Workshops
Cell Culture Engineering XV

Workshop #1: Advances in Cell Line Engineering and Protein Expression Strategies

FACILITATORS

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INTRODUCTION AND WORKSHOP OVERVIEW

The cell lines used to support commercial manufacturing are dominated by mammalian cell culture and in recent times CHO cells have been widely utilized. Despite advances in production format, cell culture medium and process intensification, cell specific productivity has remained stagnant. This work shop will focus on the state-of-the-art in both cell line engineering and protein expression. In particular, the session aims to cover the use of genome editing for creation of engineered host cells and vector optimization. In addition, we will aim to cover enabling technologies for increasing yields, speed and efficiency in cell line development as well as the future state of complex genome engineering.

WORKSHOP DETAILS

To facilitate discussion and interactions the workshop will be divided into three main sections:

1. Workshop Introduction and setting the scene
2. *Topic based speed "dating":* (3-5 presentations of ~5-10 minutes each per topic followed by discussion). Attendees will be given an opportunity to speak with as many attendees as possible in a rotating speed dating format. Prior to the workshop a survey will be distributed to gather a list of discussion points and hot topics.
3. As the conclusion of the workshop we will have a final wrap up and summary of the discussions

Specific topics and discussion points that the workshop will aim to cover:

- CHO cells and genome engineering, opportunity vs reality
- Barriers to cell line engineering and commercial use
- Cell line tool boxes – platform approach vs fit for purpose
- Expression vector engineering and novel data driven approaches to enhancing transgene expression
- Using tools to build speed during cell line development
- Cell line engineering in real time – advances in approaches for cell therapy
- Beyond CHO – custom engineered systems for industrial production of complex recombinant proteins

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Workshop #2: Opportunities for and Challenges of Process Transfer and Scale-up

FACILITATORS

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OVERVIEW

The workshop will kick-off with a few introductory slides followed by an interactive discussion on key opportunities and challenges encountered during cell culture process scale-up and tech transfers. The topics covered will pertain to cross-site transfers, CMO transfers, phase III to commercialization as well as upgrading legacy processes. The focus areas for the ensuing discussion will be determined based on the audience input on the most desired subset of topics.

Tech transfers present a wide array of opportunities including optimizing process performance, enhancing titer/yield, reducing process variability, converting a peptone based process to chemically defined, closing legacy PC/PV gaps, upgrading a process to current standards, diversifying business risk by making product at multiple sites, upgrading an unit operation and enhancing microbial controls.

Along with opportunities come challenges during any scale-up or tech transfer; some of the commonly faced challenges are listed below:

- Complexities with non-standard antibody platform process transfers – e.g. potent molecules, bi-specifics
- Cleaning validation challenges associated with high cell density processes, potent proteins
- Media mixing challenges (precipitation, incomplete dissolution) during scale-up that may potentially impact process performance
- Different operational practices between sites – e.g. use of spinners vs shake flasks vs wave bags, use of different analytical instruments to measure culture outputs, different probe technologies that may contribute towards an offset
- Differences in bioreactor mass transfer and mixing dynamics, scale off-set for parameters like pCO_2
- Raw material variability due to different sourcing origin, or due to lot-to-lot variability
- Inoculum train size differences between transfer sites posing challenges to meeting desired split ratios
- Cultural differences when transferring across the globe
- Increased assay sensitivities, improved detection in current times posing a challenge while trying to establish comparability for certain product quality attributes during process upgrades
- Strategies for scale-down modeling of external manufacturer's bioreactors
- Product quality differences and how to deal with them
- Differences in cell count or cell mass determination methods
- Implementation of new technologies at scale

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Workshop #3: Modulating Product Quality through Cell Culture Process

FACILITATORS

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OVERVIEW

Variation in critical quality attributes of protein therapeutics can affect the safety and efficacy of these products. The cell culture process strongly influences product quality, and our understanding of cause and effect relationships between the cell culture process and product quality continues to expand. Even for attributes that are not believed to directly affect safety or efficacy (non-CQAs), tight product quality control helps to demonstrate manufacturing consistency. This workshop will be a forum for discussion on recent advances enabling better control of product quality and also engineering of product quality through advanced in-process analytics and cell culture process control.

