Improving outcomes through successful technology transfer

Canping Jiang, Sr. Director, Strategy and PMO

Pharmaceutic Service Group, Thermo Fisher Scientific

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Speaker Introduction

As Senior Director, Biologics Strategy and PMO, Canping is responsible for strategy development and deployment for the Biologics drug substance Business Unit (BU) at Thermo Fisher Scientific.

Canping leads the global MSAT, oversees the standardization and improvement of key global programs such as tech transfer, process validation and manufacturing technology best practices across a network of manufacturing sites in North America, Europe and Asia-Pacific.

Canping has more than 15 years of industrial experience in biologics process development, tech transfer and commercialization including 9 years at Biogen and 5 years at Bristol-Myers Squibb (BMS).

Canping has been closely involved and made important contributions in the CMC development and BLA approval of more than 4 biologics therapeutics at BMS and Biogen, including Nulojix, Yervoy, Eloctate and Aduhelm.

ThermoFisher SCIENTIFIC

Mission:

We enable our customers to make the world healthier, cleaner and safer.

Customer focus:

We help accelerate innovation and enhance productivity for our customers, underpinned by quality.

>100,000	5,700	$1.4B	$40B
colleagues	R&D scientists/engineers	invested in R&D	in revenue

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Pharma Services Global Biologics Network

Biologics drug substance sites

- St. Louis, USA
- Princeton, USA
- Groningen, Netherlands
- Brisbane, Australia
- Lengnau, Switzerland

30 years GMP manufacturing experience

Flexible, multi-product manufacturing solutions

First in Human to commercial manufacturing

Integrated drug substance and drug product: Patheon® Quick to Clinic™ and Quick to Care™ offerings

Key Capabilities

- Cell line development: Beacon® and ambr® 15 platforms
- Fed-batch and perfusion
- > 50 K L single-use GMP capacity

Flexible Biomanufacturing Solutions

- Multiple single-use platforms deployed
- Non-proprietary media and cell lines
- Transfer at any stage
- 500 – 5000L SU Bioreactors

Expertise

- > 72 Process Development programs completed since 2017
- > 180 tech transfers executed since 2015
- 70 / 30 mAb vs. complex proteins

Experience

- 4 commercial products
- 6 PPQ campaigns 2020-2021
- > 20 late-phase, commercialization programs since 2015

Addressing need for speed to IND/IMPD

Speed is critical, but not at any cost

Quick to Clinic™ BIO

Carefully constructed integrated drug substance – drug product programs delivering transfection to IND/IMPD timelines in <13 months while balancing risk and building a strong foundation for future success

Accelerated and optimized start to finish workflow

- Drug substance and drug product work in parallel
- Use of high throughput automation solutions: Beacon® Optofluidic System, ambr® 15, ambr® 250, Tecan miniaturized purification platform
- Concurrent, co-qualification of analytical methods

