

A woman with blonde hair, wearing a dark blue sweater, is shown in profile, interacting with a large, vertical digital display. The display shows a complex, glowing blue network diagram with many nodes and connecting lines, resembling a molecular or data structure. The background is a blurred city street at night with warm lights.

Biopharmaceutical Manufacturing Innovations on the Horizon

Narendra Bam

SVP, Biopharmaceutical
Development & Supply

GSK

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1. AGILE - Integrated DS manufacturing
 2. Polychaeta – Novel Sterile product manufacturing
 3. Digital Twin
 4. Pandemic learnings
 5. Q&A
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AGILE- Integrated DS manufacturing

Integrated Drug Substance Manufacturing



Value Proposition



Reduced Facility Cost & Footprint

- Smaller facilities
- ↓ Classified space
- ↑ Volumetric productivity
- ↑ Equipment Utilization
- ↓ Hold tanks
- ↑ Single-use paths



Flexibility

- Single system can produce 100-900 kg/year
- High turndown ratio –capable of processing wide range of titers and volumetric throughput
- Mitigates facility fit limitations



Increased Process Control

- Steady state production
- Highly automated
- Reduced residence time and elimination of intermediate holds
- PAT-enabled



Supply Chain Velocity

- Scale-out model for replication
- Simplified tech transfer
- Mitigation of scale up risk

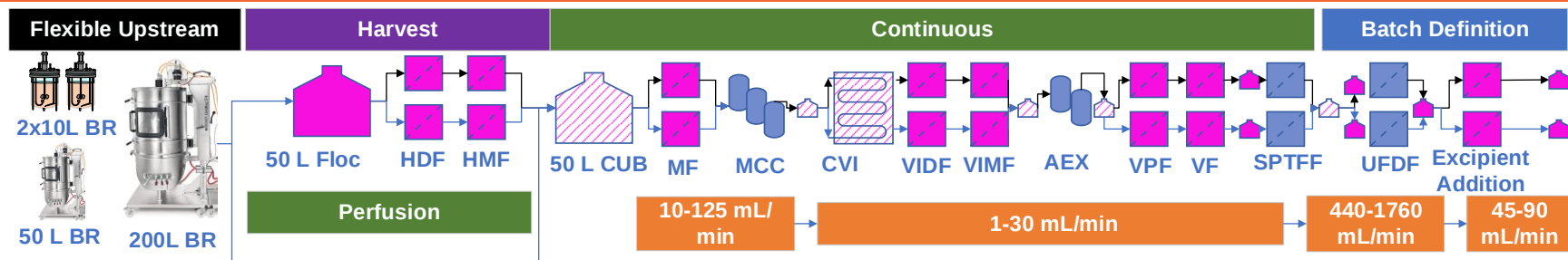


- Aligned to current platform technologies
- Maintains separation science principles employed in batch processing

Process and Equipment Design of Integrated System



R&D system to development ways of working, control strategy, demonstrate robustness



BR: Bioreactor
Floc: Flocculation
HDF: Harvest Depth Filtration
HMF: Harvest Membrane Filtration

MF: Membrane Filtration
MCC: Continuous Multicolumn Chrom
CVI: Continuous Viral Inactivation

VIDF: Post-VI Depth Filtration
VIMF: Post-VI Membrane Filtration
VPF: Viral Prefiltration
VF: Viral Filtration

SPTFF: Single Pass Tangential Flow Filtration
UFDF: Ultrafiltration/Diafiltration
PS80: PS80 Addition/Final Filtration

