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Application Note

# Implementation of Lynx® CDR Sterile Connectors in a Perfusion Application


## Abstract

The Lynx® CDR (connect, disconnect, reconnect) portfolio of sterile connectors was developed to provide advanced operational flexibility in biomanufacturing facilities, where contamination risk is an important consideration and closed processing solutions are desired. While use of these connectors in downstream applications is well-established, its use in upstream bioprocesses has not been widely explored. Of specific interest, was to understand the suitability of using the Lynx® CDR connector for the cell-containing fluid streams utilized in upstream processes, such as perfusion, where the ability to connect, disconnect, and re-connect within a single flow path on the bioreactor would be a great advantage. A two-tiered study was designed to explore both how the connector may contribute to cell shear in flow rate conditions similar to those observed in typical 200 L perfusion bioprocesses, and also to demonstrate the efficacy of implementing a Lynx® CDR connector in an actual perfusion process using an XCell™ ATF 2 System. The results of these studies support the feasibility of using Lynx® CDR connectors in cell-containing upstream applications as process performance endpoints such as viable cell density, viability, doubling time, and LDH were comparable to control conditions in both tiers of the study. In addition, the effectiveness of multiple Lynx® CDR connector actuations in the presence of cell-containing fluid streams during an operational perfusion bioprocess was demonstrated.


## Introduction

The use of single-use technologies to support manufacturing of biotherapeutics has become widespread in recent years due to their ability to provide operational flexibility while reducing costs associated with bioprocessing equipment cleaning and validation. An important offering within the single-use technologies portfolio is the sterile connector, particularly those that can be actuated in a non-sterile or “gray” manufacturing facility. While these sterile connectors are often effective in bioprocessing applications, they have historically been limited in their utilization given that the sterile connections are typically irreversible once actuated.

Recently, the Lynx® CDR Sterile-to-Sterile connector was developed with a unique design to facilitate multiple sterile connection actuations using a single assembly, in a non-aseptic biomanufacturing environment. It can be connected wet and under pressure without losing a drop of fluid, while maintaining sterility using up to six actuations. The connector is offered with several different connection type and diameter options and maintains a similar flow path amongst these various connection sizes.

**Figure 1. Lynx® CDR connector**

While its effective utilization in downstream processing seems clear, use of the Lynx® CDR connector in cell-containing upstream processes was less so. The flow path of the connector does not maintain laminar flow, but instead requires the fluid to flow through

apertures and around a stainless-steel spring within the assembly. Because this flow environment can potentially generate turbulent fluid flow, the impact of exposing cell-containing fluid to this flow path was not clear. This study was designed and conducted in order to characterize the response of cells in upstream bioprocess fluid streams where Lynx® CDR connectors were utilized.

## Application

Two related aspects of upstream bioprocessing have recently been significant process development focal areas: closed processing and perfusion applications. The basis of closed processing relies on eliminating (or minimizing) manual manipulations of cells during the process of seed train expansion to a production bioreactor. The premise of this application utilizes very high cell density cell banks that can inoculate small volume bioreactors directly from a thawing procedure and expanding high cell density and high cell viability cultures. When conducted effectively, closed processing both accelerates seed train expansion processes, and also mitigates upstream bioprocessing contamination risks by minimizing manual cell manipulations and transfers from a biological safety cabinet to a bioreactor, which requires cell handling by laboratory and/or production facility personnel.

Similarly, perfusion applications rely on the set up and maintenance of a bioreactor system where the rate of cell-free harvest is essentially matched with the rate of fresh media addition. Utilization of a perfusion application facilitates continuous processing, where a recombinant product of interest is separated from the rest of the bioreactor contents, enabling it to either be processed in real time (as it is generated), or pooled for subsequent batch purification. As with closed processing, the perfusion mode of bioreactor production can not only mitigate process contamination risk by extending process durations but can also significantly improve efficiency by facilitating greater total amount of recombinant product per unit of upstream bioprocessing time.

In both closed processing and perfusion applications, operational flexibility is often desired. For instance, cell retention devices (CRDs) used during perfusion operations can either foul or contribute unacceptable levels of product sieving, particularly when the process yields very high cell densities (and correspondingly high levels of cellular debris), and/or when these processes are extended over long durations. Conventional solutions often limit the duration and/or achievable cell density targets during a process run where the CRD can maintain acceptable performance. Alternatively, replacement of the Lynx® CRD during a process is sometimes considered, but this process can introduce unacceptably high contamination risks, or require manifolds of increased complexity. In summary, a solution for more effective bioprocessing tools has long been sought to accommodate safe and effective gray space manipulations in upstream bioproduction facilities.