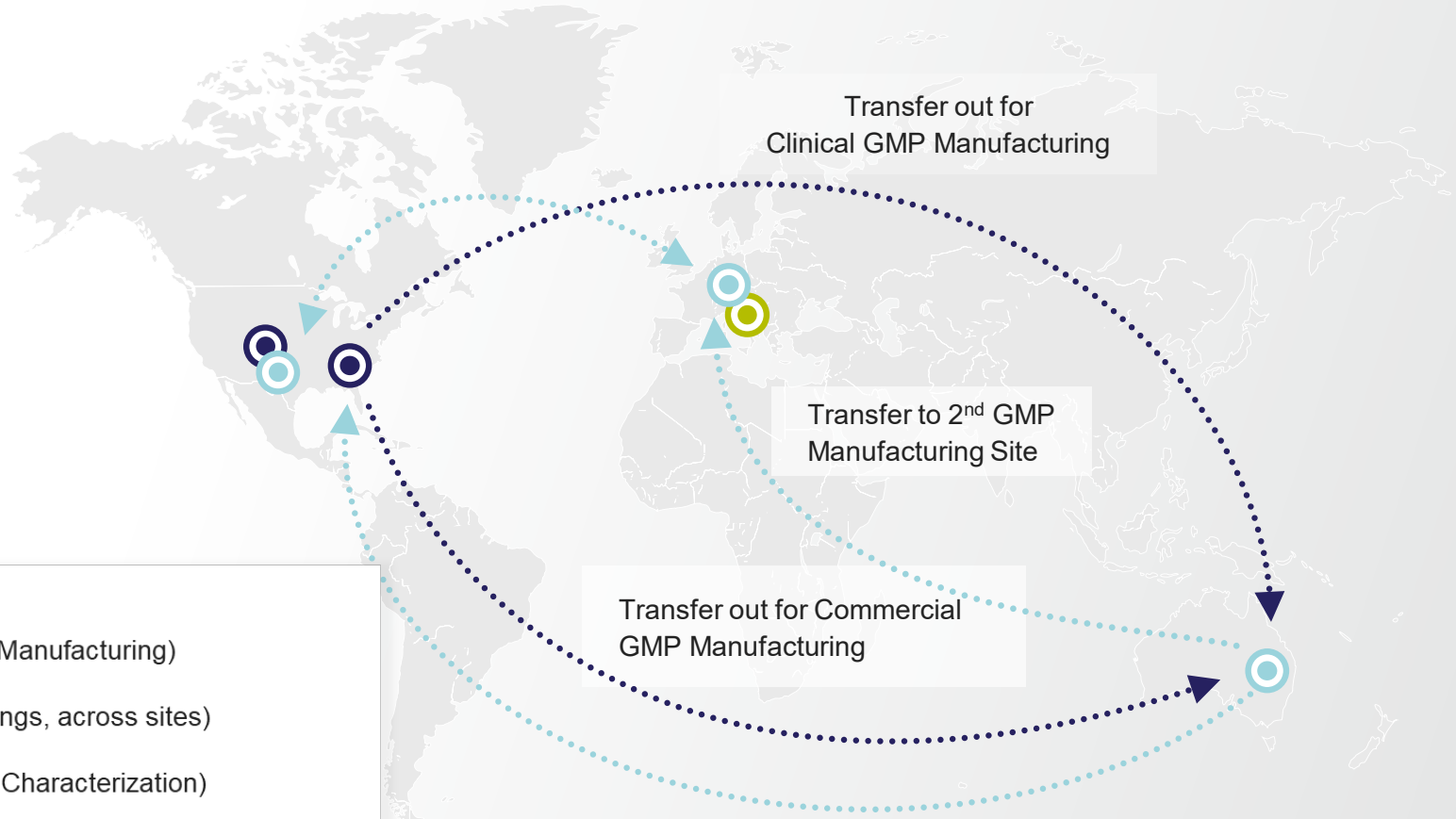
Robust platform process

- Best in class platform process designed using experience drawn from executing > 72 PD programs since 2017
- Use of the trusted and revamped Freedom™ ExpiCHO-S™ expression system to target antibody titers in 3-5 g/L range

Risk without impacting quality or future success

- Carefully constructed programs that embraces and avoids risks in equal measures to deliver speed without sacrificing quality
- Use of transient, stable pool and clonal material in equal measures | Standardized document templates | Pre-qualified vials, contact parts, and closures

Introduction to Technology Transfer



Tech transfer occurs throughout molecule development

- Client to CMO (Development lab or direct to Manufacturing)
- Development to Manufacturing (across buildings, across sites)
- Manufacturing to Development (for Process Characterization)
- Manufacturing to Manufacturing for secondary commercial site

>250 Biologics programs tech transferred globally since 2014 in Thermo Fisher BIO DS network

Keys to successful Tech Transfer

- Global Tech Transfer Policy
- Robust platform processes & analytics
- Strong inter-site communication and strong liaison between technical and PM teams
- Clear line of sight from development through to cGMP
- Application of risk management tools
- Continuous improvement through network sharing of lessons learned

Case study #1

Rapid tech transfer to support COVID vaccine development out of Brisbane site

Introduction

- During the initial onset of COVID-19, with lockdowns imposed in Australia, Thermo Fisher Scientific was asked to manufacture two molecules for COVID vaccine development as rapidly as possible.
- The first molecule, an rProtein, was to be used to produce the second molecule and needed to be manufactured under extremely aggressive timelines.

