BPA
BioProcessing Asia

BioProcessing Asia 2016

Programme and Abstract Book

Second
International
Meeting

PHUKET, THAILAND, 5–8 DECEMBER 2016

Welcome to the Second International BioProcessing Asia Conference at The Pullman Arcadia, Phuket, Thailand

It is a pleasure to welcome you to the second meeting in the BioProcessing Asia Conference Series. The Conference topics have been developed over the past year and include feed-back from BPA 2014. Sessions focus on the contribution of bioprocessing to the development and manufacture of affordable biopharmaceutical products in Asia. Morning sessions are product oriented and include discussion of processes for monoclonal antibodies, biosimilars, recombinant and plasma-derived products. The three afternoon sessions have science and technology themes: new developments in integrated process design, quality and regulatory issues and facilities and economics.

We have elected to include several Keynote and Focus Lectures to give broader overviews of current issues. Arun Chandavarkar, Joint Managing Director, Biocon Ltd., India, will open the Conference with a Keynote Address with an access and affordability theme pertinent to needs in the region. Prof Nigel Titchener-Hooker, Dean of Biochemical Engineering at UCL, London will discuss manufacturing challenges and close the meeting with a prospective view of what lies ahead. The Conference will also include Focus Lectures from distinguished thought leaders to provide background to the main Conference topics: Andrew Chang, formerly at the US FDA will discuss the regulatory environment, Günter Jagschies of GE Healthcare will take a look at global issues and Jan Bult, President of the Plasma Protein Therapeutics Association asks how clinical needs can be met by manufacturing in Asia. An important part of the Conference is the Poster Session which allows more detailed discussion of specific issues and topics.

Compared to BPA 2014, attendees will have more time to network, find friends, old and new, and discuss the contribution of bioprocessing to the provision of biopharmaceutical products for patients in Asia.

John Curling
Chair

Organizing Committee

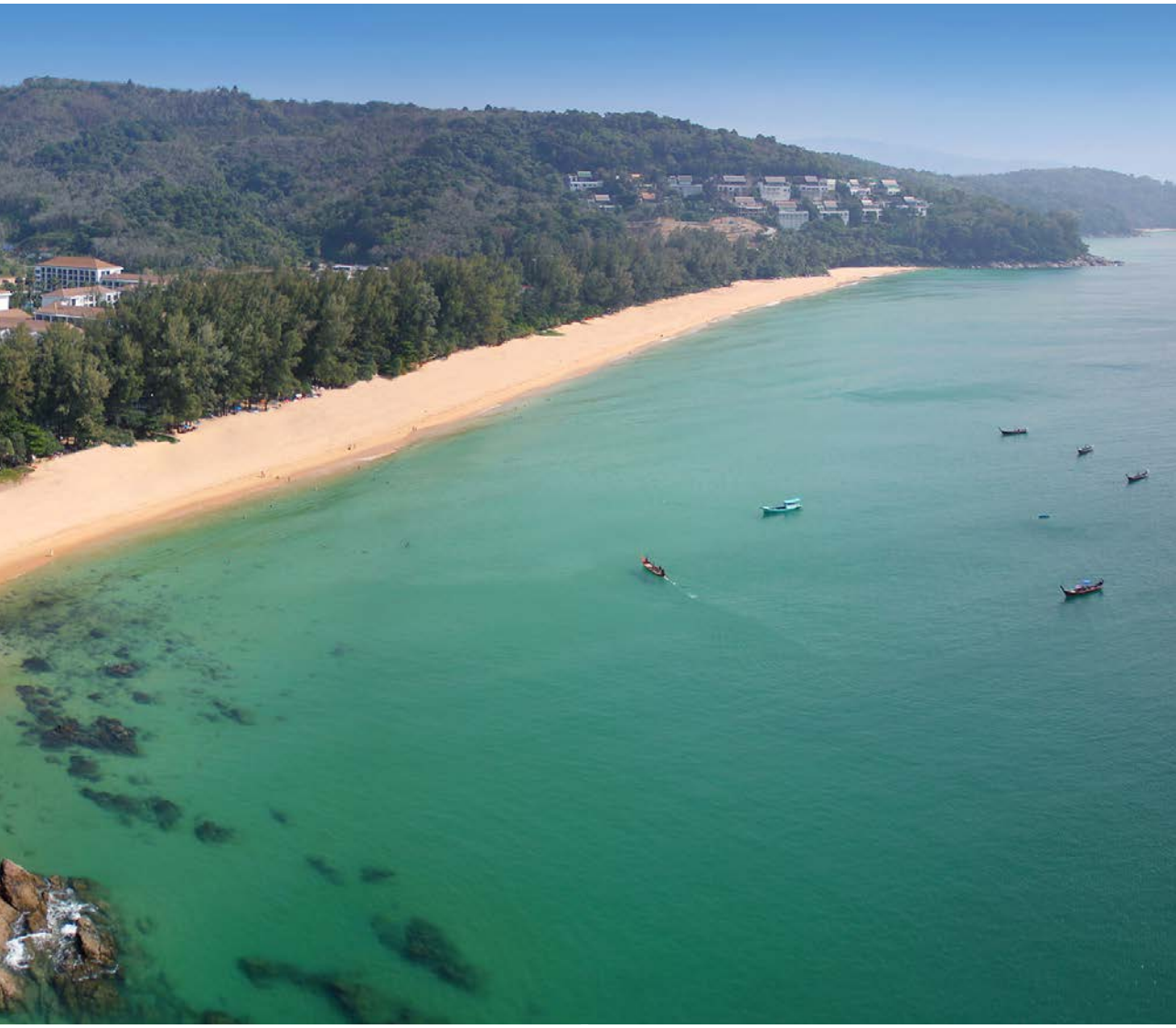
John Curling
John Curling Consulting AB, Uppsala, Sweden
john@consultcurling.se

Neil Goss
Further Options, Pty Ltd, Melbourne, Australia
neilgoss@furtheroptions.com.au

Günter Jagschies
GE Healthcare Life Sciences, Uppsala, Sweden
guenter.jagschies@ge.com

BioProcessing Asia is a science and technology focused, not-for-profit, non-commercial Conference Series. Opinion leaders and experts in bioprocessing meet every 2 years to further the research, development and manufacturing of biopharmaceutical, vaccine and blood plasma products needed in Asia.

Swedish Tax Agency Registration number 802503-6792



General information

Venue

The Conference is being held at the Pullman Phuket Arcadia Naithon Beach on the north-west shore of Phuket.

Registration

The Registration Desk, located in the Foyer of the Conference Centre, is open as follows:

REGISTRATION DESK

Monday 5 December	13.00 – 17.00	
Tuesday 6 December	07.30 – 12.00	15.00 – 19.30
Wednesday 7 December	07.30 – 12.00	15.00 – 19.30
Thursday 8 December	07.30 – 12.00	14.00 – 18.30

If you need any assistance just ask a member of staff at the Registration Desk.

