Optimization and Integration of Single-Pass, Continuous Final Formulation Technologies for mAb Purification

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INTRODUCTION

- The utilization of Pall's patented Cadence™ single-pass TFF (SPTFF) technologies is a key enabler of continuous bioprocessing initiatives. The integration and optimization of a prototype Cadence Inline Diafiltration (ILDF) module with the Cadence Inline Concentrator (ILC) with sterile filtration is key to development of a fully continuous, streamlined final formulation process platform. Coupling these continuous final formulation processes allows for further optimization and reduction of module/device flushing as well as reduction of in-process buffer consumption compared to independent operation. The implementation of this continuous final formulationtrain (ILDF/ILC/0.2 µm) successfully achieved > 3-log (> 99.9%) primary buffer species impurity removal and ≥ 20x concentration factor while delivering a 0.2 µm filtered monoclonal antibody.

OBJECTIVE

- To provide an operationally simplified data-driven approach and assessment of the SPTFF attributes for the continuous final formulation of mAbs and address the subsequent product and process development requirements.
- Offer operational and logistical improvements of coupling existing single-pass technologies for maintaining process simplicity and control.

BACKGROUND

- Cadence Inline Concentrators are well-suited SPTFF solutions for numerous bioprocess applications and have been shown to remove constraints in existing facilities via:
  - In-process volume reduction applications (i.e., post-harvest, pre-capture, tank-to-tank transfer, etc.)[1-2],
  - Process coupling runs with affinity, ion-exchange and membrane chromatography steps in batch and continuous mode showcasing enhanced productivity[3-4],
  - Increased flexibility of manufacturing capabilities with significant cost savings[5-6], and
  - Achieving high concentration formulations with custom pre-assembled modules available in various flow path configurations6.

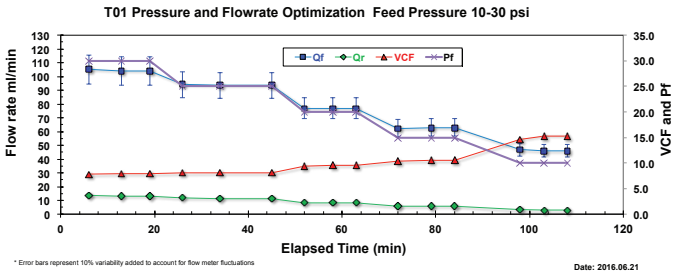
RESULTS AND DISCUSSION

High Concentration Formulations with Cadence ILC

- Cadence ILC is an important addition to the process development tool-box for platform process evaluation and is a crucial and proven enabler of integrated, streamlined and continuous bioprocessing initiatives[2-6].
- For instance, utilizing ILC for UF2 enables multiple advantages over a conventional UF system, such as:
  - Non-capital expense,
  - Lower system hold-up volumes,
  - High productivity and improved recovery (> 99%), and
  - Reduced over-concentration targets.

Figure 1

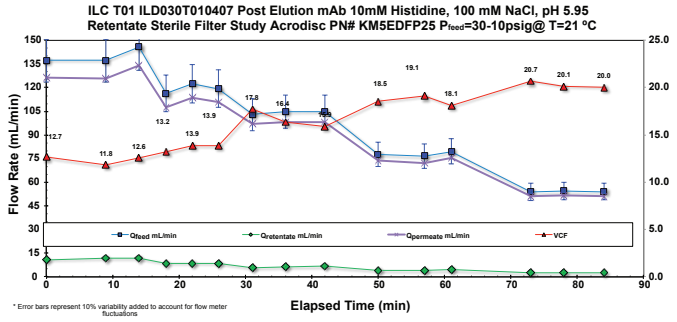
Evaluation of ILC Volumetric Concentration Factor for Final Formulation Operations (30 kDa T01 module, 0.065 m²)



- Ease of process optimization with ILC enables the generation of a design space achieved with a single module.
- By assessing the process at a wide range of operating conditions (via feed pressure control) provides a stable and reproducible performance map.

Figure 2

Integrated Cadence ILC + 0.2 µm Sterile Filter



- Implementation of 0.2 µm sterile filter provides additional back pressure to the Retentate, allowing for increased concentration.
- Integration provides sterile final product without added equipment and operator interaction for final concentration processes.

Continuous, Single-pass and/or Inline Diafiltration (ILDF)

- ILC design principles and its versatile and robust performance led to the assessment of novel continuous diafiltration strategies, which resulted in a working prototype of a novel inline diafiltration (ILDF) module.
- Feasibility runs with 10 - 80 g/L hIgG feeds resulted in successful removal efficiencies (≥ 99.9% or ≥ 3-log) between ILDF process targets and validated test data (Figure 2).

Figure 3

Performance benchmark for the continuous, single-pass, inline diafiltration module with 30 kDa regenerated cellulose membrane [Feed: 10 – 80 g/L hIgG in 0.025 M Na acetate + 0.5 M NaCl (47 mS/cm) + 50 g/L Glucose and DF: 0.025 M Na acetate + 0.05 M NaCl (6.7 mS/cm)].

