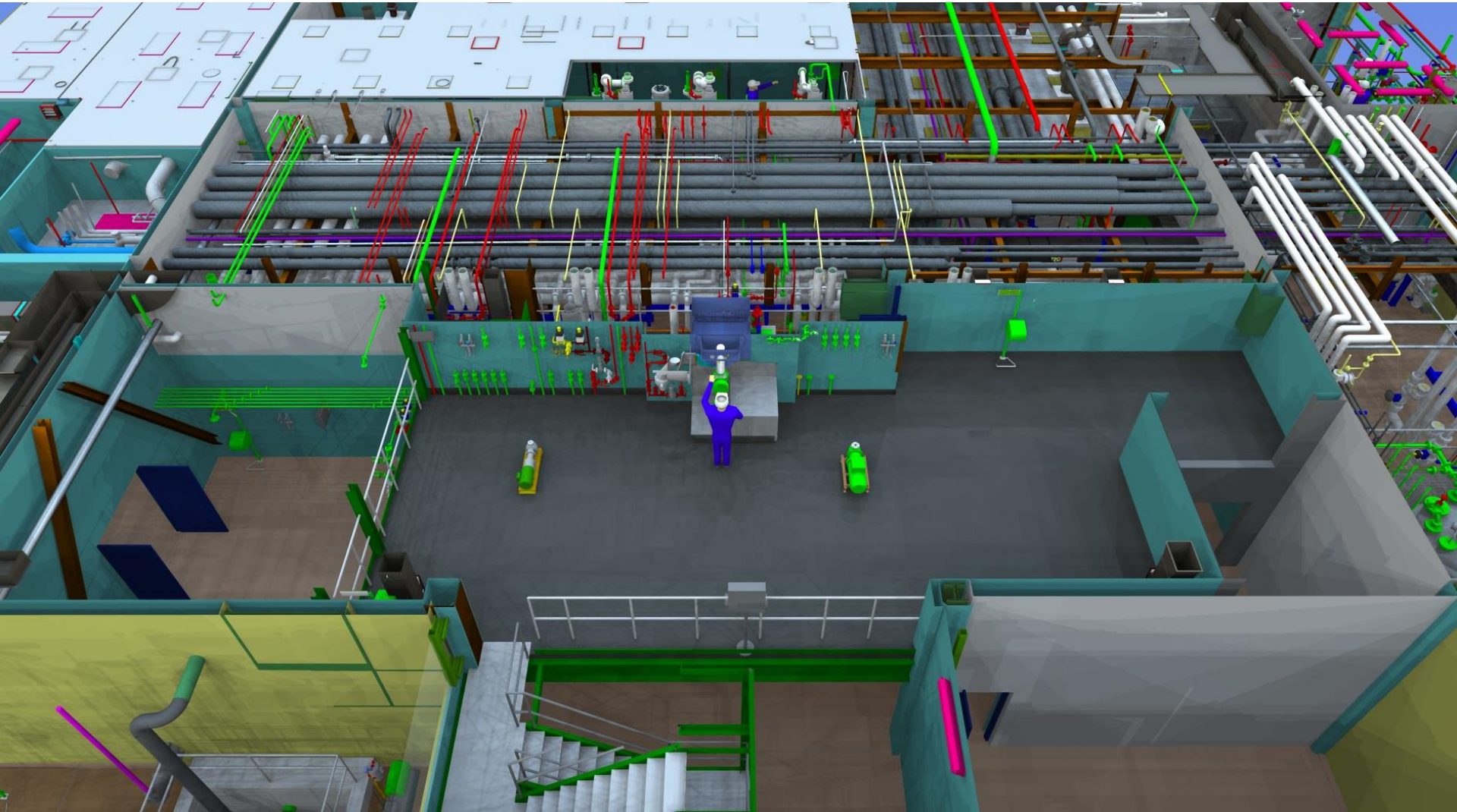
F3 Implementation



F3 Implementation



F3 Implementation



Early Project Challenges



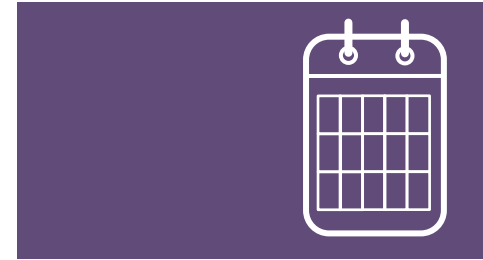
Budget

- Design to a budget or budget to a design
- Early approval vs. contingency risks