Programme and Abstract Book

Each registrant is entitled to one copy of the Programme and Abstract Book. Additional copies may be available at the Registration Desk at the close of the Conference.

Digital Programme and Abstracts

Each registrant may download an electronic version of the Programme and Abstracts. This tool is for the personal use of the attendee during the Conference and may not be used for any commercial purpose whatsoever.

Wifi

Wifi is available throughout the property. Access is available to registered guests only.

Oral Sessions

All Oral Sessions will take place in the Arcadia Ballroom in the Conference Centre. We ask you to gather in the Foyer 15 minutes before the start of each Session. We have a full programme and will need to keep to the schedule.

Speaker Ready Room

A Speaker Ready room is available adjacent to the conference room. Presenters may review their slides prior to the session and should transfer their presentations via the hotel wifi system or by memory stick. Presentations should be available to the AV personnel well in advance of the session and at least 30 minutes prior to the start of the Session.

Poster Session

The dedicated Poster Session is scheduled for Thursday morning, 8 December at 11.30. Your Poster should be put up on Monday 5 December before 15.00 and taken down after lunch on Thursday 8 December. Poster boards are labelled with the Poster Abstract number.

Coffee Breaks

Complimentary tea, coffee, soft drinks and accompanying snacks will be served at each break. Bottled water will always be available in the conference room.

Breakfast, Lunch, Receptions and Dinner

Breakfast is included for all hotel residents.

Lunch on Tuesday will be a box lunch in connection with an excursion to Wat Phra Tong and the Gibbon Rehabilitation Centre. Similarly, a boxed lunch will be provided on Wednesday under the casuarina trees at the north end of Naithon beach, also providing an opportunity to swim at the life-guard patrolled area. Observe the flags and warnings, if any, for jelly fish. Details and safety updates will be provided on Tuesday and Wednesday mornings. A light lunch will be served at the Banyan Tree Deck on Thursday.

The Opening Get-Together will be held in the Arcadia Ballroom Foyer at 18.00 prior to the opening Keynote Lecture. Dinner will be served at 20.00 at the Banyan Tree Deck. A Buffet Dinner on Tuesday evening will be at the Elements Restaurant.

You are free to make your own arrangements for dinner on Wednesday either at the hotel or any of the local restaurants on Naithon Road. We advise you to make table reservations if you choose to eat at the Pullman Arcadia.

The Closing Reception and Dinner starting at 19.00 will be held on the Poolside Deck and at the Elements Restaurant.

Dress Code

The conference and setting in this secluded area of Phuket promotes communication between participants and informal dress is suggested. The climate is tropical and comfortable clothing is recommended throughout the day and evening. There are no special requirements for evening dining.

Thailand is a multi-confessional country with a predominantly Theravada Buddhist population. We ask you to respect their traditions.

Message Centre

The Registration Desk can receive messages for you. Messages that are not sent directly to you by SMS or e-mail can be sent to the hotel at: H7488-RE@accor.com.

Check-out

The hotel check-out time is 12.00 noon. Your hotel room has been paid, according to your requested dates, through the Conference Administration. However, if you are extending your stay beyond the reservation date you will need to settle your account with The Pullman Arcadia. You will also need to settle your bill for any extra meals, bar bills, laundry and other services you may have used during your stay.

Departure

Transport from the hotel to Phuket International Airport is included in the Conference services provided. You will be asked to confirm your departure time on the Departure Board at the Registration Desk. Your pick up time will be posted on the Board.

Attendee Survey

We are interested in your opinion about the Conference Programme, structure, location, venue etc. Please fill out the survey which you will find in the registration package and hand it in at the Registration Desk. For every survey we receive we will donate US$10 to Médecins Sans Frontières.

CONTACT INFORMATION

Secretariat

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Venue

Pullman Phuket Arcadia Naithon Beach

22/2 Moo 4, Naithon Beach, Saku, Thalang, Phuket, 83110 Thailand

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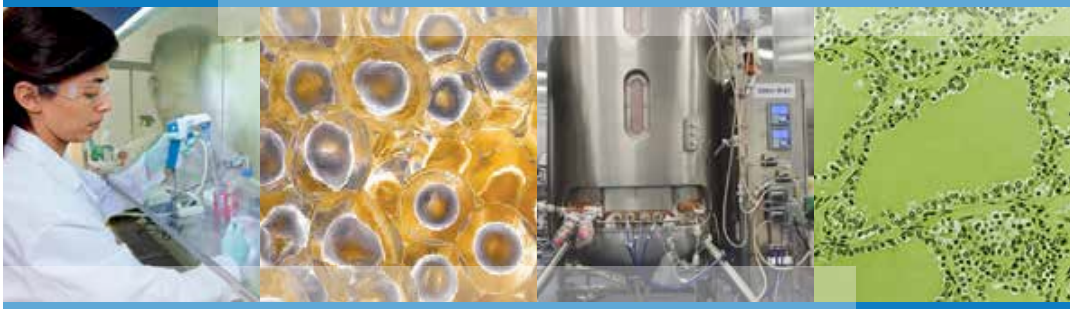

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

Amgen inaugurated its new biomanufacturing facility in Singapore at the Tuas Biomedical Park in 2014, marking the company's first manufacturing site in Asia. Built with the state-of-the-art modular, reconfigurable design that can be replicated in future facilities, this biologics facility was Amgen's first commercial-ready site aimed at increasing production capabilities and to allow greater medicine accessibility to patients around the world. Using a number of innovative technologies, this facility produces drug substances to treat osteoporosis and bone-related disorders in cancer patients.

A second facility at the same site is intended for large chemical synthesis manufacturing. This new facility will be Amgen's first commercial API facility and will produce the active pharmaceutical ingredient to treat multiple myeloma.

Most recently, Amgen opened a Singapore affiliate in 2015 to market its innovative medicines for patients suffering from serious illnesses across the region.

Amgen's expansion in Singapore further strengthens Amgen's capabilities to address the region's growing healthcare needs and provide treatments for millions of patients across the Asia-Pacific region.

For more information, visit **www.amgen.com.sg**

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Shire is the leading global biotechnology company focused on serving people with rare diseases and other highly specialized conditions. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including Hematology, Immunology, Neuroscience, Ophthalmics, Lysosomal Storage Disorders, Gastrointestinal/Internal Medicine/Endocrine and Hereditary Angioedema; and a growing franchise in Oncology.

Leading marketed products in our therapeutic areas

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NEUROSCIENCE
ADDERAL XR, BUCCOLAM, INTUNIV, EQUASYM, VYVANSE

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Our employees come to work every day with a shared mission: to develop and deliver breakthrough therapies for the hundreds of millions of people in the world affected by rare diseases and other high-need conditions, and who lack effective therapies to live their lives to the fullest.

