

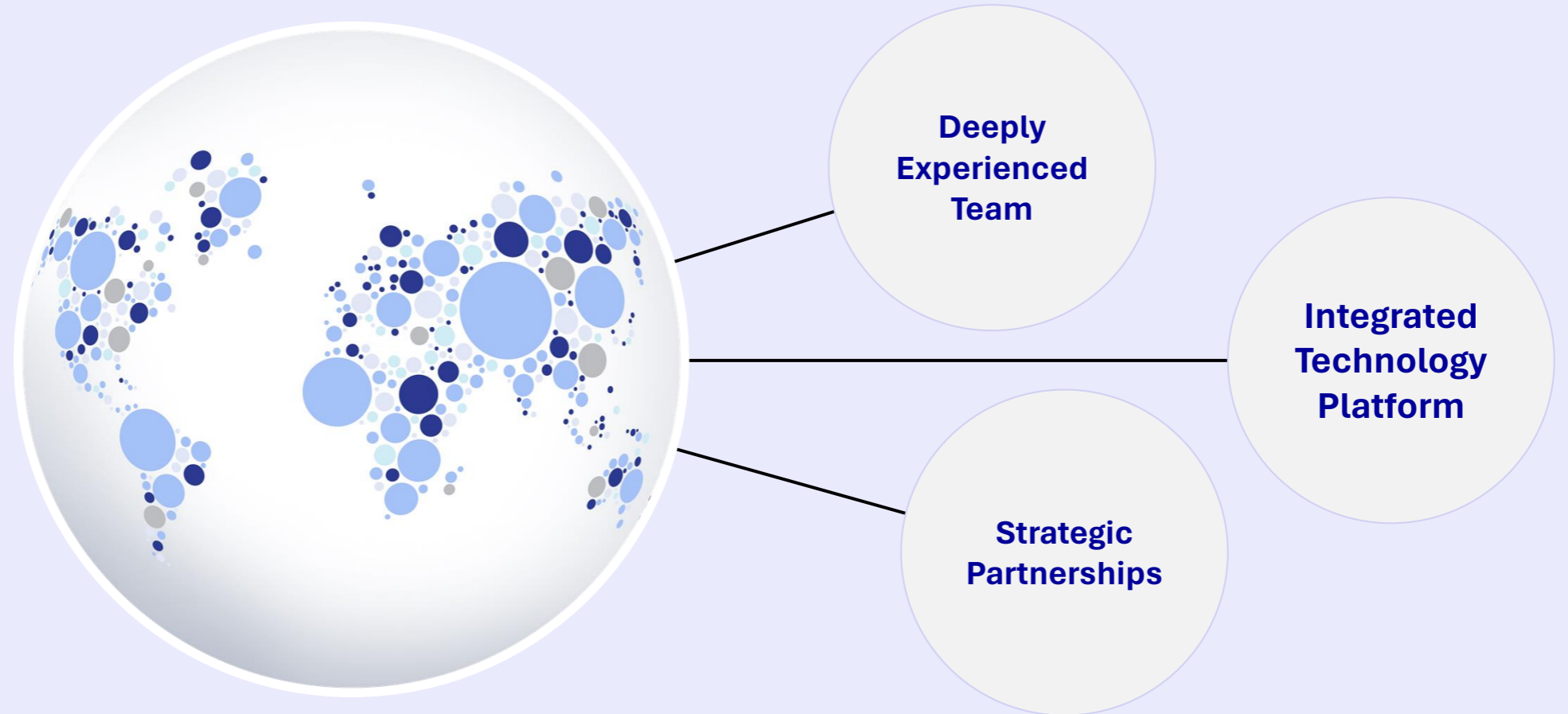
# *Achieving Continuous Manufacturing through Equipment Design*



# Just-Evotec Biologics: focus on technology to drive access

Our Mission

Design and apply innovative technologies to dramatically expand global access to biotherapeutics