Cost

- Value Engineering
- a team based exercise
- Client changes



Schedule

- Fast track;
18 months to 12
12 months to 8
- Allow design process to develop

Fast Track Design



Design Development Highly Interactive

- Significant P&ID and design document reviews
- Extensive modelling reviews



Early Piping Design

- Develop isometrics from HAZOP issue PIDs
- Client buys into element of risk
- Depending on delivery , MTO for lined pipe issued and procured at intervals



Change Management

- Expedited approval cycles
- Traceability

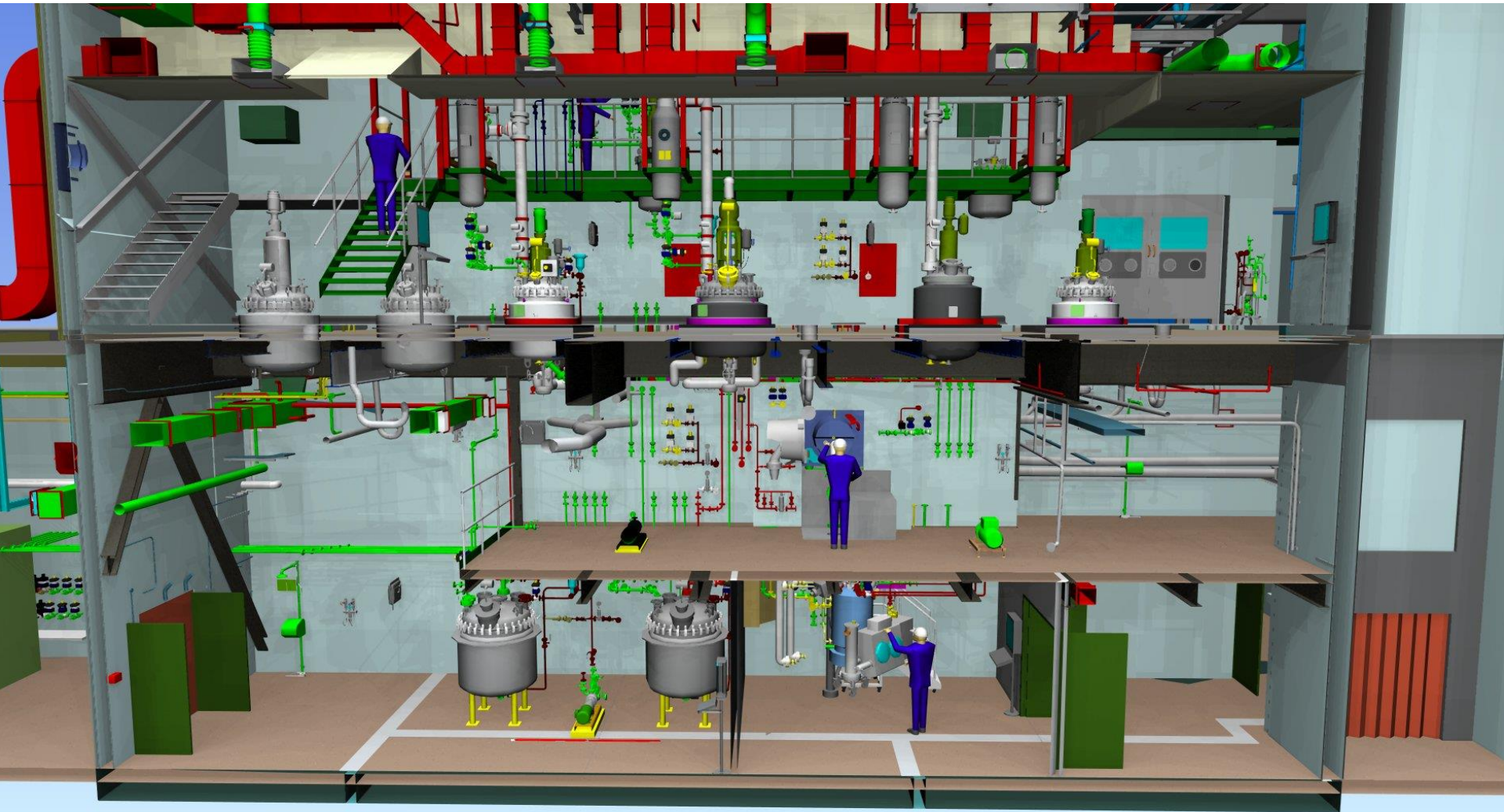
Design for everything



Candy shop

- Multiple 'process fit' evaluations
- Provision for process modules per F3 concept
- Better to omit a unit operation than reduce functionality
- Re-engineering and rolling with the punches

Design for everything



Small Scale Scope



Core Equipment

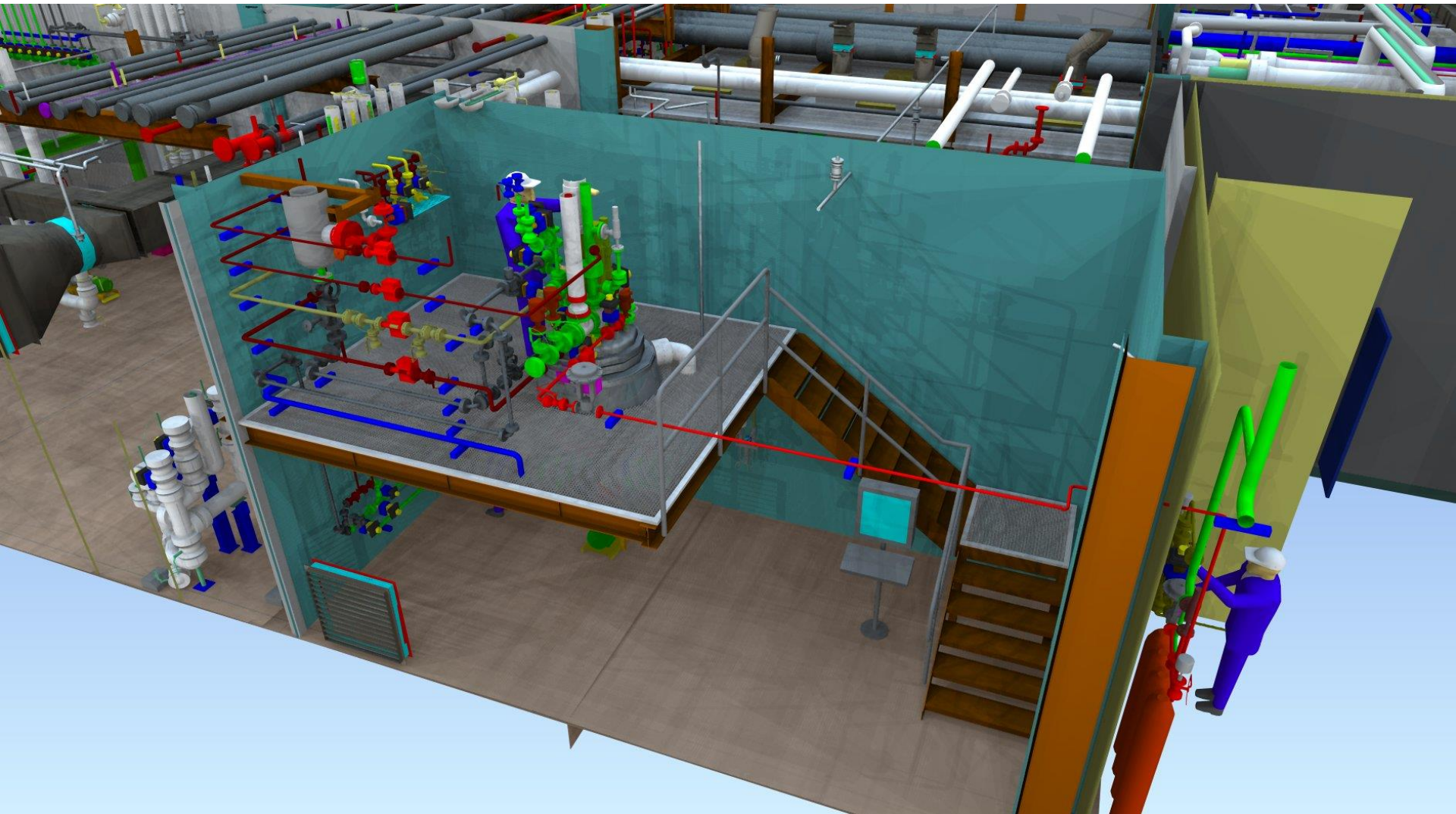
- Reactors/ crystallisers
(varying sizes and MOC)
- Hydrogenator
- Isolation device
(Centrifuge, Filter Drier)