Product background	**Ancillary material** used in a COVID-19 therapy process
Cell line	ExpiCHO-S
Molecule type	rProtein containing Fc region, highly similar to mAb
Bioreactor scale (L)	500

Brisbane, Australia clinical & commercial manufacturing site

Minimal process development data available for tech transfer or scale up

- USP: Limited transient shake flask data available
  DSP: Limited small-scale purification data available
- Quick to Clinic™ platform process was adopted and applied.
- Bill of materials was based on those already available at site and within quick reach from local suppliers.
- All at-scale USP and DSP process parameters were applied based on prior experience and knowledge.
- High process uncertainty due to unknowns around cell growth, process duration, titer, step yield, sampling requirements, etc.

Aggressive timeline expectations

- Direct tech transfer from client
- Expedited timelines "program signature to DS fill and shipment“
- Additional complications due to the pandemic
- *How was this achieved?*
  - Cross collaboration within global technical teams to integrate molecule into Quick to Clinic platform process
  - A dedicated, talented and engaged team with sole focus and priority on ensuring a successful transfer and execution
  - Close working relationship with the client
  - Our team adopted quickly to remote working and strict site segregations as the pandemic gripped and initial lockdowns took place. While this is now the "new normal," this was new way of working for our teams and stressed our site systems under aggressive timeline pressures.

Upstream processing challenges

- Immature cell culture platform process
- Variable cell growth leading to pre-culture scale-up challenges
- Use of ExpiCHO-S platform and internal experience with cell line coupled with scalability of cell line from transient to stable expression enabled rapid troubleshooting and process implementation.
- Despite numerous challenges, USP process yielded a 4X increase in expected titer and high step recovery.

Downstream processing challenges

- Immature process resulting in real-time process intervention and modification
- Higher USP titer led to multiple unplanned cycles which impacted documentation and processing time.
- Manual control of chromatography and filtration methods due to limited DSP data
- Several instances of high pressure, high/low flow rates and filter fouling throughout process requiring operator intervention
- Despite challenges, DSP process was successful yielded a high step recovery.

Representative Thermo Fisher DSP platform process

Rapid tech transfer led to favorable outcomes

- Product was successfully forward processed and used in the manufacturing of a COVID-19 therapy.
- Mammoth team effort to execute a direct tech transfer from client in **5.4 weeks** (program signature to vial thaw)

Case study #2

Continuous improvements to tech transfer processes to drive standardization and realize improved outcomes

Despite having a robust TT process, critical evaluation of the TT workflow led to identification of several opportunities for improvement:

- Digitalization
- Improved batch record formatting
- Single use standardization

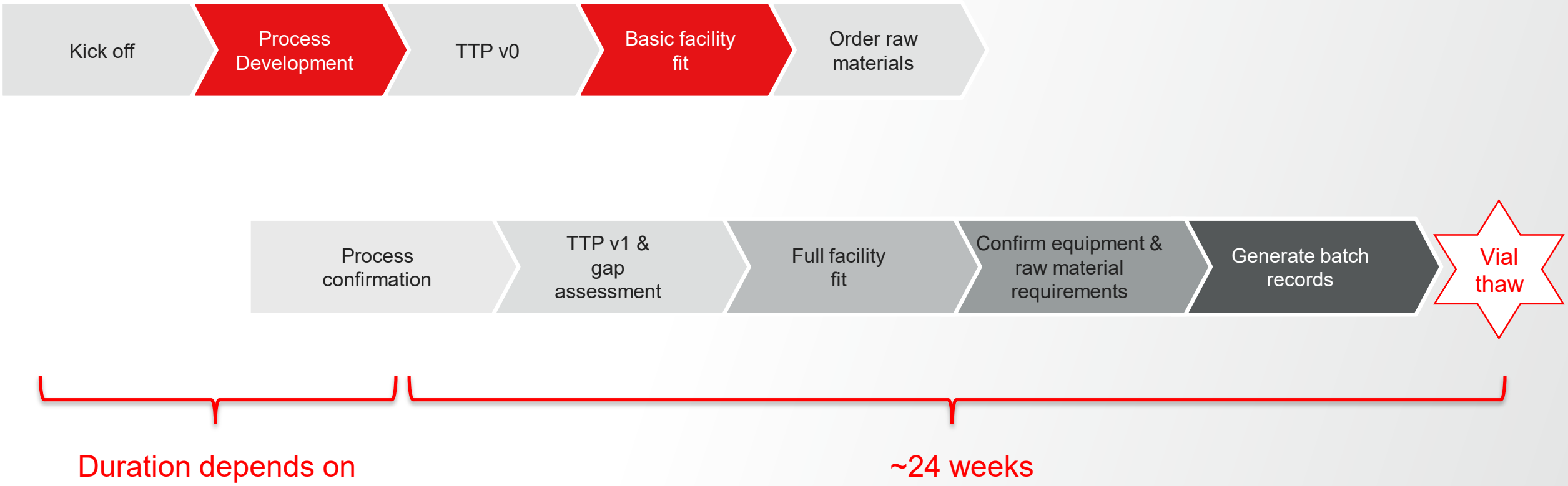
Streamlined TT workflow via digitalization