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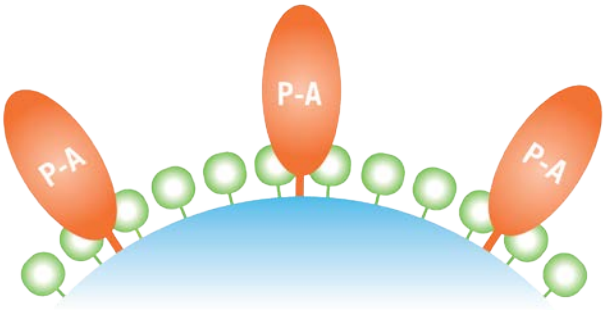
JSR Life Sciences

JSR Life Sciences is a business unit of JSR Corporation, a global company built on more than 50 years of performance material expertise and it began research in the life sciences field more than 30 years ago.

We are continually developing highly functional materials and products to meet the current and future needs of the growing biotechnology industry. Using a variety of integrated, leading-edge technologies, JSR provides materials that contribute to the manufacturing process of biopharmaceuticals, life science research applications, in vitro diagnostics and medical devices.

JSR manufactures Amsphere™ A3, a next generation Protein A chromatography resin for advanced protein separation in downstream processing of therapeutic antibodies manufacturing. Besides an outstanding high capacity, Amsphere™ A3 has an overall improved process robustness, flow characteristics, optimized impurity removal, productivity and resin lifetime.

With offices, laboratories and manufacturing facilities in Tokyo and Tsukuba (JP), Sunnyvale (CA, USA), Leuven (BE) and Beijing (CN), JSR is a research-oriented organization that pursues close collaborations with leading innovators in a number of industries that are key to the present and future welfare of human society: life sciences, elastomers, electronic materials, energy storage, display materials and optical materials.



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Modern science demands vision. We've been shaping biotechnology innovation for nearly three decades, leading the industry in antibody drug development through core technologies that include hybridoma and phage display. We've also mastered optimization to improve the safety and potency of antibody leads. We anticipate the future; we follow the science that translates into successful antibody therapeutics.

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BioProcess Technology Consultants, Inc.

From clone to clinic to commercial™, BPTC® is the world leading provider of strategic, technical, regulatory, and business Chemistry, Manufacturing, and Controls (CMC) consulting services to the biopharmaceutical industry. Whatever your company size, product portfolio, or stage of development, BPTC® provides targeted analysis, solid strategies, and desired results to achieve your objectives. Our team of consultants help you navigate the complex technical and regulatory issues of the CMC process to get you from clone to clinic to commercial™ as quickly and efficiently as possible. Collectively, we have many decades of extensive hands-on industrial expertise in the development, manufacture, quality, compliance and regulatory of biopharmaceuticals. At BPTC, we understand first-hand the many challenges of developing and commercializing new products and technologies.

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- Due Diligence Review
- Market Technology and Assessment

Meet BPTC's Senior Consultant Patti Seymour who will be presenting at the BioProcessing Asia 2016 Conference to discuss your needs and to learn more about BPTC's services.

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Programme

Monday 5 December

15.00	Registration opens | Poster setup | Arcadia Foyer, Conference Center
18.00	Welcome Reception | Arcadia Foyer, Conference Center
18.45	**WELCOME ADDRESS** John Curling, John Curling Consulting AB, Uppsala, Sweden
19.00	Access and Affordability: Technological Approaches to Address these Key Healthcare Imperatives **Keynote 1** Arun Chandavarkar, Biocon Ltd, Bangalore, India
19.45	End of Session
20.00	Welcome Dinner | Banyan Tree Deck

Tuesday 6 December

07.00	Breakfast
08.15	**SESSION 1: RECOMBINANT PROTEIN AND MAB PROCESSES**
	Chair: Dorothee Ambrosius, Boehringer-Ingelheim, Biberach, Germany
08.30	**101** A Modular HTPD Toolbox for the Development of Non-MAb Biotherapeutics Processes Matthias Berkemeyer, Boehringer Ingelheim RCV & Co KG, Vienna, Austria
09.00	**102** Ion Exchange and Multimodal Chromatography Performance for Separation of Charge Variants in mAb Purification Process Tomas Bjorkman*, Lena Karf, Anders Ljunglof, Anna Gronberg and Eva Heldin GE Healthcare, Uppsala, Sweden
09.30	**103** International CHO Process Transfer along a Global Single-Use Platform Johannes Salzbrunn, Boehringer Ingelheim Biopharmaceuticals (China) Ltd, Shanghai, China
10.00	▶ Morning Break
10.30	**104** Current Developments and Future Trends of Changing Biopharm Industries and How To make a Meaningful Assesment Using Cost Modeling Tools Priyanka Gupta, Sartorius Stedim Biotech, Bangalore, India
11.00	**105** Ultrafiltration/Diafiltration of Highly Concentrated Antibody Solutions: Experiments and Modeling for the Effects of Module and Buffer Conditions Nripen Singh*, Abhiram Arunkumar, Youngbin Baek and Andrew Zydney Bristol-Myers Squibb, Devens, MA and The Pennsylvania State University, University Park, PA, USA

11.30 **106** Development of an Efficient Manufacturing Process for Adenovirus

Mark Fitchmun[1], Mark Snyder[2], Khaled Mriziq[2]* and John Chicca[3]
1. Somatek Inc., San Diego, CA, 2. Bio-Rad Laboratories, Hercules, CA and 3. Molecular Diagnostic Services, San Diego, CA, USA

12.00 Box lunch and excursion to Wat Phra Tong and Gibbon Sanctuary

15.30 Priorities in Global Healthcare and Burden of Disease: Are We doing the Right Things in Biopharma and Vaccines?

Focus Lecture 1

Günter Jagschies
GE Healthcare, Uppsala, Sweden

16.15 **SESSION 2: EMERGING TECHNOLOGIES IN MANUFACTURING**

Chair: Nigel Titchener-Hooker, University College London, London, United Kingdom

16.30 **201** What Opportunities will Smart Polymers Bring in the Future to the Downstream Processing of Biological Products?

Milton T.W. Hearn
Monash University, Clayton, Vic., Australia

17.00 **202** A Synergistic Life Cycle Approach to Understand and Control Raw Material Variability through Collaborative Process Analytics

Gunnar Malmquist*[1] and Canping Jiang[2]
1. GE Healthcare, Uppsala, Sweden, 2. Biogen, Cambridge, MA, USA

17.30 ▶ Afternoon Break

18.00 **203** Affordable Alternative to Protein-A: Characterization of Novel Pseudo-affinity Adsorbent and Purified Antibodies

Sushmita Koley* and Sandeep B. Kale
Institute of Chemical Technology, Mumbai, India

18.30 **204** Implementation of an End-to-End Continuous BioProcessing Platform using Novel Technologies

Engin Ayturk[1], Rene Gantier[1] and Peter Levison*[2]
1. Pall Corporation, Westborough, MA, USA and 2. Pall Life Sciences, Portsmouth, United Kingdom

19.00 **205** Process Intensification with Periodic Counter Current Chromatography