Ancillary Equipment

- Head Tanks
- Receivers
- Solvent booths

Hydrogenation



Small Scale



Diversity

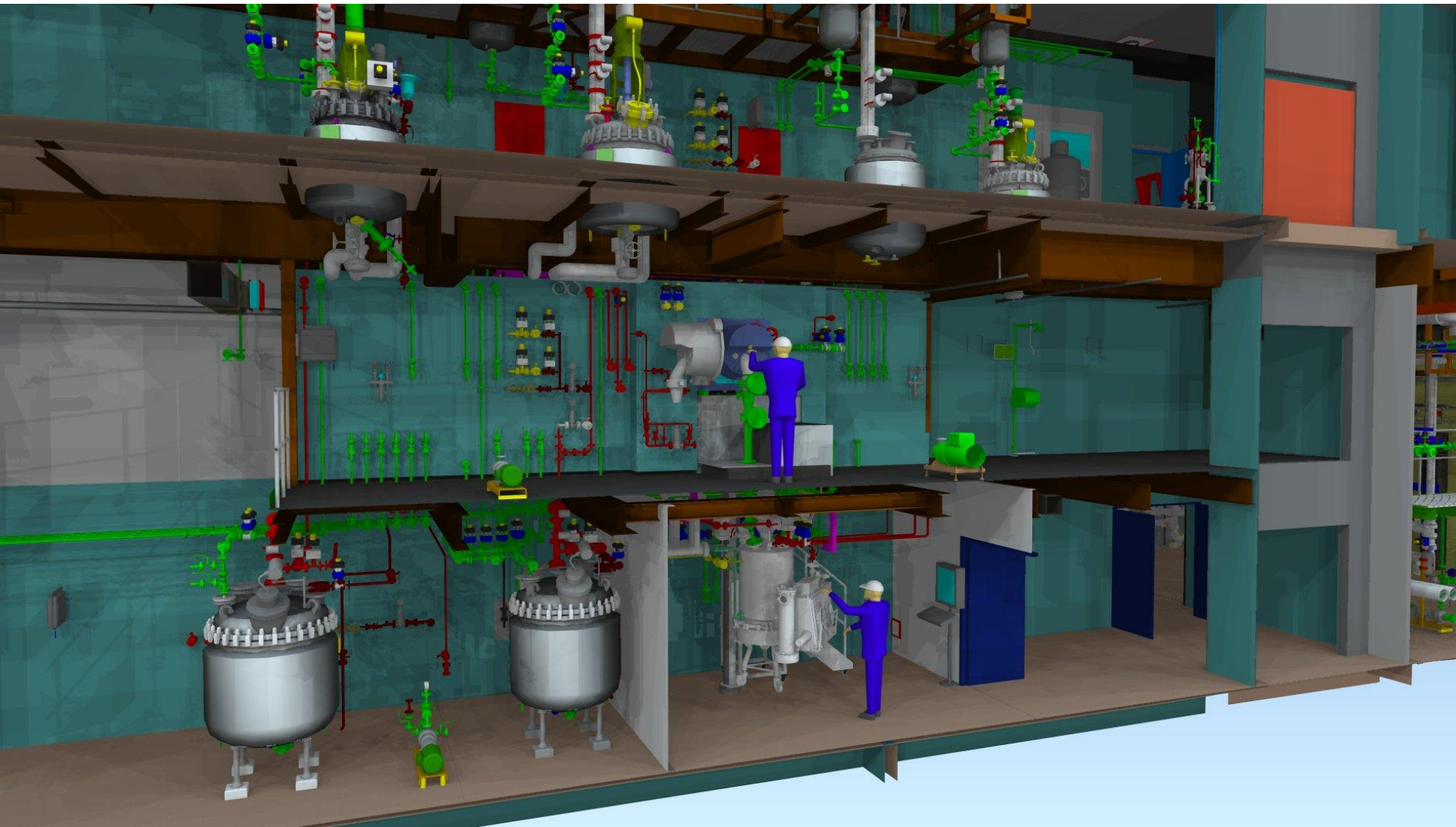
MOC

- Elastomers and seals
- Mix of Tantalum, Hastelloy and GLCS
- Agreed list of solvent and processed materials

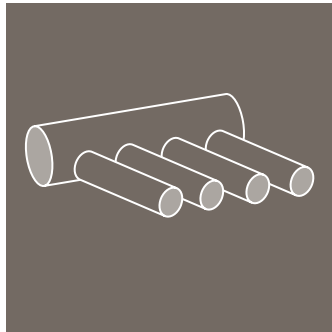
Design Range

- Agree pressure range
- Agree temperature range
- Develop HAC rating for facility