Digitalization of the TT workflow to move away from disconnected paper processes

Real time project tracking and enhanced project management tools

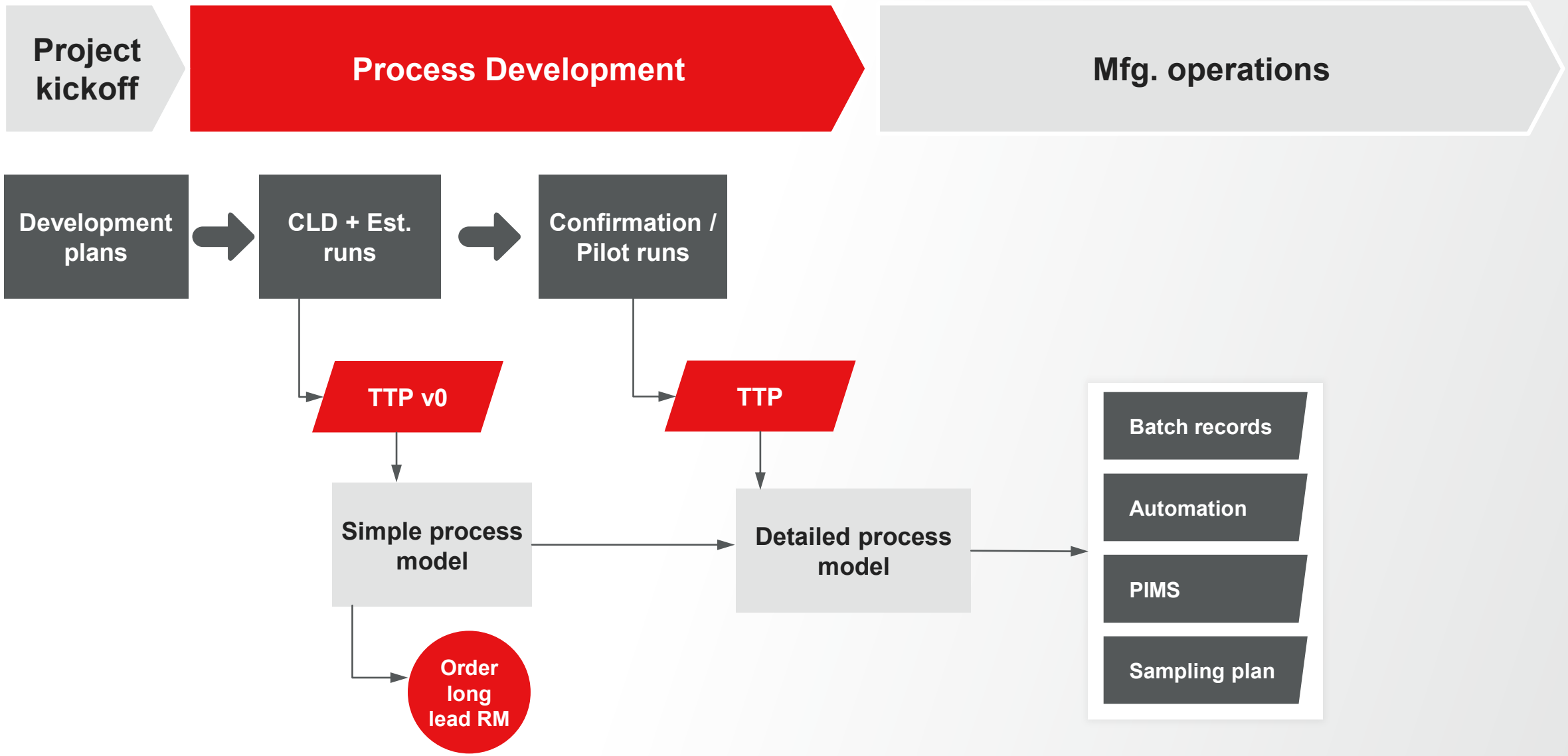