Hans Blom
GE Healthcare, Uppsala, Sweden

19.30 End of session

20.00 Dinner | Elements Restaurant

Wednesday 7 December

07.00 Breakfast

08.15 **SESSION 3: BIOSIMILARS DEVELOPMENT AND MANUFACTURING**

Chair: Scott Wheelwright, Complya Asia Co. Ltd., Suzhou, China

08.30 **301** Global Biomanufacturing Trends, Capacity, and Technology Drivers

Patricia Seymour
BioProcess Technology Consultants, Inc. Woburn, MA, USA

09.00 **302** Biosimilars in Asia

Scott M. Wheelwright
Complya Asia Co., Ltd., Suzhou, China

09.30 **303** Manufacturing Challenges of Targeted Therapies

Suzanne Farid and Nigel Titchener-Hooker*
University College London, London, United Kingdom

10.00 ▶ Morning Break

10.30 **304** A Commercial Scale Facility for Mab Drugs

Bo Xu
Zhejiang Teruisi Pharmaceutical Inc., Zhejiang, China

11.00 **305** Continuous Processing for Biosimilars

Himanshu Gadgil[1]*, and Jennifer Campbell[2]*
1. Enzene, Bangalore, India and 2. Merck Millipore, St Laurent d'Aigouze, France

11.30 **306** Continuous Processing Key Operational & Economic Factors Influencing Monoclonal Antibody Manufacture

Andrew Sinclair*, Yuki Abe and Alan Calleja
Biopharm Services, Chesham, United Kingdom

12.00 Box lunch | Drop-off at Naithon Beach

14.30 **SESSION 4: VACCINE DESIGN AND PRODUCTION**

Chair: Linda Lua, University of Queensland, Brisbane, Australia

14.45 **401** Conjugate Vaccine Development at Hilleman Labs: Lessons and Opportunities

Manoj Kumar Chhikara, Sandeep Sharma, Rakesh Rana, Anil Sood*and Gill Davinder
MSD Wellcome Trust Hilleman Laboratories, New Delhi, India

15.15 **402** Simple Manufactured Microbial Platform as Rapid and Low-cost Modular Capsomere Vaccine for Poultry Vaccination

Jarurin Waneesorn*, Anton P.J. Middelberg and Linda H.L. Lua
University of Queensland, Brisbane, Australia

15.45 **403** Status of Chinese Vaccine Industry for Moving into International Main Stream

Li Shi
Shanghai Zerun Biotechnology and Walvax, Shanghai, China

16.15 **SESSION 5: QUALITY, REGULATORY AND CLINICAL TRENDS**

Chair: Jean Bender, MedImmune, Gaithersburg, USA

A Glance at the Global Regulatory Landscapes for Biological Products **Focus Lecture 2**

Andrew Chang
Novo Nordisk, New York, NY, USA

17.00 ▶ Afternoon Break

17.30 Session Introduction: Jean Bender, MedImmune, Gaithersburg, USA

17.45 **501** Virus Clearance Validation from Western and Eastern Perspective

Rolf G. Werner
Industrial Biotechnology, University Tübingen, Tübingen, Germany

18.15 **502** United Against the Bioburden Threat

Anders Ljunglöf*, Anna Grönberg, Elin Monie, Tomas Björkman and Magnus Wetterhall
GE Healthcare, Uppsala, Sweden

18.45 **503** Development Pathways for Advanced Therapy Medicinal Products – Challenges and Regulatory Perspectives

Andy Bailey
ViruSure GmbH, Vienna, Austria

19.15 End of session

Free evening | Dine around – on your own

Thursday 8 December

07.00 Breakfast

08.15 **SESSION 6: BLOOD PLASMA DERIVED PRODUCTS**

Chair: Joseph Bertolini, CSL Behring, Broadmeadows, Vic., Australia

08.30 **601** The Dynamics of Contract Plasma Fractionation

Albert Farrugia
Kedrion S.p.A, Lucca, Italy

09.00 **602** A New Modular Approach to Plasma Fractionation

Kailing Wang* and Hari Nair
PrIME BIOLOGICS, The Gemini Science Park, Singapore

09.30 **603** Global Manufacturing Technology Transfer: the R & D Contribution

Robert Forrest, Karl McCann and Joseph Bertolini*.
CSL Behring (Australia), Broadmeadows, Vic. Australia

10.00 ▶ Morning Break

10.30 **604** Plasma Derived Medicinal Products Scene in India

Ranjeet Ajmani
PlasmaGen BioSciences Pvt Ltd, Bangalore, India

11.00 Do Manufacturing and Meeting Clinical Needs Go Together in Asia? **Focus Lecture 3**

Jan M. Bult
Plasma Protein Therapeutics Association, Annapolis, MD, USA

11.30 **POSTER SESSION**

13.00 Sandwich lunch | Group photo | Banyan Tree Deck

14.30 **SESSION 7: OPTIMIZING FACILITY DESIGN AND MANUFACTURING ECONOMICS**

Chair: Aaron Goerke, Genentech, USA

14.45 **701** Qualification of Single Use Technology for Next Generation Manufacturing at Amgen

Jim Weidner[1]* and Duncan Low[2]
1. Amgen, Singapore and 2. Amgen, Thousand Oaks, CA, USA

15.15 **702** Facility of the Future

Morten Munk
NNE Pharmaplan, Gentofte, Denmark

15.45 **703** Strategies for Enhancing Manufacturing Efficiency while Saving Time and Money

Steve Hohwald, David Cate and Aaron R.Goerke*
Genentech, South San Francisco, CA, USA

16.15 ▶ Afternoon Break

16.45 **704** Samsung Biologics: Transforming the Landscape of Biopharmaceutical Manufacturing and Its Impact in Economics in Asia

Regina Choi-Rivera
Samsung Biologics, Incheon, South Korea

17.15 **705** Design and Realization of a Worldwide Biomanufacturing Facility

David Estapé
M+W Central Europe, Stuttgart, Germany

17.45 Summing up BioProcessing Asia 2016 and looking ahead **Keynote 2**

Nigel Titchener-Hooker
University College London, London, United Kingdom

18.15 Poster Prize Presentation

18.30 **CLOSING ADDRESS** John Curling, John Curling Consulting AB, Uppsala, Sweden

19.00 Reception | Poolside

20.00 Closing Dinner | Elements Restaurant

Poster list

Thursday 8 December, 11.30

801 Characterization of Xcellerex™ Single-use Mixing and Bioreactor Systems
A. Andersson*, A. Castan, T. Smith and J-A. Burdick
GE Healthcare, Uppsala, Sweden

802 CaptureSelect™ Affinity Purification and Detection; Enabling Development of Next Generation Biotherapeutics
Frank Detmers* and Pim Hermans
ThermoFisher Scientific, Leiden, The Netherlands

803 Continuously Improving Bioprocess: A Highly Productive and Scalable Continuous Chromatography Approach
Xhorxhi Gjoka, Rene Gantier and Mark Schofield*
Pall Life Sciences, Westborough, MA, USA