Intermediate Scale Section



Interconnectivity



Use of manifolds
and hoses

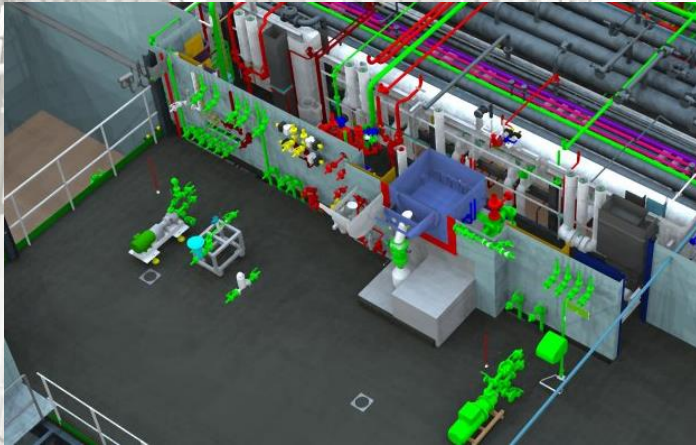
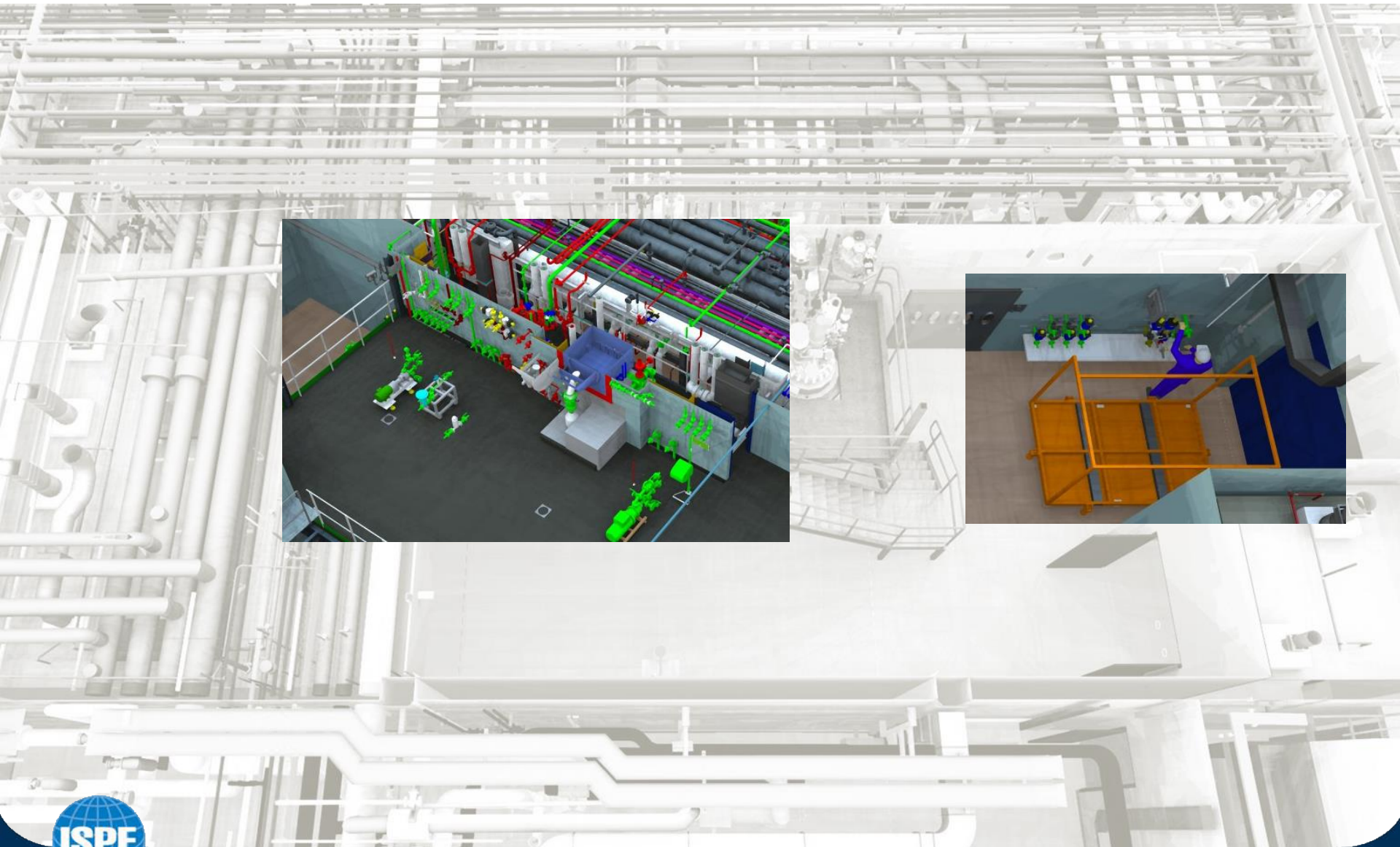