When the Lynx® CDR sterile connector was designed, its use in multiple upstream and downstream bioprocessing applications was anticipated. Utilization of this connector in the downstream operating space was anticipated to be relatively straightforward given validation of the sterility claim over several actuations, and its use in relatively clean fluid streams was minimally impacted by potentially turbulent flow through the device. Conversely, suitability of the use of the Lynx® CDR sterile connector in upstream bioprocessing applications was less clear, given that these fluid streams can potentially contain large concentrations of mammalian cells with potential susceptibility to mechanical shear stress in non-laminar liquid flow prevalent when these connectors are utilized.

It has been well-documented that mammalian cells, including Chinese hamster ovary (CHO) cells, which are very commonly used in biotherapeutics production, can be susceptible to mechanical shear.[1] When exposed to shear, the plasma membranes of CHO cells can lose their integrity, resulting in loss of their intracellular homeostatic environment, which can cause a loss of cellular viability, recombinant protein secretion productivity, or both.

The goal of this study was to understand CHO cell shear susceptibility when grown in the presence of the Lynx® CDR connector in the cell flow path. More specifically, two parallel experimental evaluations were conducted. Firstly, cells were grown in typical growth conditions using a 20 L glass bioreactor (19 L working volume) that had been modified to incorporate a tubing loop containing a pair of Lynx® CDR connectors. This set up was employed in order to assess a basic feasibility baseline related to fluid flow rates and frequencies (rates) of cell exposure to potential shear conditions in the Lynx® CDR connector under flow conditions typically required to accommodate a 200 L perfusion bioreactor process.

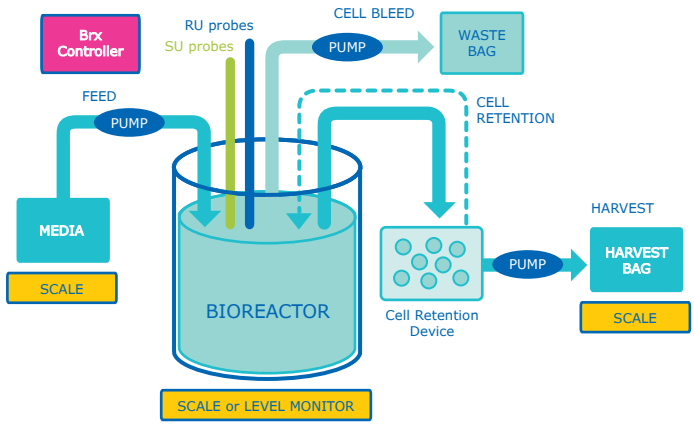


**Figure 2.** Schematic depiction of a perfusion set up in bioreactors. The bioreactor is fed with fresh media at the same rate at which spent media is removed. A cell retention device is used to separate spent media from cells in the bioreactor generating the recombinant product. In some applications, cell bleeds are periodically conducted to maintain operational control within the bioreactor.

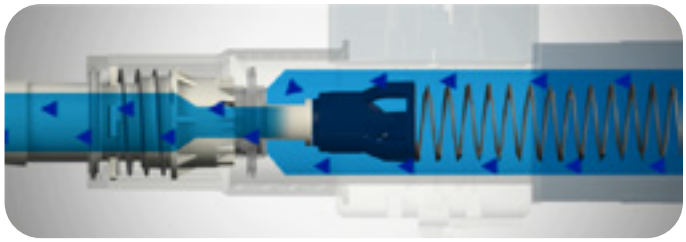

**Figure 3.** The Lynx® CDR Connector flow path diagram. Note that the diagram depicts fluid flow from right to left. Fluid movement occurs around internal components within the actuated device; it is not strictly a straight through path.

In the second experimental evaluation, CHO cells were grown in a 20 L (10 L working volume) perfusion bioreactor process utilizing an XCell™ ATF 2 System which was connected, disconnected, and reconnected to the bioreactor system by a single Lynx® CDR connector several times during the trial. This parallel study was conducted to demonstrate how the use of the Lynx® CDR connector in the cell-containing fluid flow path could deliver comparable results to a perfusion bioreactor set up which used welded tubes only, and to evaluate the potential to facilitate cell retention device replacement *in situ* while maintaining sterility in a cell-containing flow path after multiple actuations were performed.

## Study Design

Two parallel studies were designed and executed to both evaluate the contribution (or lack thereof) of the Lynx® CDR connector to mechanical cell shear, and also to determine the feasibility of using the Lynx® CDR connector in a perfusion application where the connector is present in a cell-containing flow path.