Single Use

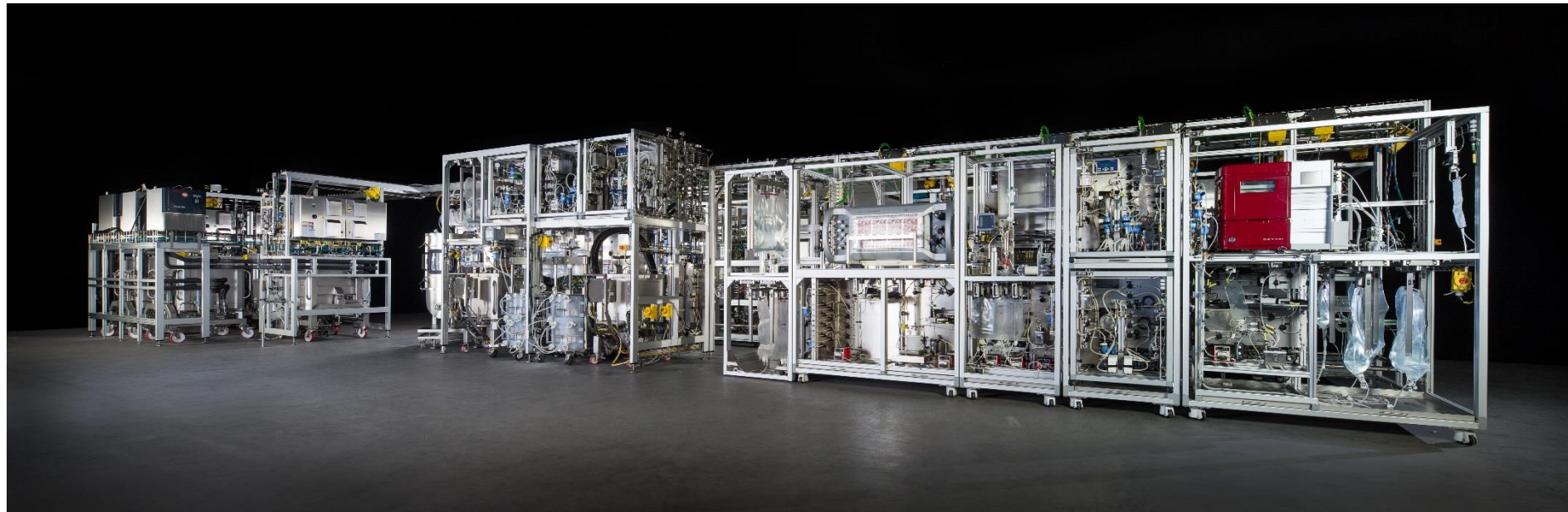
Reusable

Design Philosophies

- Flexible throughput
- Semi-continuous
- Single Use
- Modular
- Easily Upgrade UOs
- Duty-Standby Filtration
- Automated
- Fed-Batch or Perfusion



Overall Skid (Front)



Overall Skid (back)



– Continuous production demonstrated for multiple GSK mAbs with comparable quality attributes to fed-batch material