Real time data sharing

Typical TT process flow and timelines



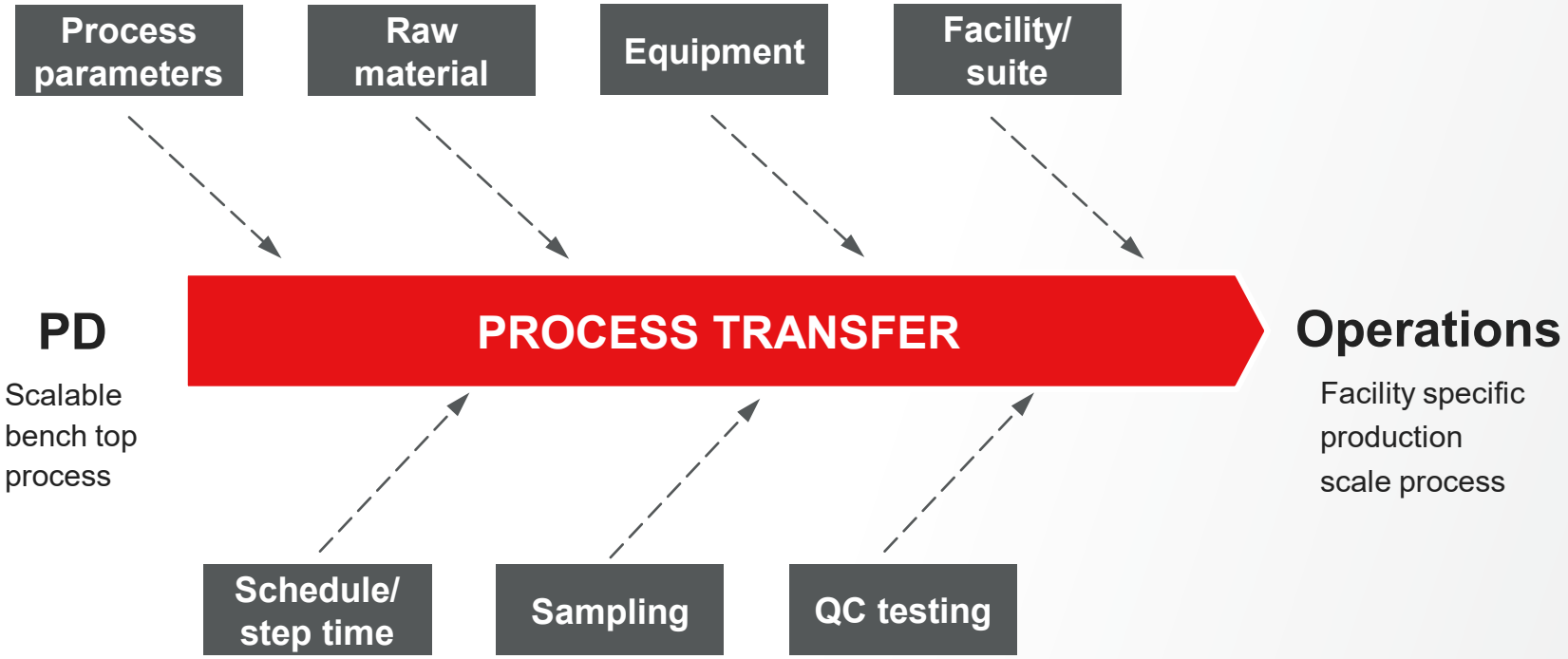
Technology Transfer (TT)
Technology Transfer Protocol (TTP)
Raw Material (RM)