### A. Evaluation of Mechanical Shear Exposure to CHO Cells in a Flow Loop

In this study, a 20 L glass bioreactor (19 L working volume) connected to a Lynx® CDR connector-containing tubing loop was used to evaluate how cell shear generated by the Lynx® CDR connector flow path (Figure 3) would impact cell culture performance. The external tubing loop was also connected in line to a Levitronix® pump (PuraLev 600 SU pump, 3000 RPM, 16.5 LPM) in order to facilitate circulation of the cell-containing fluid stream from the bioreactor and through the tubing assembly. Duplicate tubing assemblies were utilized in this study; differing only by the presence or absence of Lynx® CDR connectors. The loop lacking the Lynx® CDR connectors served as an experimental control.

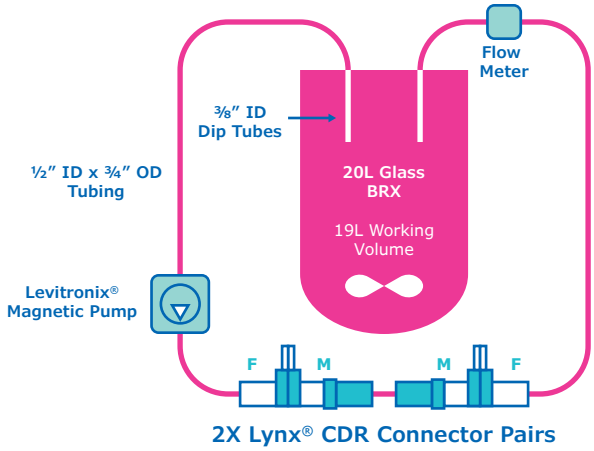


**Figure 4.** Schematic depiction of the cell shear loop assembly employed for Study A. A tubing loop containing 2 Lynx® CDR Connector pairs was aseptically connected to a 20 L glass bioreactor. A Levitronix® pump was used to circulate a cell-containing fluid stream through the experimental system at 16.5 LPM.

The flow rate of cell-containing liquid stream through the external loop was controlled by a Levitronix® bearingless, magnetically coupled, centrifugal pump that has been designed specifically for low shear cell culture applications.[2] Its operational setpoint of 3000 rpm was chosen based on historical experience which indicated this to be an acceptable speed having minimal impact on cell culture performance. The flow rate achieved at this set point, 16.5 LPM, is similar to that typical of a 200 L perfusion process using an XCell™ ATF 6 System.

This study sought to assess the initial feasibility of using the Lynx® CDR connectors in generic perfusion applications. Therefore, a pair of connectors, i.e. a set of 2 male-female couplings, were used to represent bioreactor configurations where a loop is required for connecting and operating the cell retention device. The 1.5" TC female connector was chosen as a "best case" option due to the least anticipated internal flow path constrictions. It was coupled with a ½" hose barb male connector in order to accommodate the tubing size used throughout the bulk of the tubing loop. The connected pairs were positioned in the loop in series, one with the fluid entering the female side first, the other entering the male side first, to ensure any pressure drop differences caused by flow direction could be accounted for (see Figure 4). A control study using a comparable length of tubing yet lacking the Lynx® CDR connectors was included in order to separate the contributions to cell shear made by the tubing and pump assembly versus the Lynx® CDR connectors. More specifically, a tubing loop consisting

of primarily ½" ID silicone tubing was connected via 2 x ⅜ inch dip tubes installed in the headplate of a 20 L glass bioreactor with a 19 L working volume. Using Equation 1 below the max wall shear rate through the tubing could be calculated.[1] At the specified flow rate of 16.5 LPM, and considering the sections of the loop with ⅜ inch inner diameter dip tubes, the calculated max shear rate at the wall in the loop was 3241$s^{-1}$. Although effects of exposure to max shear rates may vary for different cell lines and media compositions, this value falls in line with a suggested upper limit of exposure around 3000 $s^{-1}$ as reported in literature.[3]

$$\gamma_{max} = 32Q / \pi D$$

**Equation 1.** Shear rate equation for laminar flow in a capillary where γmax is the shear rate at the wall, Q is the volumetric flowrate through the tube and D is the inner diameter of the flow path tubing.[1]

## B. Evaluation of Lynx® CDR Connector Mechanical Shear Exposure to CHO Cells in a Perfusion Process

In this study, a 20 L perfusion bioreactor was set up using an XCell™ ATF 2 System in conjunction with one Lynx® CDR connector in order to evaluate the feasibility of using these multi-use sterile connectors in a perfusion application.

