TECHNICAL NOTE

REDUCE COST, INCREASE QUALITY, AND SHORTEN CYCLE TIME IN UPSTREAM MANUFACTURING SCALE CELL CULTURE WITH A SINGLE-USE HEAT EXCHANGER

SCOPE

The purpose of this technical note is to present the benefits of the new DHX Single-Use Heat Exchanger and its areas of application:

- Upstream Cell Culture Equipment Configuration
- Benefits of Single-Use Temperature Control / Heat Transfer
- Heating / Cooling Capabilities in a Single Pass

INTRODUCTION

Manufacturing biopharmaceutical products on an industrial scale has required scaling up a variety of techniques that were previously only practiced at bench scale. This includes highly technical and notoriously difficult processes such as cell culture; maintaining living cells in a tightly controlled sterile environment.

Successful cell culture on a large scale requires close control of the culture environment in terms of temperature, pH, removal of waste products, and addition of fresh nutrients. In order to produce high yields of the desired protein, precise control over these parameters at every step in the process is required. To meet FDA requirements, stringent cleaning and sterilization is also required between each batch.

Large-scale cell culture is typically performed in one of 2 ways; in the bioreactor (concentrated batch-fed), or perfusion, where fresh medium is continuously fed to the culture suspension, and metabolic waste products removed. Both process models have different economic benefits, and manufacturing companies have continued to push the limits of these technologies to reduce production scale and increase protein titers, necessitating ever-tighter control over the process parameters.

Large-scale cell culture is complicated by issues such as contamination of the product stream with bacteria, viruses, and other potentially harmful agents.[1] As a response to these concerns over sterility, there has been an increasing move towards single-use systems. With a goal of reducing the cleaning requirements CIP (clean in place) and SIP (steam in place), while ensuring high levels of sterility and zero batch-to-batch contamination.[2]

SINGLE-USE SOLUTIONS

Because of the inherent contamination problems, single-use bag systems including, filters, buffer bags, and final bulk product storage containers have all gained widespread acceptance, and are common-place in biopharmaceutical manufacturing. More recently single-use bioreactors for cell culture, single-use TFF systems for harvest, and disposable options for downstream processing are being adopted.[2][3]

WEAK LINKS IN THE CHAIN

However there still remain several weak links in the biopharmaceutical manufacturing process flow where, due to the lack of a suitable single-use alternative, engineers have no option but to incorporate stainless steel equipment into their process. This results in the need for time consuming cleaning (CIP/SIP), and greatly diminishes the overall benefits of a single-use process flow. [1]

Two of the biggest gaps in the single-use process flow are process sensors (to monitor parameters such as temperature and pressure) and heat exchange. Up until now there have been no viable single-use alternatives available, although this is changing with the introduction of the first single-use sensors, and now with the advent of the DHX Single-Use Heat Exchanger *(Figure 1)*.

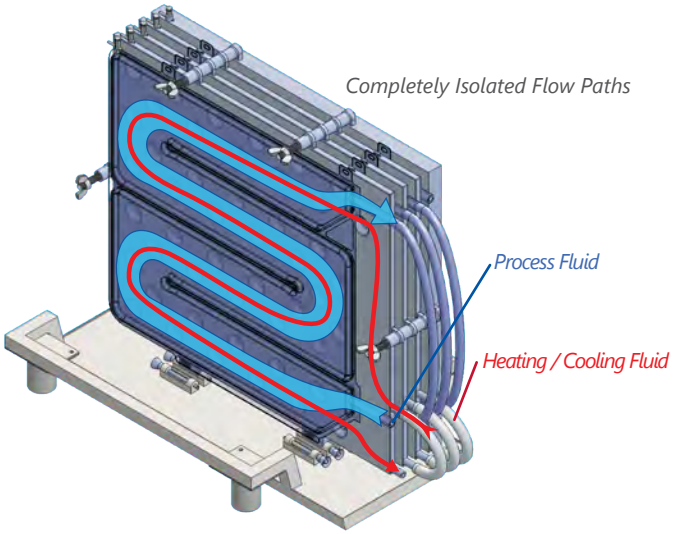


Figure 1: *Cutaway view of the DHX Heat Exchanger*

THE IMPORTANCE OF TEMPERATURE CONTROL AND HEAT EXCHANGE

Figure 2 (below) shows the typical equipment configuration for upstream cell culture, highlighting the problem areas where manufacturing engineers are forced to either accept undesirable temperature differentials, or accept a sub-optimal temperature control solution with large hold-up volumes and extended residence time.

Without an available high capacity single-use heat exchanger, manufacturing engineers have been forced to choose one of two sub-optimal options:

1. Insert a stainless steel multi-use heat exchanger into the process. This sacrifices the benefits of a full single-use set up, with part of the equipment needing to undergo a lengthy CIP/SIP process, resulting in prolonged downtime and expensive capital equipment.