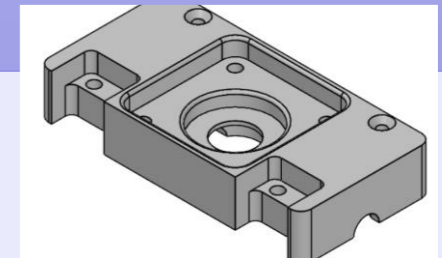
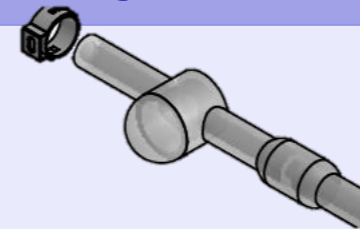
# Partnership Successes

## Shared Engineering Mindset

- To bring our manufacturing platform to life we needed a partner that shared values:
  - Vision
  - Flexibility
  - Integration
  - Quality
- The relationship would also need to grow as we did: equipment would need to facilitate technology and design improvements
  - Lifecycle approach to systems and technology
  - Existing systems are updated instead of obsoleted
  - Look for novel solutions, and perform the engineering analysis to support

### Pressure Cup Example

- Developed own single use pressure sensor
- Supply chain shortages: brought the missing functionality in-house
- New technology -> found a better way to machine these parts and manifolds
- Developed a step-by-step plan to implement improvement while supporting our need to stay in prdxn
- Detailed implementation plan; robust testing schedule

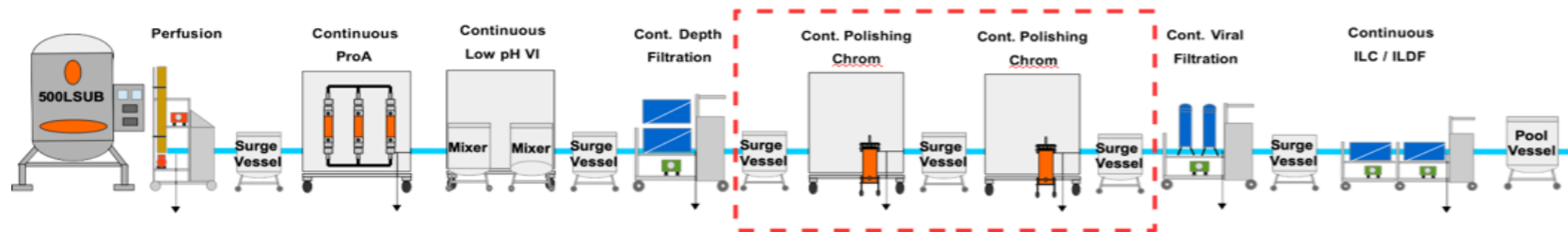




# Single Use Chromatography

## Polishing Steps and Column Packing

- Systems can be operated in batch or continuous mode
- Wide turn down ratios allow for a greater range to accommodate operations
- Onboard inline dilution capabilities allow for the use of concentrates
- Single-use flow paths and instrumentation minimize product change over time and cleaning qualification





# Automation

## A Driver for Alternative Systems

### Automation Enables our E2E Platform

- Coordinates operations between skids, adjusts flowrates to account for differences in processing time
- Provides the ability to Hold and Resume individual equipment without stopping the train

### Driver towards Repligen Chromatography

- Allows us to coordinates operations between our skids and deal with variability without operator interaction.
  - DeltaV commands adjust for differences in processing time
- Automation is operable in both batch and continuous as well from the skid or external DCS.
- Advanced processing with off the shelf systems can prove difficult
  - Bugs, delays, and system communication breakdowns become critical quickly in non-batch ops
- Method editor sequencing is highly configurable, adaptable to our varied processes
  - Ensure CSV compliance
  - Communicates with MES