Polychaeta- Novel Sterile Drug Product manufacture

Polychaeta – Novel Drug Product Liquid Vial Filling System

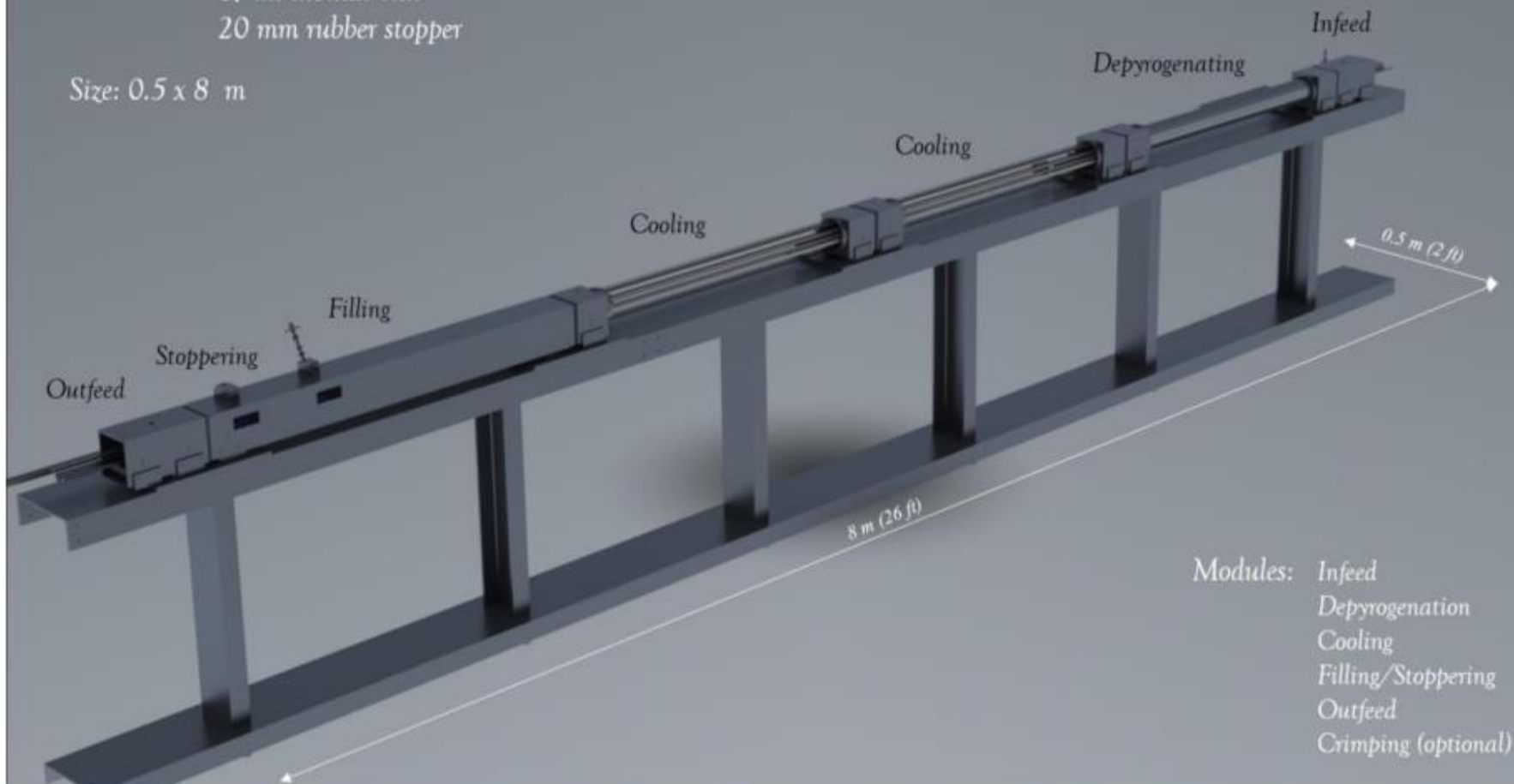


Background

- Traditional aseptic filling lines work well for high volume products; however, they do not meet the needs of a varied product portfolio including small batches of high value: they are too complex and lack flexibility.
- Several small sterile filling technologies are being offered on the market; however, they often require a change in the primary packaging (i.e. plastic vials, snap caps, stoppers in trays, all of them typically supplied in gamma irradiated tubs) and remain functionally complex.
- GSK is developing an innovative aseptic filling line, named Polychaeta, which is simple in its design and operation, utilizes standard packaging components while enhancing sterility assurance for patient safety.
- The technology is designed to support small volume clinical and commercial manufacture of liquid biotherapeutics, chemical entities & potentially vaccine biologics. The characteristics of this technology are well suited for potential implementation to support sterile filling surge capacity needs during an emergency or pandemic (i.e. COVID 19)

Throughput: 10-30 vials/min using:
17 ml tubular vial
20 mm rubber stopper

Size: 0.5 x 8 m



Modules: Infeed
Depyrogenation
Cooling
Filling/Stoppering
Outfeed
Crimping (optional)

Simple.