Current state: Tech transfer workflow overview



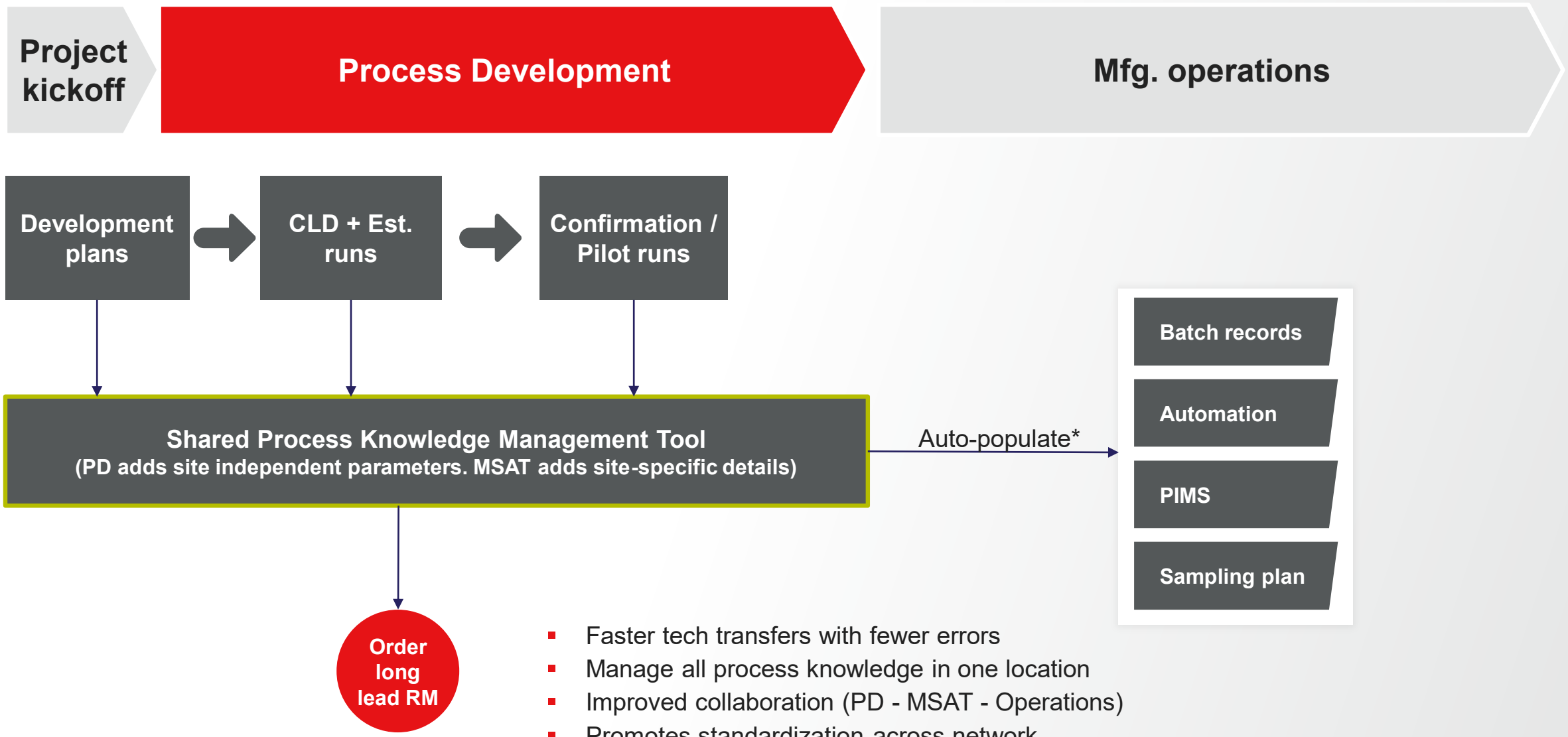
Current state: Tech transfer executed with disconnected paper-based documents