Specific questions that the workshop will address by surveying across the industry will include:

- What are the critical elements of product quality?
    - glycosylation/glycosylation/glycosylation
    - other major variant forms (charge, size)
    - other minor variant forms (sequence variants, trisulfides, etc.)
    - Are there other CQAs to consider?
- How does product quality affect efficacy/safety? Are structure/function studies adequate?
- Can CQAs be controlled adequately through process engineering? What are the remaining challenges?
- What is the impact of raw material variability on product quality?
- How are in-process analytics helping in controlling product quality? What improvements are needed?
- What are some strategies to develop robust processes when the understanding of CQAs early in development is still lacking and process capability knowledge is limited?
- What are the common challenges to comparability linked to product quality – upon scale-up, developing biosimilars, process/site changes?
- How are health authority expectations changing? What are some of the strategies for meeting these expectations?

FORMAT

Our objective is to facilitate active discussion among the participants by encouraging sharing of information and open dialogue on the topics of the workshop. An interactive activity at the beginning of the workshop will allow participants to provide additional suggestions and to focus the discussion. Participants will then be asked to work through specific questions using examples and case studies to brainstorm and illustrate successful solutions/approaches.

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Workshop #4: Next Generation Manufacturing Design: Batch to Continuous

FACILITATORS

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OVERVIEW

Process and platform improvements have repeatedly improved the capabilities of biomanufacturing through the years, consistently pushing productivities to higher levels. These activities have cascading effects when adopted and implemented in a commercial manufacturing environment.

In this workshop, we will discuss various next generation manufacturing design(s) for biologics production and attempt to explore the impacts (both advantageous and disadvantageous) on process development, process transfer and validation, facility design and commercial manufacturing.

We will enlist the audience to consider various next generation manufacturing designs, including but not limited to:

- High-density, high-productivity fed-batch cell culture
- Concentrated fed-batch
- Continuous perfusion +/- continuous clarification
- Continuous perfusion integrated with downstream operation(s)
- Alternate host systems continuous culture+/- perfusion

Some impacts that we will explore together might include:

- Fast to clinic
- High throughput or scale down models
- Process characterization
- Tech transfer
- Process scale up/down
- Process analytical technology (PAT)
- Single-use technology
- Process economics
- Facility design
- Batch testing and release
- Regulatory considerations

Our goal is to facilitate a lively and interactive discussion where we encourage open dialogue and sharing of experiences from all participants. We will start with a quick check-in with participants for additional suggestions and prioritization of topics for the group to tackle. Please feel free to forward comments to us before the meeting.

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Workshop #5: Increasing Speed to the Clinic while Ensuring Future Manufacturability

FACILITATORS

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OVERVIEW

Aesop's fable of the tortoise and hare no longer applies to biopharmaceutical development. Far too often the small Biotechs' rush to Phase 1 causes delays or large gaps for late stage development, while the slower processes of big pharmaceuticals ensure success but are usually late to the market. The advances in technology, regulatory understanding, and competitive landscape warrant close consideration of acceleration options without sacrificing later manufacturability.

We will discuss options within discovery and early CMC development to accelerate programs into Preclinical and Phase 1 studies with a focus on 'acceptable' risk and overall short timelines to market. We will facilitate an interactive discussion on the themes of speed and risk. The workshop participants will contribute to and leave with a better understanding of questions such as:

Theme 1: Increasing speed to clinic and market

- How can development activities be front-loaded into discovery effectively with representative material and qualified 'for-purpose' assays?
- How can we predict better manufacturability from early biophysical data and limited process data?
- How do ICH guidelines influence early development decisions, especially about speed and quality?
- How can platform processes be effective with non-platform therapeutics?