2. Utilize a different piece of single-use equipment (such as a jacketed mixing tote) in place of a heat exchanger. With a significant sacrifice in terms of heat transfer, as the jacketed mixing tote was never designed for rapid cooling (or warming) of solutions. The much lower heat transfer rate results in the whole process taking longer to complete. The collected material is also subject to an extended residence time, with increased hold-up volume, as the desired temperature cannot be reached quickly in a single pass.

These solutions are not ideal, each bringing a series of problems that manufacturing engineers have had to contend with. With the advent of the DHX Single-Use Heat Exchanger, there is now a solution.

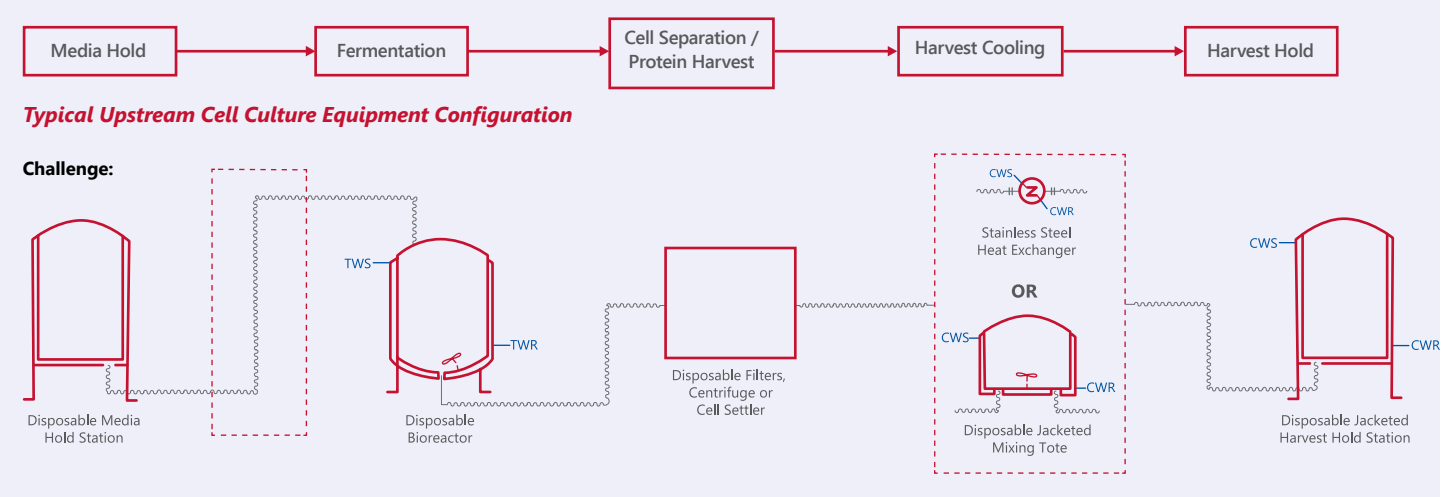


Figure 2. *Typical upstream cell culture equipment configuration. Weak points are highlighted in dashed boxes.*

THE DHX SINGLE-USE HEAT EXCHANGER

The DHX Single-Use Heat Exchanger offers significant advantages for cell culture at the manufacturing scale, allowing manufacturing engineers to build temperature control into their process without having to sacrifice the benefits of single-use. Figure 3. Below illustrates some of the critical points in a typical cell culture process where the DHX system can drive benefits. For the first time it is possible to add temperature control into the cell culture process flow while retaining a complete single-use set up; enabling 100% confidence in sterility without the requirement for CIP/SIP, and increasing the quality of finished product through uniform temperature control.

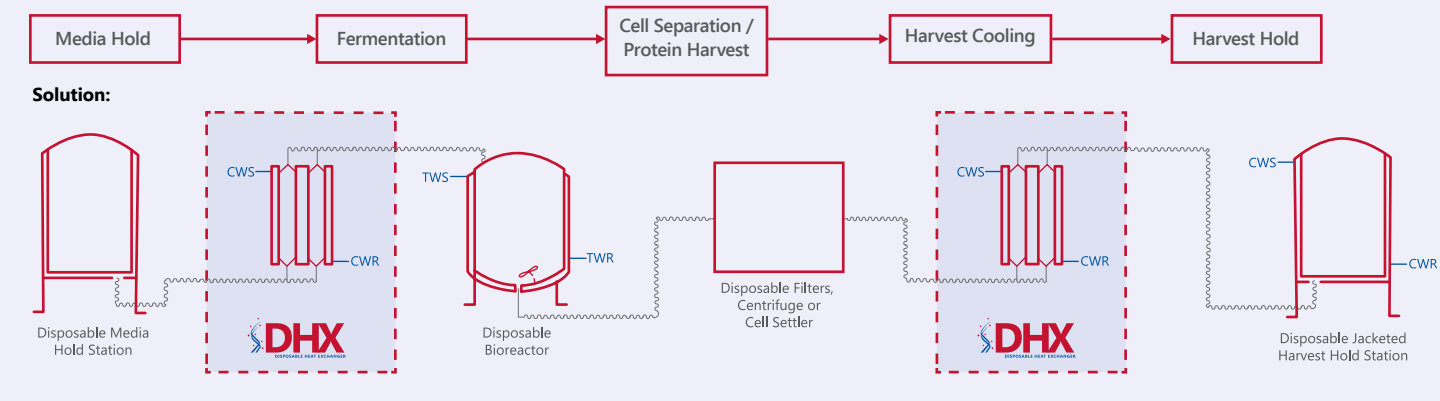


Figure 3. *Utilizing DHX heat exchanger in upstream cell culture*

KEY USES AND BENEFITS OF THE DHX SINGLE-USE HEAT EXCHANGER.