- Many inputs needed to execute transfer successfully
- Process data inputs are stored in different locations, sometimes difficult to locate
- Inputs are manually integrated into disconnected documents and spreadsheets to define the process being transferred



Integration of these inputs into one application that can be accessed simultaneously by PD and MSAT would result in faster transfers with fewer errors

Optimized state: Streamlined workflow via digitalization



- Faster tech transfers with fewer errors
- Manage all process knowledge in one location
- Improved collaboration (PD - MSAT - Operations)
- Promotes standardization across network

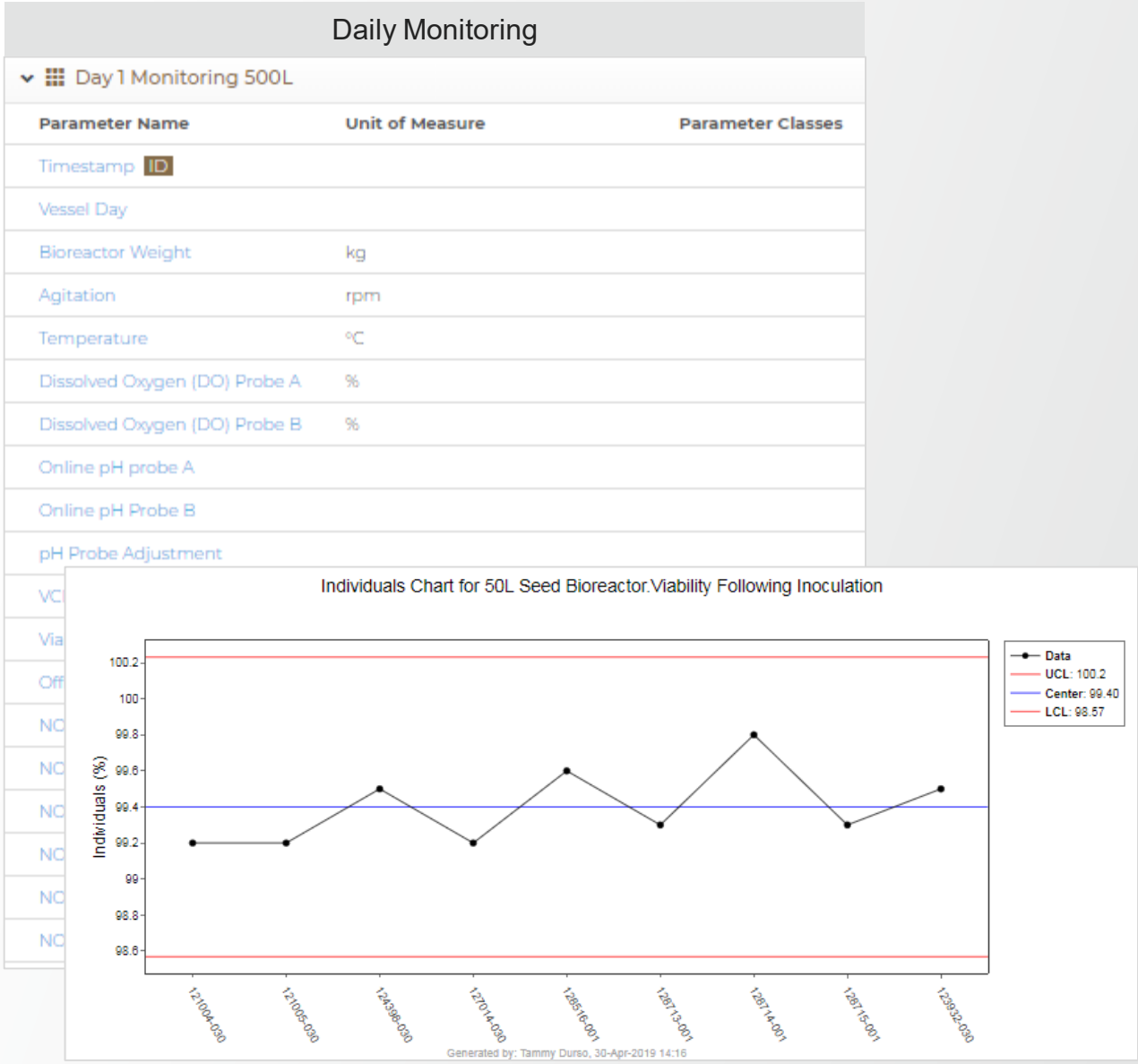
** Desired future state*

Optimized state: mysupply tool for real time client visibility to programs

Real time data sharing

Skyland PIMS® data sharing application used for all customer programs

- Secure cloud-based software
- Key process and product data from the batch record is entered into PIMS on the day it is generated.
- Client can log into system remotely and view their product data as the batch is progressing
- Includes data trending capabilities for process monitoring and CPV reporting applications

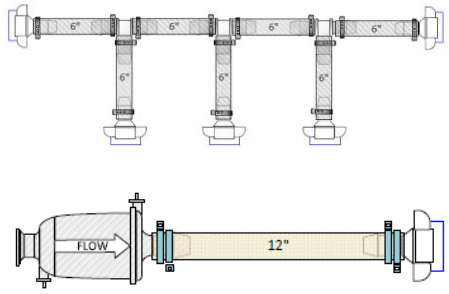


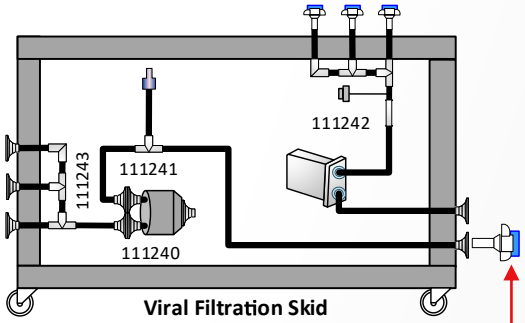
Single-use standardization

- Modular assemblies defined to standardize processes and build reliability across every unit operation and site