# Single Use Chromatography Skids

## Polishing Chromatography and Column Packing

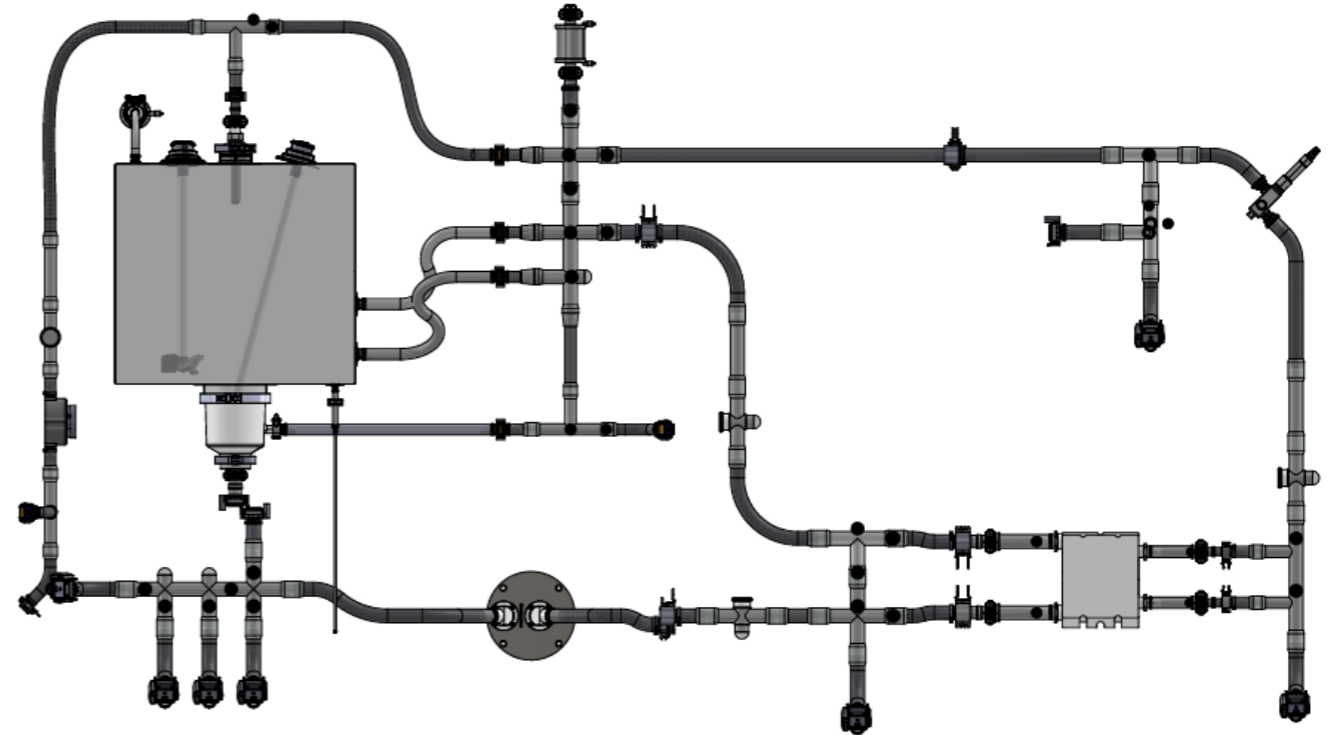
| Element                    | Value Proposition in Design  |
|----------------------------|--|
| • Automation               | <ul style="list-style-type: none"><li>• Ability to perform batch or continuous</li><li>• Automation designed by Repligen with Just-Evotec input</li></ul>  |
| • Inline Dilution          | <ul style="list-style-type: none"><li>• Concentrated buffers allow for reduction in footprint and prep requirements</li></ul>  |
| • Column Packing Alignment | <ul style="list-style-type: none"><li>• Column packing skid designed on our chrom skid base design<ul style="list-style-type: none"><li>• Allows for flexible use – backup equipment</li></ul></li><li>• Added packing arm and conductivity sensors for column performance testing</li><li>• Pre-defined automation for HETP and asymmetry calculation</li></ul> |
| • Critical Instrumentation | <ul style="list-style-type: none"><li>• Clamp-on flow sensors on each channel as well as pre-column</li><li>• Dual wave-length UV pre and post column</li><li>• Alignment between design and instrumentation on column packing and polishing chrom</li></ul>   |
| • Footprint                | <ul style="list-style-type: none"><li>• Small system footprint critical to optimize the reduced clean room space within the J.POD<sup>(R)</sup> facility design</li><li>• Mobile through the facility (different layouts for hybrid vs. continuous processing)</li></ul>   |



# Purification Tangential Flow Filtration System

## Ultrafiltration and Diafiltration

- Challenges for a single-use TFF system:
  - Can the manifold handle the pressure necessary?
  - How do we sanitize the system?
  - Minimize system hold up?
  - Mixing in the vessel?
  - Recovery strategy from the vessel?