804 Acoustic Wave Separation – A Scalable Disruptive Technology for Continuous Clarification of Fed Batch Cell Culture Prior to Capture Chromatography
Peter Levison[1]*, Ron Farkash[2] and Michael Collins[2]
1. Pall Life Sciences, Portsmouth, United Kingdom
2. Pall Corporation, Westborough, MA, USA

805 The Use of Extractables Data from Silicon Tubing for Toxicological Risk Assessment
Sade Mokuolu
Bio-Process Systems Alliance, Waterlooville, United Kingdom

806 Selecting the Right Sterile Connector for Your Single Use System
Ray Dallago
SaniSure, Camarillo, CA, USA

807 Scale-up in the Single Use Age: Design Matters
Colin Jaques*, Rita Barros Costa, Peter Berry and Anthony Beaney
Lonza Biologics, Slough, United Kingdom

808 Breaking Through Current Chromatography Operating Barriers: Integration of a Novel Modular Chromatography Scaffold and Resin Design to Achieve a Hyper-productive Capture and Fow Thru Processes
Marty Siwak[1]*, Alpana Naresh[1] and Gaston de los Reyes[2]
1. JSR Life Science, Sunnyvale, CA, USA
2. SPF Innovations LLC, Somerville, MA, USA

809 Manufacturing Technologies to Enable Process Intensification
Andrew Clutterbuck
Merck, Molsheim, France

810 Designing Mammalian Cell Culture Facilities with Adventitious Agent Barriers
Joe Runner
Genentech, South San Francisco, CA, USA

811 Selective Exclusion of Hepatitis B Virus-like particle in Negative Chromatography Using Polymer Modified Ion Exchange Adsorbents: Adsorbent Size and Grafted Polymer Architecture

Hon Wei Ng*, Fu Xiang Micky Lee, Yeo Gek Kee Chua and Beng Ti Tey
University Malaysia, Pahang and Monash University Malaysia, Selangor, Malaysia

812 Production of Mycophenolic Acid by Penicillium brevicompactum in Solid State Fermentation Using Various Agro-waste as Substrate

Gopal Patel* and Chand Banerjee Uttam
National Institute of Pharmaceutical Education and Research, Mohali, India

813 Developing Down-stream Processes for Producing Recombinant Proteins Suitable for Clinical Trials. CSIRO Working With the Biotechnology Industry – Two Case Studies

William J. McKinstry
CSIRO, Parkville, Victoria, Australia

814 Broadening Clarification Solutions for Vaccines

Li-Jun Sim*, Sarah Le Merdy, Youness Cherradi and Claire Scanlan
Merck Pte Ltd, Singapore, Millipore SAS, Molsheim, France, Merck Chemicals, Belgium, EMD Millipore Corporation, MA, USA

815 Quality by Design (QbD) to Tangential Flow Filtration (TFF) Operations

Karen Chan*, Herbert Lutz, Renato Lorenzi, Yanglin Mok and Subhasis Banerjee
Merck Pte Ltd, Singapore

816 Novel Protein L-based Chromatography Resin for Affinity Purification of Antibodies and their Fragments

Toru Tanaka*, Hidetaka Kobayashi, Kosuke Araki, Shigeru Nakatani and Kazuaki Muranaka
Tosoh corporation, Shunan, Japan

817 Fast Trak Your Molecule to Market

Dev Chandran
GE Healthcare, Bangalore, India

NOTES

Access and Affordability: Technological Approaches to Address these Key Healthcare Imperatives

Keynote 1

Arun Chandavarkar

Biocon Ltd, Bangalore, India

arun.chandavarkar@biocon.com

NOTES

A Modular HTPD Toolbox for the Development of Non-MAb Biotherapeutics Processes

101

Matthias Berkemeyer

Boehringer Ingelheim RCV & Co KG, Vienna, Austria

matthias.berkemeyer@boehringer-ingelheim.com

Increasing demand on quality and product understanding together with decreasing timelines make high throughput process development (HTPD) strategies a prerequisite for manufacturing development of new biotherapeutic drugs. This applies even more for non platform proteins like classical non-antibody proteins or the so-called "new format" products. For example, non-MAb protein therapeutics such as Fab, scaffold or Vhh domain antibodies, etc. can be efficiently expressed in *E. coli* either as insoluble inclusion bodies (IBs) or in their soluble form in the bacterial cytoplasm or periplasm. Accordingly, manufacturing processes, the expression systems and the downstream unit operations are as diverse as the bandwidth of molecular formats. To lever this complexity, Boehringer-Ingelheim Biopharma Austria has established a holistic approach based on a HTPD toolbox that integrates the whole process chain. Automated screening modules for e.g. bacterial clone selection, main culture optimization, cell disruption, inclusion body preparation and refolding, chromatography media screening as well as optimization of chromatography conditions, can either be applied as standalone modules or in combinations as miniaturized process chains. The resulting HTPD workflows allow for the necessary flexibility but at the same time fulfil the need for simplicity and general applicability. Using this approach, the correlation between different upstream conditions (up to 24 simultaneously) and the recovery properties of IBs can be determined in one single HTPD workflow on a 96-well plate. The IBs obtained can be further processed by high-throughput methods to optimize the solubilization, refolding and capture conditions. This talk will lead through our flexible HTPD platform and its diverse applications ranging from early stage process development to late stage optimization and characterization studies for commercial processes.

NOTES

Ion Exchange and Multimodal Chromatography Performance for Separation of Charge Variants in mAb Purification Process

102

BPA BioProcessing Asia

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Biologics account for more than 150 bn USD in global sales revenue, constituting 27% of the total pharmaceutical market. Six of the top-selling mAbs, accounting for more than 60 bn USD, will lose exclusivity in the next few years, making the market available for biosimilars (i.e., highly similar versions of the originator product). To secure safety and efficacy, many different attributes of the biosimilar must be comparable with the original product. Being large molecules, mAbs are subjected to many modifications, causing microheterogeneity. The modifications almost always take place during cell culturing. Some modifications affect mAb charge variant distribution and must be carefully controlled. However, the occurrence of charge variants are often not fully controllable in the bioreactor and instead need to be separated in downstream chromatography steps. Separation of charge variants is challenging and requires extremely high selectivity, while often resulting in low yields. This paper presents separation of mAb charge variants in a polishing step. The work includes chromatography resin screening, in which the performance of traditional cation exchange resins and multimodal resins such as Capto™ adhere ImpRes and Capto MMC ImpRes was compared. Process optimization was conducted to achieve efficient removal of unwanted charge variants at reasonable yield. The impact of chromatography resin characteristics (e.g., ligand density and particle size) on charge variant separation will be discussed.