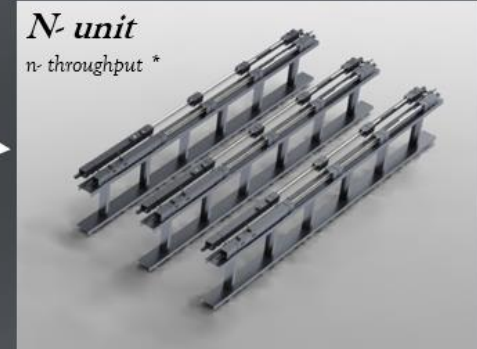
- one single frictionless transport system
- no sensors inside the machine
- GSK can troubleshoot & maintain
- small footprint (0.5 x 8 m)

Agile.

- all units demountable for machine wash and reassembly
- machine is inexpensive (approx. 350K€ estimated for the first GMP unit)
- one machine could be dedicated to a single vial size
- **modular**

Enhanced Aseptic Assurance.

- entire machine *truly sterilizable* (dry heat)
- no glove ports
- grade “C” or less background environment
- reduced environmental monitoring



Functions: Depyrogenation
Filling
Stoppering
Crimping (not ill.)

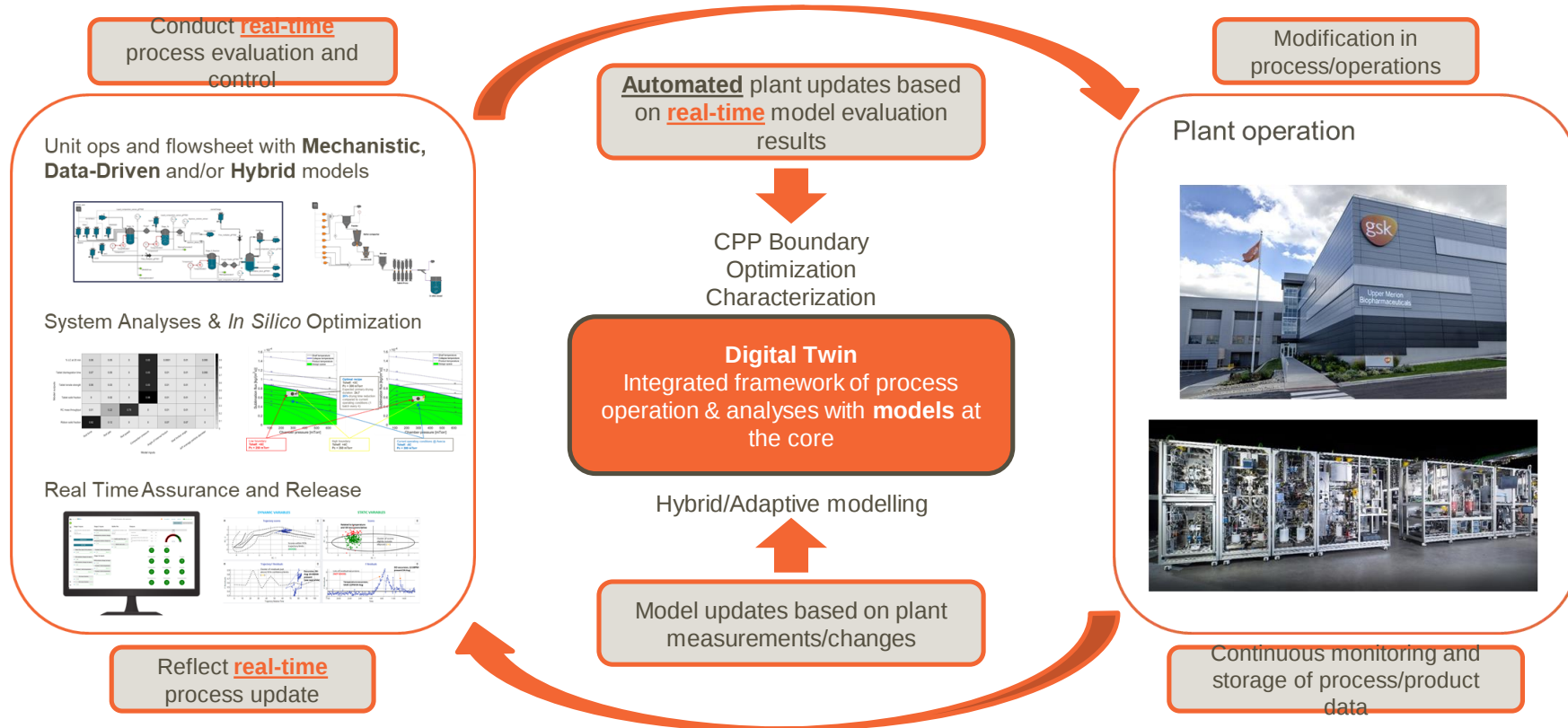
Prototype has been built and feasibility demonstrated