Theme 2: Balancing risk versus speed

- Do we need a radical overhaul of process development to keep up with new accelerated clinical development pathways?
- How do we implement Phase-appropriate GMP/QA-oversight?
- What tools or information are we missing to increase speed to clinic?
- How do organizations make decisions on acceptable risks?

Our goal is to facilitate a lively and interactive discussion where we encourage open dialogue and sharing of experiences from all participants through roundtable discussions. Please feel free to forward comments to us for additional suggestions and prioritization of topics for the group to tackle ahead of the meeting.

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Workshop #6: Lessons Learned on Quality by Design Approach through Process Development and Characterization

FACILITATORS

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OVERVIEW

Most companies have already adopted different elements of the QbD approach to process development and characterization including risk assessments, DoE experimental designs and advanced statistical analysis. This workshop will focus on how we could incorporate these elements together into claiming post-approval flexibility, how this would differ from current/ traditional approaches and what would the benefits be.

We will cover two major themes as outlined below and find answers to several key questions:

Theme 1: QbD Strategy: From Data to Filing and Operational Flexibility

1. What are the different types of design space claims that we could file (e.g. multivariate or multistep design space or specific unit operation design space)? What would the nature of these claims be compared to a traditional filing (e.g. control strategy definition with parameter classification/ limits, commitment for post-approval plans)?
2. What additional design/ data would we need to support these claims (e.g. process-PQ modeling, linkage studies)?
3. How much post-approval flexibility would we get by exercising these claims in a QbD filing (e.g. process/ parameter change management)?

Theme 2: Operational Aspects of QbD Implementation

1. What are the pre-requisites of a scale-down model for QbD filing (e.g. management of scale offsets, statistical rigor)?
2. How does QbD translate into Manufacturing (e.g. tech transfer documentation, batch records, management of deviations)?

Our goal is to facilitate a lively and interactive discussion where we encourage open dialogue and sharing of experiences from all participants. We hope that every participant can take back some new learning with them after this workshop. We will start with a quick check-in with participants for additional suggestions and prioritization of topics for the group to tackle. Please feel free to forward comments about the potential topics of discussion to us before the meeting.

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Workshop #7: Advances in Analytical Methods and Their Use for Process Characterization

FACILITATORS

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OVERVIEW

Process Characterization is a vital late stage process design activity which aims to develop in-depth process understanding so that effective and robust control strategies can be developed for production. Completion of process characterization studies are an important development milestone. Process characterization studies and the associated analytical testing require significant resources and time. Advances in analytical methods for rapid screening and use of high-throughput methodologies are greatly desired to analyze the large number of samples generated during these studies to assess the product quality. In addition, it is desirable to assess product CQAs directly from harvest, or with minimal purification, which is challenging for non-antibody biologics.

This workshop is aimed at gathering industry expertise and case studies, challenges and pain points involved in development and implementation of advanced/new methodologies, regulatory strategy and experience, and potential risks and mitigations.

Themes for discussion:

1. Application of high throughput analytical methods to assess product quality (CQA's) during process characterization:
    a. Bridging between rapid/high throughput methods and qualified product analytical methods
    b. Challenges and pain points involved in implementation
    c. What can and cannot be detected? Could include metabolites, proteins, and glycosylation characterization methodologies etc.

2. Application of new/advanced Analytical Methods for process characterization beyond product release:
    a. Assays to characterize the product directly in harvest matrix (key CQAs)
    b. Rapid product quality assessment for non-antibody proteins
    c. Detection of cell culture metabolites (beyond glu/lac/gln/glt), HCPs, proteases.
    d. Use of in-situ probes for culture metabolites.
    e. Raw materials challenges / analytics to characterize/assay 'good' vs 'bad' lots.
    f. Assays to determine the residual concentrations of most of critical media components such as insulin, dextran, methotrexate, hydrolysates etc.