NOTES

International CHO Process Transfer along a Global Single-Use Platform

103

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This talk will demonstrate and show case a successful process transfer for a mammalian product between two sites in the global BI network based on a fully disposables US and DS technology platform. The disposable platform, which was developed in the BI development organisation in Germany, was used to enable a fast-track process transfer to the clinical supply facility in China. While China faces an increasing demand of high-quality biopharmaceutical drugs at the same time there is a shortage in qualified manufacturers. Boehringer Ingelheim is establishing a show case in close cooperation with authorities in order to enable a suitable Market Authorization Holder (MAH) concept in China, thus enabling product companies to make use of skillful Contract Manufacturing Organizations (CMOs) to produce high-quality products for the Chinese market. While this talk will explain BI's global platform, it will further show the application for a client project in China and also give a brief introduction into the facilities.

NOTES

Current Developments and Future Trends of Changing Biopharm Industries and How To make a Meaningful Assesment Using Cost Modeling Tools

104

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There is a definite paradigm shift happening in how Biopharm industries are discovering, developing and manufacturing drugs. With the growing competition not only in developed nations but also in developing nations, need for production of faster and cheaper drugs is essential. Companies are for example moving from batch to continuous in monoclonal antibody (MAbs) production to cope with this need. With the growing market in the field of Biosimilars the industry is looking for the most cost effective way to manufacture the drug, which must not only be the first to market but, also more affordable for larger patient population. With a limited number of targets for Biosimilars and over 600 companies developing products across the globe the competition is very intense. The field of vaccine production is also advancing rapidly. Again the drive to produce more cost effective vaccines is becoming key as to how a vaccine manufacturing is planned at an early stage. There is also a huge potential in the field of Antibody Drug Conjugated (ADC) with more than 300 ADC's in development at various phases and only 2 ADCs on the market. The industry is still trying to establish the most robust production schemes which not only are productive but also fast and cheap. This talk is going to provide a brief overview of not just recent trends in the production of MAbs, vaccines and on Antibody Drug Conjugates (ADC) but will focus on process economics. Developing a production process is one step but to understand and establish a process which also reduces the production cost is becoming key in standing out from the competition. The talk will show how cost modeling tools can be utilized to not only understand the process economics but also shed light and help in process development at an early stage.

NOTES

Ultrafiltration/Diafiltration of Highly Concentrated Antibody Solutions: Experiments and Modeling for the Effects of Module and Buffer Conditions

105

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Antibody products are formulated at high concentrations to enable administration at high doses since the volume that can be delivered by injection is limited. The high-concentration of antibody solutions poses a great challenge for manufacturing using standard tangential flow filtration due to the viscosity restrictions and osmotic pressure effects during the ultrafiltration/diafiltration (UF/DF) unit operation. The objective of this work was to examine the effects of the membrane module design and buffer conditions on both the filtrate flux and maximum achievable protein concentration during the ultrafiltration of highly concentrated antibody solutions. Experimental data were obtained using different screened cassettes and in the presence of specific excipients that are known to alter the solution viscosity. Data were compared with predictions of a recently developed modified polarization model that accounts for the complex thermodynamic and hydrodynamic behaviour in these systems, including the effects of back-filtration arising from the large pressure drop through the module due to the high viscosity of the concentrated antibody solutions. Model calculations were in good agreement with experimental data in cassettes having different screen geometries. The change in buffer conditions also affected the UF/DF behavior, with the increase in viscosity causing a significant decrease in filtrate flux (at high mAb concentrations) and maximum achievable mAb concentration. These results provide important insights into the key factors controlling the filtrate flux including the buffer conditions and maximum achievable protein concentration during UF/DF of highly concentrated antibody solutions as well as a framework for the development of enhanced ultrafiltration processes for this application.

NOTES

Development of an Efficient Manufacturing Process for Adenovirus

106

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Large-scale downstream processing of viruses for clinical applications poses challenges different from those for many other biotherapeutics. These challenges mostly arise from the size and complexity of the virus.Here we present purification results of a cGMP-ready process developed for a recombinant adenovirus. The two-step column process results in an adenovirus preparation with high yield and very low host cell protein (HCP) and DNA contamination, comparable to clinical grade products. This process is readily scalable, simple, rapid, and efficient and is thus well-suited for the production of clinical grade viral vectors.

NOTES

Priorities in Global Healthcare and Burden of Disease: Are We doing the Right Things in Biopharma and Vaccines?

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The Global Burden of Disease Report (GBD) shows both major progress in the battle against infectious disease, and very significant gaps in our coverage of disease via drugs or vaccines and via the general healthcare system offerings too. The world is split in two regarding the severity of these issues, the impact on the populations, and the outlook for areas to prosper as a result of this. At the same time the profile of disease burden goes through a rapid shift from communicable to non-communicable disease, a development that will have accelerating effects as populations are rapidly ageing, especially in Asia but really everywhere. Comparing this future scenario with the landscape of current new drug and vaccine developments, we can state that there are more gaps: most new drug development happens in the western world with initial strong focus on the relatively wealthy populations in these areas and their disease priorities. Established price levels turn into an affordability issue when the disease profile of the West also becomes the one of the East and the South. A large group of diseases have no solution or no satisfactory solution and where that is paired with market failure i.e., the fact that a population cannot afford therapies or even vaccines, the motivation to develop these solutions suffers from lack of financial attractiveness. Biosimilars are an approach to address affordability. Unfortunately, they are copies of ageing drugs and do not offer new tools to the doctors and their patients. This presentation will provide the audience with food for thought and discussion: the future of biopharmaceuticals will depend on whether we find the answers, either in the technologies we use or in the business models we follow in this field.

NOTES

What Opportunities will Smart Polymers Bring in the Future to the Downstream Processing of Biological Products?

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The development of new separation materials linked to a better understanding of their underlying separation mechanisms has been actively pursued over the past two decades by both academia as well as industry. When applied to bioprocessing and, in particular, to biochromatography, the objectives of this scientific effort have been to achieve greater selectivity, higher resolution, faster speed, enhanced handling capabilities and overall improved productivity. Of these factors, control over selectivity at the level of both analytical and preparative capabilities has remained the single most challenging objective for the downstream processing of biological products. One current approach to accommodate variation in feedstock composition or operational conditions, yet allow selectivity and scalability to be manipulated at the same time, is to use 'smart' stationary phases that have tuneable physical and functional properties. In this manner, separation selectivity can be adjusted through the use of a suitable external stimulus, thus providing access to separation systems that should serve in the future at the industrial scale as more efficient platform technologies for the recovery of biological products as part of an integrated downstream processing campaign. In this presentation, recent progress in the design, synthesis and use of several new classes of stationary phases capable of achieving multi-dimensionality in their adsorption properties will be described. These new stationary phases, formed by surface immobilisation or 2D/3D printing methods with suitable porous support materials and pre-formed block co-polymers or alternatively in situ grafted polymeric systems, can change their binding properties in response to the application of an external stimulus. Drawing upon batch and packed bed binding studies, surface charge determinations and other physical characterisation techniques carried out under different formats and conditions, important insights have been obtained into the controlling capture and release mechanisms of these novel stimuli-responsive materials. Practical applications have also revealed considerable scope for their use in energy efficient, waste-reduced chromatographic purifications of low and high molecular weight biological products generated by recombinant DNA/cell culture methods or during process stream recovery [1-5]. This presentation will examine different aspects of this potential and compare their benefits to other recent advances associated with the use of smart polymers in bioprocessing.