- Engagement with FDA Emerging Technologies team provided valuable feedback
- EMA feedback being obtained
- May require re-thinking of some of the EU Annex 1 requirements due to completely closed system
- Being integrated as the front-end for the continuous lyophilization development ongoing at GSK

Digital Twin Framework for Pharmaceutical Manufacturing

Advanced process control to improve Quality, Safety and Efficiency



Partnership with Regulatory Authorities



How can we work together to deliver the digital transformation?

- Leverage opportunity for model-based control offered by ICH Q12 'performance-based' approach to deliver:
 - Updated Quality Framework to enable advanced process control and model-driven, real time process optimization including use of AI approaches
 - Clear guidance for model verification/validation, maintenance and lifecycle management including post-file model optimization/updates
- Drive greater alignment with Global Regulatory Authorities on acceptance of advanced model-driven approaches
 - Global regulatory divergence is a significant barrier
 - Risk that some Global markets where product will be filed may not accept model-based approach despite EU/US approval drives more conservative approaches

COVID-19 Pandemic forced technology adoption



Supply chain resilience severely tested and identified several key opportunities

- COVID mabs progressed rapidly (<12mo to emergency use authorization from FTIH) enabled by frequent and open communications with regulatory agencies
 - Reduced Process validation requirements at time of filing
- Need easier post-launch change mechanisms to enable site transfers for increasing production to meet unexpected demand for existing products
- Raw material supply shortages and long lead times
 - Critical reagents, single-use components, filters
 - What regulatory mechanisms can be put into place to qualify alternate raw materials?
- Need for increased remote and virtual inspections due to travel restrictions
 - Develop good practices to enable successful remote inspections
 - Use of virtual technologies (see next slide)
 - Need for global regulatory agency cooperation and mutual recognition of inspections

Technology: Smart Glasses - Tandem

Hardware: RealWear; Software: Apprentice Field Suite



Overview:

- Remote colleagues can observe what you see.
- Service expert diagnosis of equipment, reduced equipment downtime, and transfer of organizational tribal knowledge.
- Guided tours of automation systems for remote audiences without the need for gowning.

Key Benefits:

- Global collaboration, Subject Matter Expert (SME) troubleshooting for process/method transfers, qualification, and training without travel.
- External vendor contact to immediately resolve critical issues, diagnose problems, and come to resolutions faster without the need for travel expenses.
- Regulatory inspections



realwear



PPRENTICE



Manufacturing innovation can solve healthcare problems of the future



- *Supply Chain Agility* with modular and integrated drug substance and drug product manufacturing
- *Reduced Cost of Goods* via process intensification and continuous processes
- *Enhanced process understanding and control* via digital twin
- These can only be enabled by regulator-innovator partnership to reduce barrier to entry
- Global regulatory agency cooperation needed to enable rapid industrialization of emerging technologies
- COVID-19 pandemic has forced adoption of virtual and digital technologies that should be standardized
- COVID-19 therapeutics have shown possibilities for drastically reducing cycle-times by taking smart risks underpinned by platform knowledge and regulatory flexibility



Questions?

Dawn
Pharmacist
UK