Use of mobile and
movable
equipment

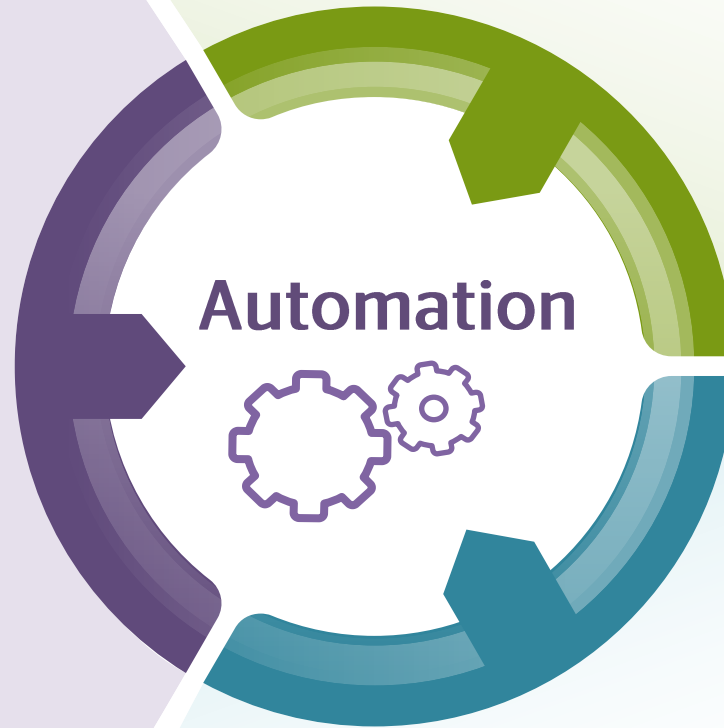


Plug and Play -
fixed / mobile
equipment and
skids

Interconnectivity



Manumatic



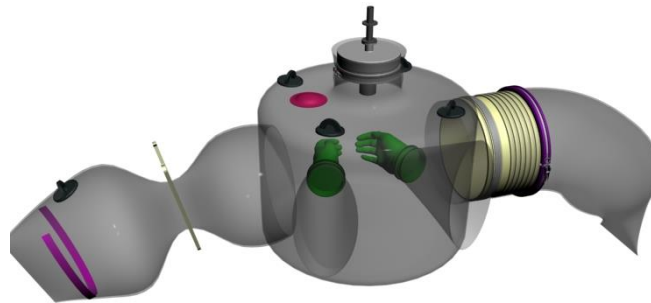
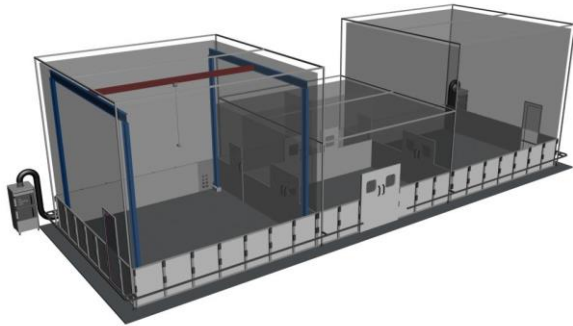
Automated standard operations