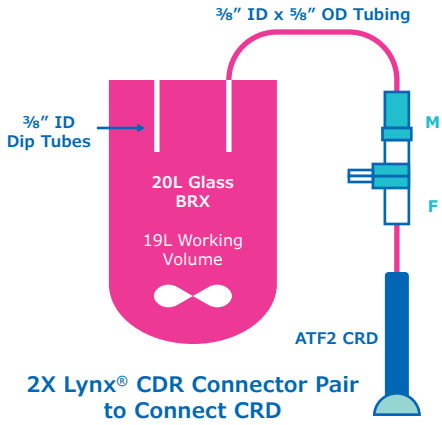


**Figure 5.** Schematic depiction of the XCell™ ATF 2 System-based perfusion operation utilizing a Lynx® CDR Connector pair employed for Study B. The XCell™ ATF 2 System was sterilely connected to a 20 L glass bioreactor using the Lynx® CDR Connector, flexible tubing, and a submerged dip tube installed in the head plate of the bioreactor.

A 20 L glass bioreactor (10 L working volume) was connected to the XCell™ ATF 2 System using a Lynx® CDR connector, and operation in perfusion mode was conducted over 15 days at 1.5 LPM set point through the XCell™ ATF 2 System. An in-house proprietary CHO-S GS cell line expressing a human IgG monoclonal antibody was used to inoculate the bioreactor containing the chemically-defined ExCell® HD Advanced perfusion cell culture media.

Operational conditions used for both parts (A and B) of the study design are shown in the table below:

**Table 1.** Bioreactor operational conditions utilized in study design parts A and B.

| Process Variable | Value | |
|---|---|---|
| Study Conducted | Study A: Lynx® CDR Connector in External Loop | Study B: Lynx® CDR Connector Mediated Perfusion |
| Bioreactor Volume | 20 L | 20 L |
| Working Volume | 19 L | 10 L |
| Cell Line | CHO-S | |
| Recombinant Protein | Human IgG | |
| Cell Culture Media | ExCell® HD Advanced Perfusion | |
| Inoculation Density | 0.3 - 0.8 x $10^6$ cells/mL | 0.5 x $10^6$ cells/mL |
| Agitation Rate | 350 RPM | |
| Temperature | 36.5 +/- 0.5 °C | |
| pH | 7.0 +/- 0.05 (microsparge $CO^2$, 1M sodium carbonate pump) | |
| Dissolved Oxygen (% air saturation) | 50% (air, $O_2$ cascade) | |
| Perfusion Device | N/A | XCell™ ATF 2 System |
| Number of Lynx® CDR Connectors in Set up | 2 Pairs | 1 Pair |
| Lynx® CDR Connector Type | 1.5" TC female with ½" male hose barb | 3/8" female hose barb with 3/8" male hose barb |
| Flow Rate through Lynx® CDR Connector | 16.5 LPM | 1.5 LPM |
| Cell-Specific Perfusion Rate (pL/cell/day) | N/A | 50 |

At various intervals, aseptic cell samples were collected from the bioreactors used in each study. Trypan blue-mediated automated cell counting was employed to determine cell density concentrations and cell viability. In addition, extracellular LDH concentrations on sample supernatants were determined using a Roche® Cedex BioHT metabolite analyzer, as per manufacturer instructions. In addition to regular bioreactor sampling, the Lynx® CDR connector used in Study B was repeatedly actuated (disconnected and reconnected) over several days during the study to evaluate if the connector reconnection maintained sterility of the experimental system.

## Results

### A. Study A - Evaluation of Mechanical Shear Exposure to CHO Cells in a Flow Loop

A 20 L bioreactor utilized in this study was inoculated with 0.75 x $10^6$ cells/mL and operated based on the parameters described in Table 1. An external aseptic tubing loop employing Levitronix® pump assembly was employed to test how the cells would respond to repeated shear exposure within the Lynx® CDR connector. The same tubing assembly lacking a Lynx® CDR connector (but maintaining the same overall tubing length) served as an experimental control for cell shear that resulted solely from exposure to the external loop and pump alone.

The bioreactor was inoculated in a batch mode of operation over the course of 3 to 4 days to assess whether the cells were negatively impacted by exposure to the shear present in the experimental system. As shown in Figure 6, the viable cell density between the experimental and control studies were negligibly different.

Similarly, the cell doubling time was consistent amongst the two experimental conditions that were evaluated, and with previously established growth rates reported for CHO cells used in recombinant protein production. The doubling time comparison is shown in Figure 7.

Perhaps not surprisingly, the cell viability profiles between the two cell shear studies were very similar as well (shown in Figure 8), as were the LDH profiles reported in Figure 9. These cumulative results suggest that the presence of two connected Lynx® CDR ½" male and 1.5" TC female connectors do not contribute significant cell shear to the CHO cell culture used in the study with fluid path flow rates up to 16.5 LPM. Note, because the flow rates achieved in this study were more typical of a 200 L perfusion bioreactor, yet the study was conducted with only a 19 L working volume, the rate at which cells were exposed to the inner flow path of the connecters resulted in an exaggerated exposure frequency. The cell culture performance remained comparable to the control condition despite this worst-case exposure frequency, further supporting the feasibility of using the Lynx® CDR connector in the perfusion application.