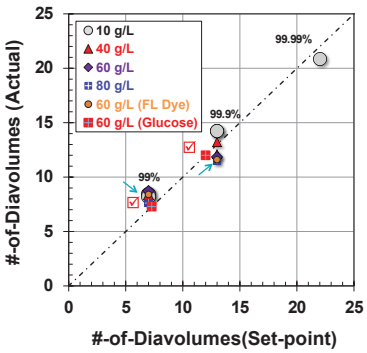
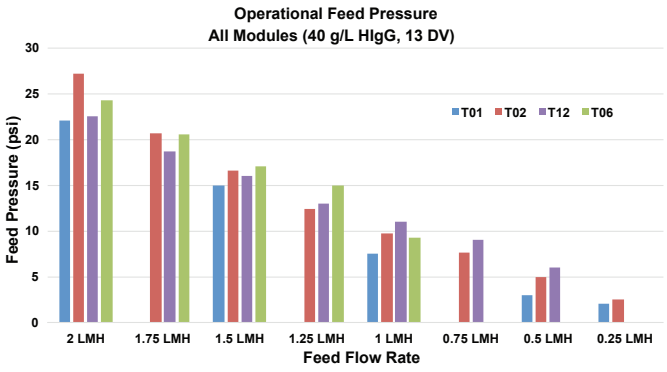


Figure 4

Scalability of Cadence ILDF (Feed Pressure vs. LMH)



- ILDF process scalability shown up to >50x scale-up.
- Scalable feed pressure performance across device flow range providing predictable operational results.

Figure 5

Streamlined Continuous Final Formulation Steps with Virus, ILDF, ILC, and Sterile Filtration

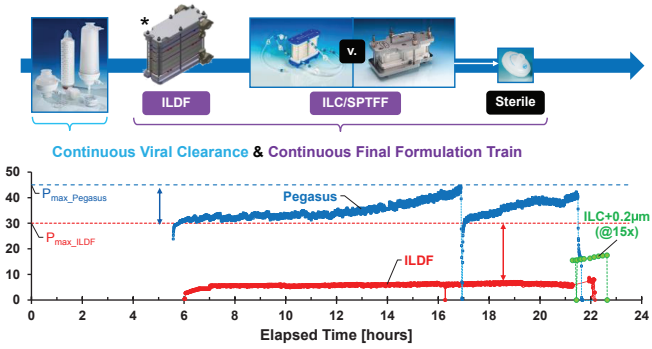
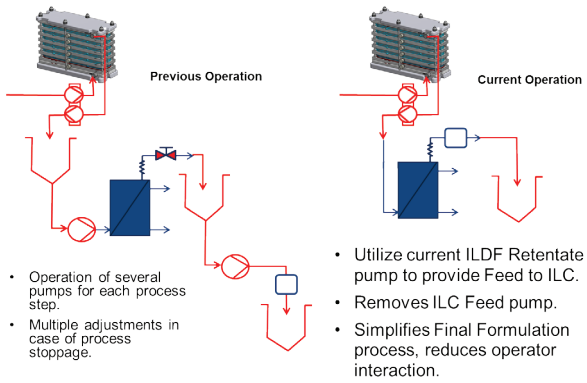


Figure 6

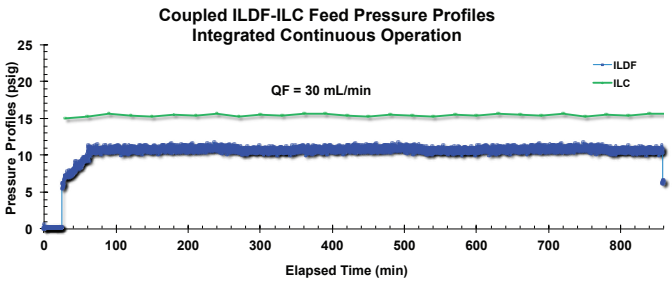
Complete Integration of Final Formulation Technologies



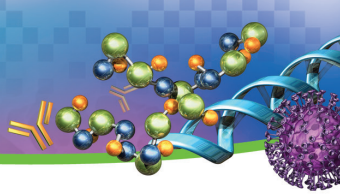
- Utilization of a single pump to control Feed and Retentate of ILDF maintains concentration throughout processing.
- ILDF Pump provides feed to the Cadence ILC module without the need for a surge tank or additional pumping equipment.
- Integrating 0.2 µm sterile filter to the Cadence ILC Retentate removes need for surge tank and additional equipment.
- Streamlines ease of use operation of SPTFF technologies.

Figure 7

Coupled Cadence ILDF-ILC-Sterile Final Formulation Step



- Process stability maintained throughout duration of integrated continuous process.



- Cadence ILC technology platform
  - Provides large operation window and flexibility of concentration factors with minimal control.
  - Presents versatile capabilities for the processing of biologics.
  - Is scalable, flexible and available in various formats and configurations in order to address molecule- and process-specific customization needs.
  - Can remove constraints in existing facilities and increase the flexibility of manufacturing capabilities by increasing productivity and facilitating further use of disposables.
  - Enables process coupling and integrated continuous bioprocessing.
- The Cadence ILDF design and ease-of process control
  - Addresses an innovation gap for the biopharmaceutical industry.
  - Completes the product/technology offering for the realization of continuous final formulation.
  - Brings the Biopharm industry one step closer to the realization of an end-to-end integrated continuous bioprocessing platform via the integration of ILDF/ILC/SPTFF technologies.
- Cadence ILDF-Cadence ILC-Sterile Coupling Integration
  - Provides streamlined approach to final formulation processing.
  - Eliminates multiple surge tanks and operational equipment in between process steps.
  - Reduces operator interaction required for development and process control.

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