Interlocking

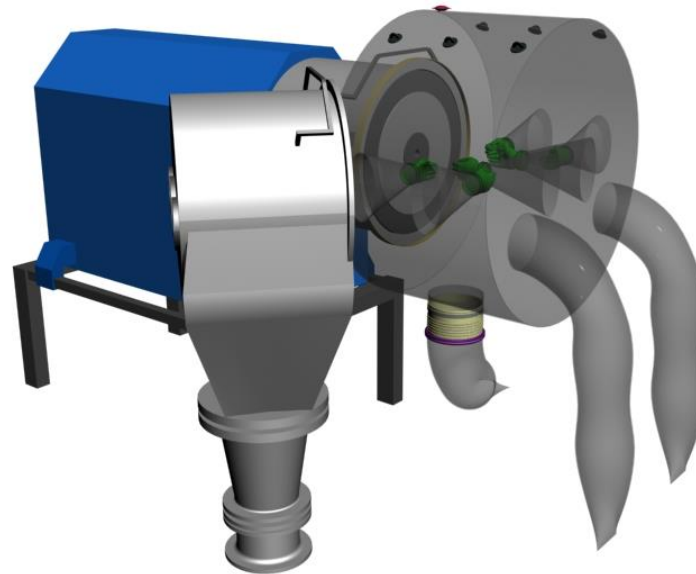
Intermediate Scale Plan 1SR FLR



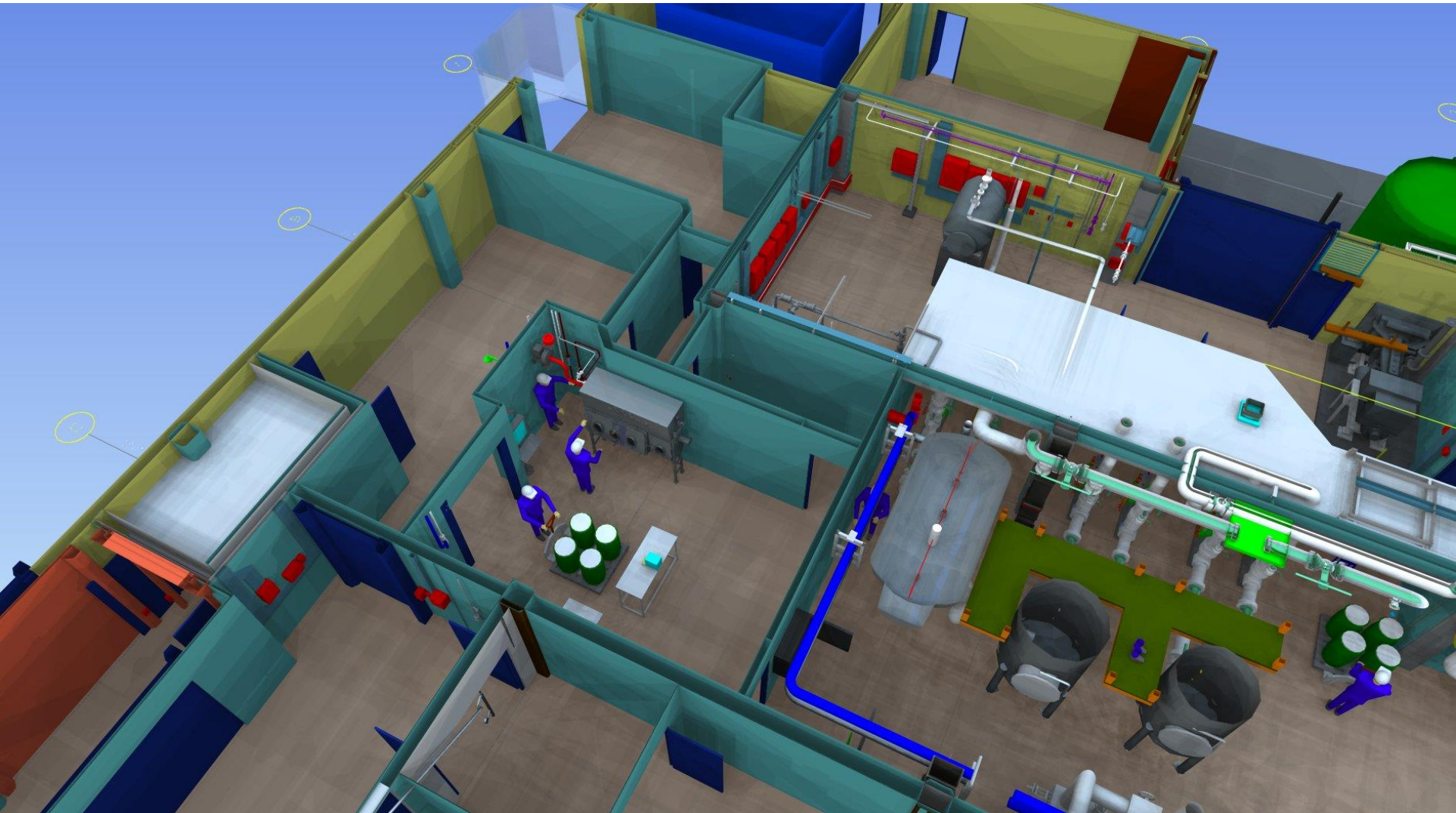
Containment



Scalable technology
to OEB4 / OEB5



Dispensary



Engage with All Stakeholders from Outset

- Include in Early Reviews & 3D Interactions
- Solicit Opinions

Optimise trade-off between 'Best' Layout v. Minimum Hold-Up

- Vertical Stack-up Preferred
- Never Base Design on Large Scale API Equipment



Lessons Learned

Value Engineer From the Outset

- Agree Scope Early – Late Design Changes are Major Impacts
- Track All Changes

Never Underestimate Piping or Instrumentation Design

- Maintenance and Operator Access Must be Incorporated
- Only Vessels are Small Scale!

Current Industry Trends (reprise)



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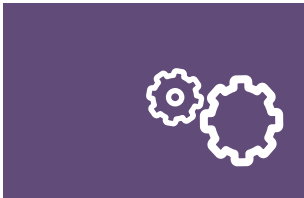
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Flexible Approach

Project Success

Integrated Team

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