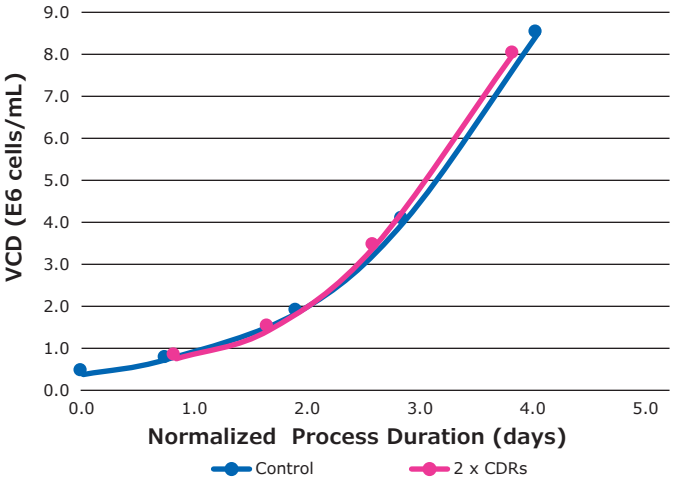


**Figure 6.** Cell growth curves for control (blue lines) and Lynx® CDR connector-containing (pink lines) fluid streams. Viable cell densities were measured daily. Because the inoculation density in the CDR-containing fluid stream trial was significantly higher than that of the control condition, the process duration parameter was normalized to allow the data set to be compared more easily. To normalize the data, instead of using a duration time "zero" for the Lynx® CDR connector-containing fluid stream at inoculation, the duration value assigned was instead matched with the duration value of the control condition at the corresponding VCD.

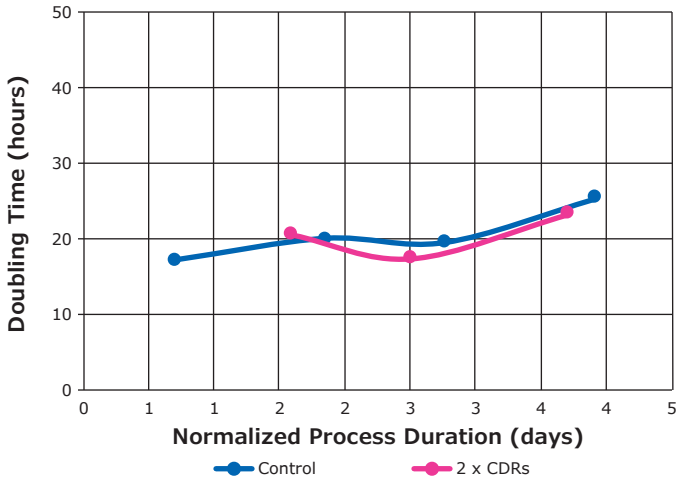


**Figure 7.** Cell doubling times for control (blue lines) and CDR-containing (pink lines) fluid streams. Because the inoculation density in the CDR-containing fluid stream trial was significantly higher than that of the control condition, the process duration parameter was normalized to allow the data set to be compared more easily. To normalize the data, instead of using a duration time "zero" for the CDR-containing fluid stream at inoculation, the duration value assigned was instead matched with the duration value of the control condition at the corresponding VCD.

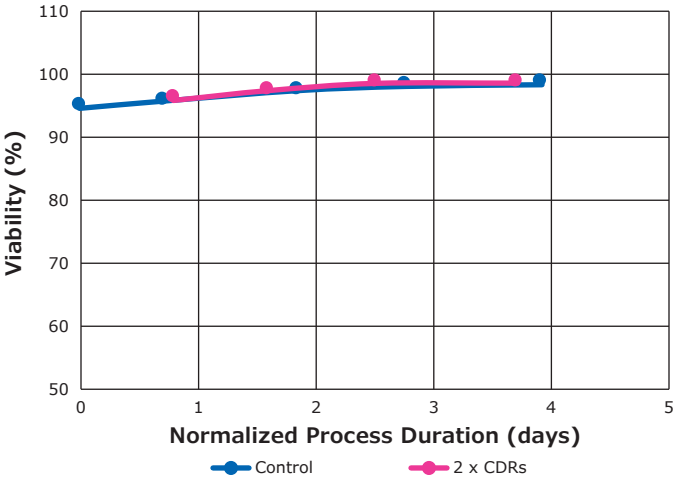


**Figure 8.** Cell viability curves for the cell-containing control (blue lines) and Lynx® CDR connector-containing (pink lines) fluid streams. Because the inoculation density in the CDR-containing fluid stream trial was significantly higher than that of the control condition, the process duration parameter was normalized to allow the data set to be compared more easily. To normalize the data, instead of using a duration time "zero" for the Lynx® CDR connector-containing fluid stream at inoculation, the duration value assigned was instead matched with the duration value of the control condition at the corresponding VCD.