Reduced Infrastructure Requirements

A high capacity heat exchanger eliminates the need for a cold room / warm room and enables full-scale manufacturing to be performed in one-room, at ambient temperature simplifying the setup and reducing overall cost.

Reduced Processing Time

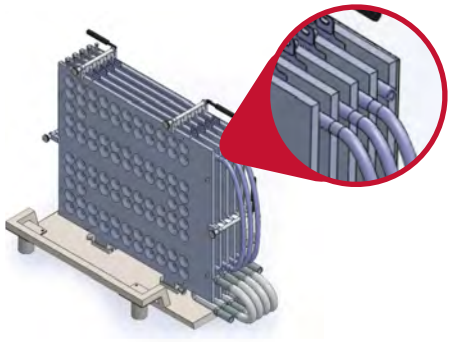
The turnaround time for a stainless steel production line is measured in days, the turnaround time for a single-use production line in hours. By replacing stainless steel heat exchangers with the DHX, the production line can be rapidly turned around and put back in action.

Improved Product Consistency

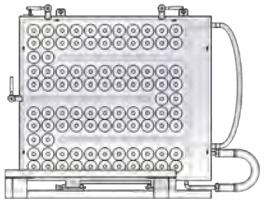
The DHX Heat Exchanger gives engineers the ability to incorporate temperature control at multiple points in their manufacturing process. Enabling greater control and optimal temperature at every stage, resulting in greater consistency from start to finish.

Eliminate Waste

Compared to the DHX Heat Exchanger, alternative temperature control solutions such as jacketed mixing totes, or jacketed holding stations have large hold-up volumes, meaning excessive waste. If the process solution is expensive, or difficult to produce this waste can quickly add up.

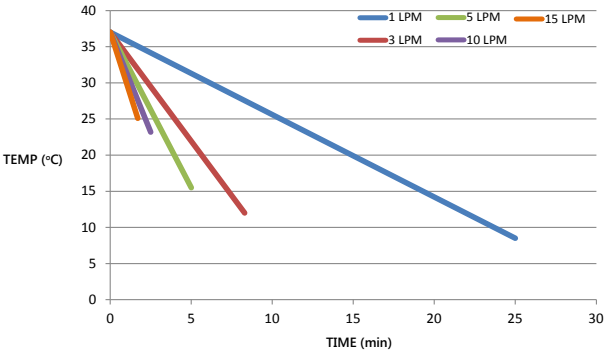


A plate and frame design promotes efficient heat transfer. Single-use bags fit tightly between the stainless steel plates.



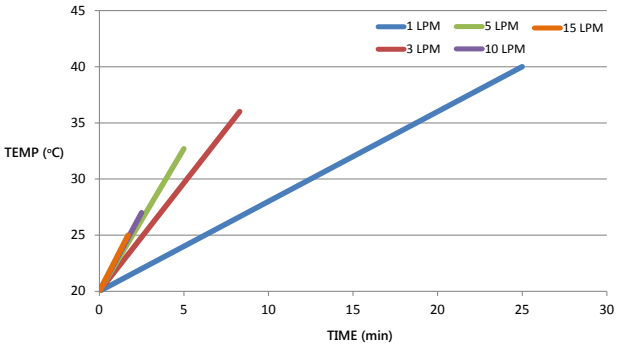
Serpentine flow paths of process fluid and heating/cooling fluid maximize heat transfer.

DHX Cooling Efficiencies



DHX Cooling Efficiencies Measured by Temperature vs. Time

DHX Heating Efficiencies



DHX Heating Efficiencies Measured by Temperature vs. Time

CONCLUSION

The DHX Single-Use Heat Exchanger brings together the class leading heat transfer properties of a high capacity plate and frame heat exchanger concept, with all of the advantages of single-use into one unit. This provides manufacturing engineers with greater control over their process than has previously been possible, without having to forego the benefits of a single-use process line .

REFERENCES

1. Q7 Good manufacturing practice guide for active pharmaceutical ingredients (Q7). International committee on Harmonization. 2000
2. Single-use disposable technologies for biopharmaceutical manufacturing. Shukla A, Gottschalk U. Trends in Biotechnology, Volume 31, Issue 3, 147-154, 26 November 2012
3. Single-use Products for Bioproduction: Available Options for Cell Culture and Downstream Processing. Jones S. American Pharmaceutical Review, 01 May 2011.