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NOTES

A Synergistic Life Cycle Approach to Understand and Control Raw Material Variability through Collaborative Process Analytics

202

BPA BioProcessing Asia

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A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the design space established. So far, biologics process development and characterization efforts, even under the QbD paradigm, have mostly focused on variability associated with the production process itself, leaving significant room for improvement to better understand and control raw material (RM) variability. This leads to a situation where commercial manufacturing is usually the first place to experience the impact of RM variability, resulting in consequences of lengthy manufacturing investigations and batch rejection. In an attempt to solve this conundrum, this case study will illustrate a synergistic life cycle approach to understand and control RM variability through data sharing and collaborative process analytics between a biologics manufacturer (Biogen) and a chromatography resin raw material supplier (GE Healthcare). The essence of this approach is to continuously assess RM variability through the process lifecycle by analyzing combined data from RM and drug substance processes, and to retire RM risk by continuous process understanding and control improvement. To enable this approach, data aggregation systems, multivariate data analysis capability and open collaboration between both sides are critical elements. We believe this type of process analytics collaboration between drug substance manufacturers and raw material suppliers will be much more powerful than each party acting alone, but will also require a different mindset and relationship.

NOTES

Affordable Alternative to Protein-A: Characterization of Novel Pseudo-affinity Adsorbent and Purified Antibodies

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Therapeutic proteins have made a significant impact in diagnostic and curative research in the past two decades. These include monoclonal antibodies (mAbs), polyclonal antibodies (pAbs), plasma proteins like albumin, coagulations factors, vaccines, etc. The purification of these important classes of proteins needs stringent compliance with the regulations for meeting appropriate quality and safety. Also, the process must be economical so as to make these products affordable. The current industrial processes use Protein A chromatography as a major step during purification, which is not only expensive ($9000-$12000/L) but also utilizes very low pH conditions leading to aggregation of antibodies and the leaching of the ligand. These are the deleterious process-related products which are to be stringently controlled since they are responsible for immunogenicity reactions. The aim of the present work is to overcome the limitations of the conventional Protein A adsorbent while at the same time generating affordable therapeutic products. 'ISep', a pseudo-affinity adsorbent, is an alternative to Protein A which has been designed by studying the X-ray crystallographic structure of the complex formed between the B domain of Protein A and the Fc portion of IgG. With the help of molecular docking studies, potential ligands were screened and selected. The selected ligand was then grafted onto a rigid polymethacrylate-based matrix (particle size 90 µm, pore size 400 Angstrom). The developed adsorbent was observed to favour Langmuir type of isotherm and showed a static binding capacity (Qmax) of 41.67mg/ml. The strength of binding in terms of affinity constant (Kd) was 2.8x10-6 M which is in the range of an affinity ligand (i.e. 10-4 M to 10-8 M). The selectivity of 'ISep' was demonstrated by purification of mAbs and pAbs from CCS and human plasma, respectively at a preparative scale wherein elution could be performed at pH ~7.0, unlike the harsh low pH conditions used for Protein A. The integrity and purity of the antibody were confirmed by SDS-PAGE and size exclusion chromatography (SEC) which provided 95% purity and 2% aggregation, complying with the regulatory standards. Additional characterization was provided by analytical techniques such as FTIR, LC-MS (for intact mass), glycan profiling, peptide mapping, etc, Fluorescence spectroscopy and CD is currently underway to study the higher order structure of the antibodies. Most remarkably, the cost of this novel adsorbent is estimated to be one-fifth the cost of commercially available Protein A adsorbent. This presents 'ISep' as a potentially affordable alternative to the conventional platforms for the purification of pAbs and mAbs.

NOTES

Implementation of an End-to-End Continuous BioProcessing Platform using Novel Technologies

204

BPA BioProcessing Asia

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One significant opportunity for evolutionary change in the biopharmaceutical industry is the widespread adoption of integrated continuous bioprocessing for biologics manufacturing. Key to its success is the availability of novel upstream and downstream technologies that will not only reduce facility footprint, capital expenses and product cost of goods (CoGs), but also will increase process productivity, flexibility and further facilitate the utilization of single-use and/or disposable technologies. In this context, the suite of cutting-edge technologies we have evaluated to enable cost effective and reliable implementation of continuous bioprocessing of biological drugs, included the Cadence™ Acoustic Separator, exploiting acoustic wave separation technology (AWS), Cadence Inline Concentrators within the single-pass TFF (SPTFF) platform, the Cadence BioSMB PD multicolumn continuous chromatography platform using a KANEKA KanCap A™ based platform and novel continuous diafiltration strategies, to address the innovation gap to provide a simplified solution for the continuous final formulation step. By utilizing a 20L CHO fed-batch cell culture bioreactor with cell density range of $25x10^6$ – $30x10^6$ cells/mL and 65 to 90% cell viability, multiple in-house feasibility runs were conducted through a novel integrated continuous bioprocessing train of unit operations. For instance, while achieving 90% continuous clarification yield for the processing of a batch with 1.25 g/L titer, $25x10^6$ cells/mL with ~70% viability, this new process platform was able to deliver 2 g/h mAb for the continuous purification train utilizing a stable 4-fold continuous concentration step for the integration of continuous clarification and continuous capture trains. With the coupling of the novel continuous polishing, continuous viral clearance and continuous final formulation steps, such platform, with the current PD-scale bioreactor capacity, this process will generate 1 g/h mAb. This presentation will provide a risk-based and data-driven overview of an integrated continuous bioprocessing platform and highlight the requirements, challenges and opportunities for product development, process monitoring, validation, control and automation.

NOTES

Process Intensification with Periodic Counter Current Chromatography

205

BPA BioProcessing Asia

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In the recent years, there has been a strong trend in the bioprocess industry towards process intensification and increased process control. The key driver behind this is the aim to reduce production costs, while maintaining product quality and throughput in the manufacturing of biopharmaceuticals. These changes rely heavily on introduction of continuous processing technologies, process analytical technologies (PAT), and increased use of automation solutions. As a consequence, different approaches for continuous and/or semi-continuous upstream and downstream processing are being evaluated in the biopharmaceutical industry. In particular, compared with chromatographic steps performed in batch mode, continuous chromatographic mode processes has the potential to increase chromatography resin capacity utilization, eliminate or minimize the need for intermediate hold-up steps, and reduce equipment footprint. These benefits can in turn have a positive impact on the process economy. In this context, we here describe the implementation of our chromatography product portfolio for continuous processing based on four column periodic counter-current chromatography (4C PCC), including the ÄKTA™ pcc 75 system and the protein A-based MabSelect SuRe™ pcc resin for monoclonal antibody purification. The dynamic control functionality provided by the system allows for automatic adjustment to fluctuations in the feed composition or variations in resin dynamic binding capacity of the individual chromatography columns. The ability to use UV cells with different path lengths enables flexibility in designing and optimizing the continuous capture step, for example, with regards to monitoring both high and low titer feeds. The trending functionality of the system also allows for monitoring of potential changes in the capacity of individual columns with time. Processes that can benefit from continuous processing using PCC include a wide variety of target molecules ranging from antibodies and recombinant enzymes to vaccines. Key words: periodic counter current chromatography, dynamic control, protein A capture, process analytical technologies