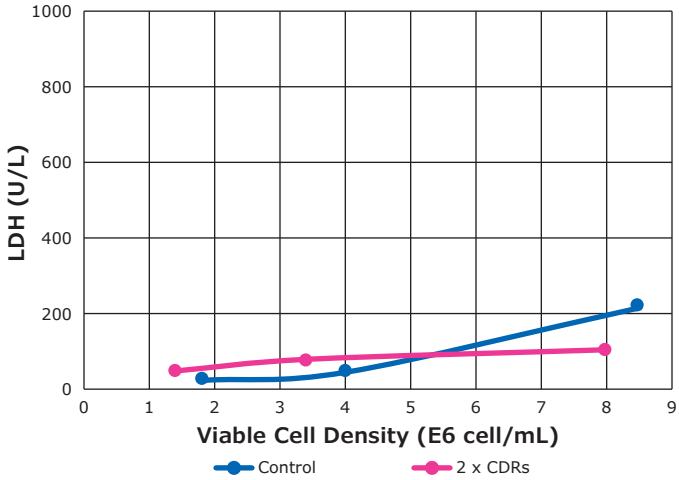


**Figure 9.** Lactate dehydrogenase (LDH) curves for control (blue lines) and Lynx® CDR connector-containing (pink lines) cell-containing fluid streams.

## B. Study B - Evaluation of Lynx® CDR Connector Mechanical Shear Exposure to CHO Cells in a Perfusion Process

A 20 L (10 L working volume) bioreactor utilized (studies leveraged as historical data controls were inoculated at approximately 0.37 x $10^6$ cells/mL) in this study was inoculated with 0.5x$10^6$ cells/mL and operated based on the parameters described in Table 1. The XCell™ ATF 2 System was connected to the bioreactor by a Lynx® CDR connector. This set up was employed to test how the cells would respond to repeated shear exposure in a de facto small-scale perfusion application utilizing the Lynx® CDR connector.

The perfusion culture progressed until the viable cell density reached approximately 60 x $10^6$ cells/mL, after which a constant, manual cell bleed was initiated to maintain the cell mass at approximately this cell density level over the remaining course of the experiment was initiated to maintain the cell mass at approximately 50 x $10^6$ viable cell/mL for the the next several days of the experiment. In addition, repeated actuations (2 per day) of the Lynx® CDR connector were performed on study days 9, 10 and 11 (shown by arrows in Figure 10), in order to evaluate if the cell-containing fluid stream would remain both aseptic as well as closed (i.e. no fluid leaks) after repeated reconnections of the connector. The flow rate of the XCell™ ATF 2 System diaphragm pump was re-initiated between each Lynx® CDR connector actuation.

Figure 10 demonstrates that a perfusion process was achieved and successfully maintained at the target cell density over most of the study duration. Cell bleeds were initiated on study day 7 in order to maintain the bioreactor cell density at approximately 50 x $10^6$ cells/ml, although some variability in maintaining this cell density targets were observed around study days 12 to 13, due to variability in the manual cell bleed procedure. In addition, cell bleeds were stopped between days 14 and 15 in order to confirm that the cells were still in the exponential growth phase and that the Lynx® CDR connector could support high cell densities (i.e. 80 x $10^6$ cells/ml). Both the uptick in growth once the cell bleed was discontinued and the consistent maintenance of culture viability levels close to 100% over the duration of the study suggests that the presence of the Lynx® CDR connector did not negatively impact the effectiveness of the perfusion process.

In addition to maintaining high cell viabilities over the perfusion study, comparison of cell doubling times between XCell™ ATF 2 system-mediated perfusion studies (in the presence or absence of a Lynx® CDR connector) revealed no significant differences over a wide range of cell densities. These observations are shown in Figure 11. The reported doubling times in this graph were plotted until cell bleeds were implemented in the exponential phase of cell growth to maintain cell densities within the desired cell density range. The control in this case refers to a historical perfusion process with the same cell line, media and general bioreactor conditions where the XCell™ ATF 2 System was connected using a tube welder.