# Purification TFF Skid

## Ultrafiltration/Diafiltration

| Element                            | Value Proposition in Design   |
|------------------------------------|---|
| • Manifold Design                  | <ul style="list-style-type: none"><li>• High pressure operation required robust tubing<ul style="list-style-type: none"><li>• Braided silicone used for manifold components</li><li>• Machined valve blocks (exoskeleton) provide tubing support where braided is infeasible</li></ul></li></ul>  |
| • System Hold Up                   | <ul style="list-style-type: none"><li>• Small holdup volume &lt; 1L</li></ul>   |
| • Mixing                           | <ul style="list-style-type: none"><li>• Single use recirculation vessel with tulip shape (sump)</li><li>• 2 agitator heights – optimal mixing</li><li>• Single-use impeller design - insert the agitator shaft externally</li><li>• Option to connect an external vessel to scale</li></ul>   |
| • Recovery                         | <ul style="list-style-type: none"><li>• Multiple recovery methods<ul style="list-style-type: none"><li>• Flow path same as product through recovery port</li><li>• Reverse recovery using the addition pump</li></ul></li><li>• Nearly equivalent to system hold up volume</li><li>• Collection line from recirc vessel to mitigate pool dilution during recovery</li></ul> |
| • Enabled for Changeover Operation | <ul style="list-style-type: none"><li>• Designed to enable use of external recirc vessel for NaOH sanitization<ul style="list-style-type: none"><li>• Retentate return to drain</li></ul></li><li>• Integrity test operations can be done online<ul style="list-style-type: none"><li>• MFC and clean air connections, automation recipe base provided</li></ul></li></ul>  |





# Harvest Tangential Flow Filtration System

Harvest Perfusion



## Harvest Perfusion Process

- Continuous harvest perfusion
- Enables higher yields per volume, supports very high cell densities

## Repligen: KPS 2000

- 2-pump system
  - Creativity required in designing for scale up
  - Combines pre-gamma'd single-use manifolds and custom-built assemblies to allow multiple filter and permeate configurations
  - Toulouse system underwent design iteration; lessons learned being retrofitted to J.POD<sup>(R)</sup> facility in Washington



# Perfusion TFF Skid

Harvest Perfusion

| Element  | Value Proposition in Design   |
|--|---|
| <ul style="list-style-type: none"><li>• Component Integration</li></ul>        | <ul style="list-style-type: none"><li>• Mounted flowmeters directly on filter stands at an angle for optimized flow readout</li><li>• Focus on use of right flow sensor for right application: mix of Levitronix and ultrasonic, clamp-on</li></ul>             |
| <ul style="list-style-type: none"><li>• Automation Flexibility</li></ul>       | <ul style="list-style-type: none"><li>• DeltaV native system, with PLC setup transferred between sites for easier code transfer</li><li>• Installed a simplified software version to allow for easier troubleshooting</li></ul>                                 |
| <ul style="list-style-type: none"><li>• Manifold Design Improvements</li></ul> | <ul style="list-style-type: none"><li>• Redesigned tubing assemblies to eliminate unnecessary sizing changes, reduce shear stresses</li><li>• Scaled up tubing sizes to allow for larger processing volumes</li></ul>   |
| <ul style="list-style-type: none"><li>• Scalability</li></ul>                  | <ul style="list-style-type: none"><li>• Increasing production sizing calls drives additional filters, sizes</li><li>• Need system to fit range of production SUB output</li><li>• Able to ramp up to increased flow rates as platform shear increased</li></ul> |

QUESTIONS  
AND ANSWERS