  - Benefits: supply chain and inventory forecasting simplification, improved reliability, less variability in product contact surfaces, streamlined validation, improved traceability
- Impact from global supply disruptions minimized by harmonizing manifolds across multiple manufacturing sites and leveraging the ThermoFisher supply chain

Platform SU manifolds created with standard sub-components connect different pieces of equipment:

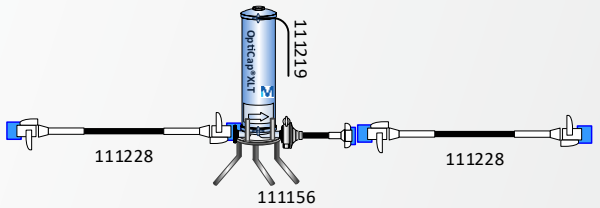
- Aseptic connectors
- Filters
- Tubing

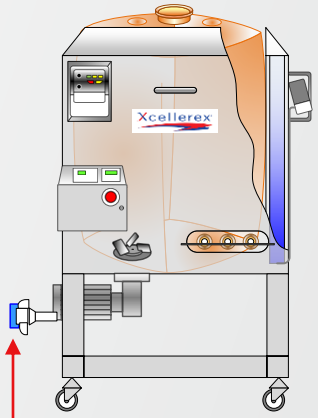




Site specific hardware with compatible connector

Platform SU manifold





Site specific hardware with compatible connector

Unique Strength of Thermo Fisher in Manufacturing Pandemic Response Products

- ☒ Critical materials used in manufacture of these products
- ☒ Capacity to produce at clinical/commercial scale
- ☒ Expertise to develop, transfer and execute manufacturing and analytics for these products
- ☒ Services to support large scale clinical trials and distribution of clinical materials.
- ☒ CMC/Regulatory services to support clinical and commercial filings
- ☒ Global commercial distribution and logistics capabilities
- ☒ Digital systems that enable efficient/effective execution in our plants and visibility to our customers.
- ☒ End to end service and integrated program that reduces the number of hand offs and allows agile execution.

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