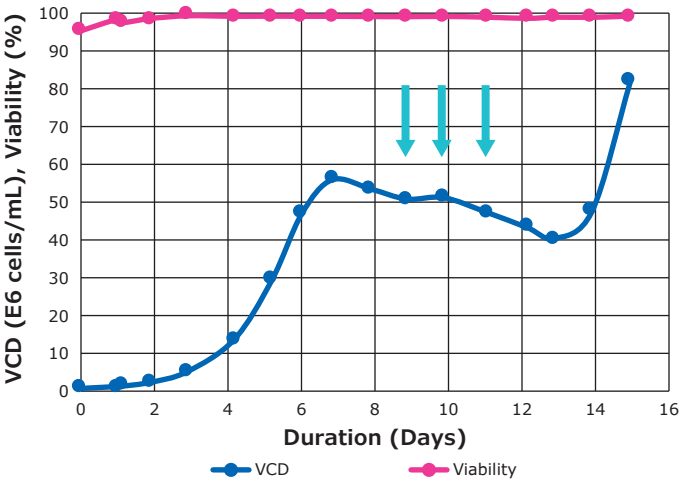


**Figure 10.** Cell growth (blue lines) and viability curves (pink lines) for an XCell™ ATF 2 System-mediated perfusion process utilizing a Lynx® CDR Connector pair connection of the CRD to the bioreactor. Vertical arrows on study days 7, 8, and 9 indicate where the Lynx® CDR connector was disconnected and reconnected during the perfusion process.

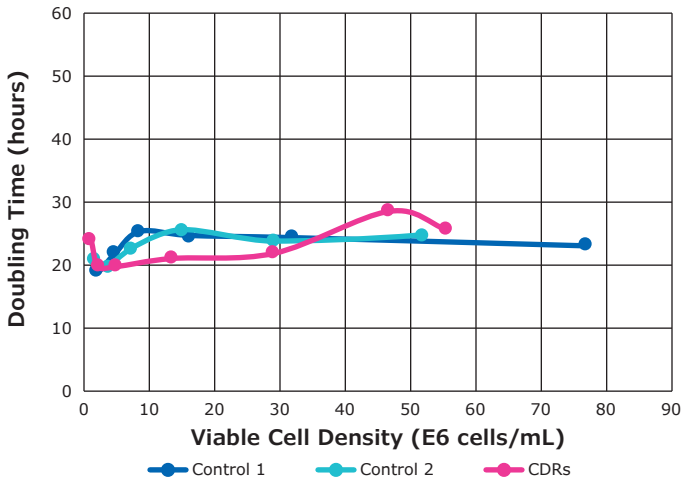


**Figure 11.** Doubling times for an XCell™ ATF 2 System-mediated perfusion process in the presence (pink lines) or absence (blue lines) of a Lynx® CDR Connector pair in the cell-containing fluid path between the bioreactor and CRD.

Figure 12 summarizes the levels of LDH measured in XCell™ ATF 2 System-mediated perfusion studies conducted in the presence or absence of a Lynx® CDR connector. One Lynx® CDR connector facilitated-perfusion study was compared to two historical control studies lacking the connector in the perfusion set up (the second independent control was added as an additional reference point to demonstrate experimental consistency in the test system). In all instances, the levels of LDH trended upwards at similar rates over the duration of the study as the cell densities increased. In addition, the total amount of LDH detected in all experimental conditions did not differ significantly. These results further support that the presence of the Lynx® CDR connector in a perfusion bioreactor assembly did not contribute significantly to cell shear *per se*.

Lastly, the impact of the presence of the Lynx® CDR connector on sieving of the cell retention device (i.e. the XCell™ ATF 2 System filter assembly) was evaluated (Figure 13). Sieving was calculated as the percentage of recombinant product present in the perfusate versus that present in the contents of the bioreactor (i.e. the retentate). While sieving progressively decreased over the duration of the perfusion studies (presumably due to XCell™ ATF 2 System filter fouling), differences in the extent of sieving between the Lynx® CDR connector study and control study were negligible. This observation further supports that there were minimal operational differences in the perfusion process regardless of whether a connector was used.