3. Survey to determine areas most of interest as the suggested topics are very diverse.

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Workshop #8: Applications of Omics Technologies

FACILITATORS

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PANEL

To be finalized

OVERVIEW

For future biopharmaceuticals the ongoing development of new/improved OMICS tools will increasingly allow to design and control cell line and process along development and also later during production. The omics data that becomes exponentially available is converging biotechnology to a point, where enough knowledge will be generated in the regulatory, metabolic and secretory modules of the cells, to reach a level of understanding that enables to control and optimize quantity and quality of the product.
This CCE workshop will provide a forum for a discussion on the development and application of OMICS technologies, like genomics, proteomics, glycomics, lipidomics and metabolomics. From method development over robust use of omics tools to early attempts to define/characterize product and control process, the audience will discuss current uses and future trends on how systems biotechnology "coordination" of OMICS knowledge will push cell culture, be it for proteins, vaccines or cell and gene therapies.
We encourage active engagement from the participants to share their use cases and perspectives on opportunities, challenges, strengths and limitations of OMICS tools.

SCOPE/CONTENT

The following topics are a starting point for discussion, but we would like to solicit additional topics for the workshop from the attendees:

1. New developments and technical aspects of OMICS technologies
    a. High-throughput not only in genomics
    b. Successes and limitations
    c. Latest developments
    d. Topics from attendees

2. Use of OMICS technologies
    a. Process understanding for process development, upscale, transfer and optimization
    b. Cell culture media development and customization
    c. Early clone screening and clone selection
    d. Cell adaptation (e.g. from adherent growth to growth in suspension)
    e. Biosimilar development
    f. Topics from attendees

3. Regulatory considerations
    a. Experience with regulatory authorities on the use of omics technologies
    b. Use of OMICS technologies to support design space filings
    c. Usage of OMICS technologies for QA/QC
    d. Use of OMICS technologies to justify changes of licensed products
    e. Topics from attendees

Our goal is to facilitate a lively and interactive discussion where we encourage open dialogue and sharing of experiences from all participants. We will start with a quick check-in with participants for additional suggestions and prioritization of topics for the group to tackle. Please feel free to forward comments to us before the meeting.

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Workshop #9: Empowering the Next Generation of Cell Culture Scientists and Engineers: Training and Funding

Facilitators

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OVERVIEW

This CCE XV workshop will provide a unique opportunity to engage your colleagues in an extended and dynamic discussion about empowering the next generation of cell culture scientists and engineers. Workshops at recent conferences have mostly focused on training and funding at the associates, bachelors, and masters level. The findings from those workshops will be briefly summarized. This particular workshop will then focus on the training and funding of research and education at the doctoral level. Some specific topics will include:

- Industry funding of doctoral research, ranging from fundamental to applied projects, performed in the university setting and/or at company sites. This will include a discussion of pre-competitive, fundamental research funded by industry consortia, sometimes in combination with funding from government sources.
- Funding of doctoral research by foundations and other charities. Success stories, challenges, and opportunities?
- Ensuring relevance of academic research. Large numbers of papers get published by academia and industry concerning new technologies. Many of these technologies are ultimately not implemented at commercial scale, sometimes because they have major flaws identified only after further testing in an industrial setting, are simply too late, or work well but only for certain cell lines. Ultimately, following a series of journal publications does not often point to actual challenges still facing industry. Can this be corrected with publication of follow-on tests at larger scales or with different cell lines, including failures as well as occasional investigations concerning why things didn't eventually work out as expected? Can relevant research topics be identified via regular cross-industry white papers on pre-competitive challenges? Other suggestions to correct this situation will be encouraged.

Our goal is to stimulate and enable a lively and interactive discussion, with broad participation from all. We will start with a quick check-in with participants for additional suggested specific topics for discussion, to complement those listed above. We wish to encourage open dialogue and sharing of experiences, expecting that the energy and passion of the attendees will create a sense of shared ownership for the direction, content, and success of "our" (collective) workshop.