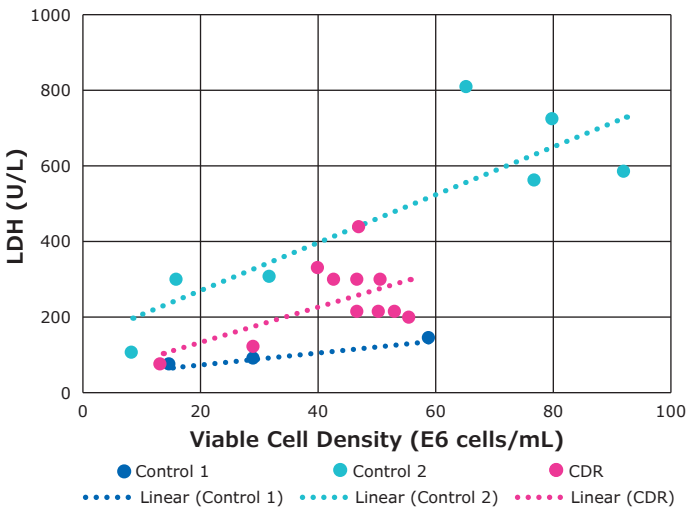


**Figure 12.** Lactate dehydrogenase (LDH) levels reported as a function of viable cell density in the presence (light blue points) or absence (dark blue and pink points) of a Lynx® CDR Connector pair in the cell-containing fluid path. The data from the two control studies (dark blue and pink points) shown here were generated in two independent experiments.

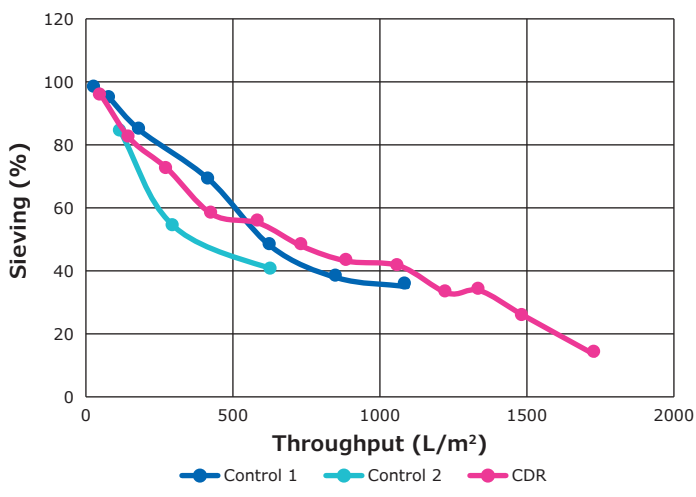


**Figure 13.** Sieving profiles of an XCell™ ATF 2 System-mediated perfusion process in the presence (pink lines) or absence (blue lines) of a Lynx® CDR Connector pair in the cell-containing fluid path. Sieving percentage is reported as a function of the Lynx® CDR connector filter throughput (total L/m²).

## Discussion

These studies were conducted in order to demonstrate the feasibility of utilizing a Lynx® CDR connector in upstream bioprocessing applications employing CHO cells for recombinant protein production. The studies were conducted in two parts. Initially, cells that had been repeatedly passed through an external tubing loop were analyzed to understand to what extent they responded to exposure to cell shear. Cell shear conditions were created in the presence or absence of Lynx® CDR connectors in order to understand how this connector specifically contributed to cell shear under relevant processing conditions.

This first study demonstrated that the presence of the connectors did not contribute significant exposure of CHO cells to cell shear compared to the control experimental conditions. In this study, the flow rate (16.5 LPM) was chosen in order create conditions representative of a 200 L perfusion bioprocess employing an XCell™ ATF 6 System. The inclusion of a pair of Lynx® CDR connectors in the cell-containing flow path had no impact on the cell growth, viability or doubling time growth profiles, demonstrating that cell-damaging shear did not occur due to the presence of this device under perfusion application-relevant conditions. In addition, the generation of extracellular LDH, an indicator of cell viability loss, was comparable between experimental (i.e. the loop containing two Lynx® CDR connectors) and control conditions over a range of cell densities.

In the second study, the performance of a perfusion bioprocess was evaluated when a Lynx® CDR connector was employed to connect the XCell™ ATF 2 System to the bioreactor. The performance of this process was compared to a control process lacking the connector in the XCell™ ATF 2 System flow path. Similar to the first study, the cell doubling time and LDH generation profiles were consistent between the control and Lynx® CDR connector processes. Put another way, no impact on process performance was observed. Like the first study, these observations further support that use of the Lynx® CDR connector use in perfusion applications to mitigate operational risks associated with cell retention device fouling is reasonable. In addition, multiple actuations of the connector during the perfusion study was effective, in that no contamination, liquid leakage nor cell shear impact was observed.

In summary, the results of these studies demonstrate the feasibility of employing the Lynx® CDR connector in upstream (cell-containing) applications in the case of cell retention device-based perfusion processes, the Lynx® CDR connector has the potential to address cell retention device fouling risks. Utilization of the connector can permit cell retention device replacement in process development and/or production facility gray spaces during an operational perfusion bioprocess. The advantage of this capability is clear, in that early termination or sub-optimal performance of perfusion processes can potentially be mitigated by having operational flexibility to replace fouling cell retention devices during perfusion processes.

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