NOTES

Global Biomanufacturing Trends, Capacity, and Technology Drivers

301

BPA
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Biologic-based drugs are an increasingly important part of the product growth strategies for pharmaceutical and biopharmaceutical companies. As the number of commercial products and pipeline candidates grows, a crucial issue facing the industry is the current and future state of biomanufacturing capacity, the availability of that capacity, and the technologies impacting upstream and downstream bioprocessing. Pharmaceutical and biopharmaceutical companies and contract manufacturing organizations (CMOs) are aligning their strategies to not only address capacity but to address greater complexity in supplier risk, the competitive forces of innovator biologics and biosimilars, and the adoption of advanced biomanufacturing technologies.

NOTES

Biosimilars in Asia

302

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Many companies are pursuing development and marketing of biosimilars in Asia. In this presentation we review the status of products on the market and under development. We also consider the scale at which companies are planning to manufacture their biosimilar products. From available information we will deduce the different strategies that are being pursued by companies in Asia. Some of the strategies to be considered include: domestic market only; domestic market followed by third world foreign markets; domestic market followed by western markets; and western markets followed by domestic markets. The rationale behind the selection of reactor size and facility design will also be explored.

NOTES

Manufacturing Challenges for Future Biologics

303

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The past decades have seen biopharmaceuticals begin to dominate the drug development pathway and already we can see potent biologics bringing benefits to populations on a truly impressive scale. There remains much to do before we can claim however that the benefits of our burgeoning capabilities in the life sciences are fully translated into treatments, delivered globally. That challenge, of enabling the exquisite power of biologically-derived drugs and treatments to benefit world-wide populations, will require significant engineering innovation. This talk will look at some of these development and illustrate potential solutions driven by work from the Department of Biochemical Engineering at University College London (UCL); a pioneer in the field. Challenges will be used to illustrate the nature of the advances made and of the path ahead. The first is the need to move rapidly from promising drug candidate to a robust and efficient process. Here UCL created the concept of ultra scale-down (USD) which can enable process insights to be gained with a few 10's of mL of material. Second is the need to make best decisions, be that at the level of technology choice or on a portfolio of drugs for development. So called Decisional Tools have been deployed to address such questions and to provide critical direction to research efforts as drugs move toward manufacture. Finally we need, as engineers, to understand better the ways in which complete bioprocesses behave so that we can design and operate processes with confidence. A key example is the capacity to gain detailed insights into the processes of chromatographic performance loss. Here the ability to scrutinise at an individual bead level can create rich information for the biochemical engineer. The talk will be supported with relevant industrial examples to demonstrate how our capacity to engineer global biological solutions continues to advance the translation of exciting life science into commercial outcomes.

NOTES

A Commercial Scale Facility for Mab Drugs

304

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The design, construction, installation and validation of a commercial scale biopharmaceutical manufacturing facility is a process filled with challenges. This is an example of an actual facility that is currently nearing completion. Teruisi Pharmaceutical Ltc. is a Chinese company committed to developing Mab-based high quality novel and bio-similar products for both Chinese and international markets, and to successfully setting up a cGMP-compliant facility that meets international quality standards. In this presentation we will walk through features and challenges in the design and other activities needed and being developed. This presentation will also include many of the general issues that must be dealt with when bringing a facility of this kind into operation and we will also discuss a few of the specific challenges unique to construction in China.

NOTES

Continuous Processing for Biosimilars

305

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One of the often overlooked advantages for Biosimilars is that Biosimilar developers have access to technologies far superior to those which were available during original product development. Advances in automation, single use systems, CD media, PAT, etc., have made modern Bioprocess far more robust and predictable. Hence, it is imperative that biosimilar companies access these new technologies. End-to end connected-continuous Bioprocessing promises significant advantages enabling higher productivity than batch processing, while effectively reducing equipment footprint, cost of goods, water consumption and process time. Potential reduction in COGs and significant reduction in CAPEx are especially attractive for start up ventures, which do not have access to traditional manufacturing plants. Enzene's strategy for taking continuous bioprocessing for mAbs from bench to plant will be discussed. The presentation will also review Merck's current platform for continuous processing and show data. The presentation will highlight how collaboration between technology companies and startup biotech companies can provide the catalyst for tipping the curve from disconnected to continuous Biomanufacturing.

NOTES

Continuous Processing Key Operational & Economic Factors Influencing Monoclonal Antibody Manufacture

306

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Significant progress has been achieved over the last ten years in defining the continuous downstream processes with the incorporation of chromatography, ultra-filtration technologies and other batch operations in a continuous operation. For this analysis we use the BioSolve Process modelling package, to address the specific questions relating to the economics of continuous processing from a unit operation and a whole process perspective, taking into account the entire supporting infrastructure including buffer, media solutions and utilities. In this work the upstream (USP) and downstream (DSP) processing are considered separately so as to explore the impact of configuration and scale on the process economics. We examined mixed mode operation to determine the optimum mix of continuous and batch processes by looking at a total of 4 options at 3 different scales: 100 kg/yr, 500 kg/yr and 2000 kg/yr. Downstream options used a mixture of single use and stainless steel technologies. For a given process there was found to be an optimal configuration which considers bioreactor pooling, batch sizing for continuous operations and buffer make up. Hold strategies were determined taking into account the scale of operation. We were able to determine those factors that impacted on configuration costs for each option. It was found that it is important to optimise these factors before comparing the options at different scales. Specifically we determined the following:

- The implications of continuous processing in terms of economics, configuration and capital requirements when comparing batch to continuous processing.
- There are important differences between USP and DSP when considering continuous processing and that these should be considered independently of one another.
- The key factors that influence the cost effectiveness of a perfusion operation compared to a fed batch cell operation is directly related to efficiency of media use. This is less important at small scale, (100 kg/yr) but dominates at larger scale (2000 kg/yr).
- Scale of operation has an impact on the selection of continuous versus batch processing and the effects on capital and CoG is not necessarily linked.
- The role of single use technologies in continuous processing These findings provide valuable insights into the cost drivers that underlie continuous operations. Furthermore, they provide indications on the role of continuous bioprocessing and identify those factors that require optimisation if the potential of continuous processing is to be realized now and in the future.

NOTES

Conjugate Vaccine Development at Hilleman Labs: Lessons and Opportunities

401

BPA BioProcessing Asia

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Millions of deaths happen annually around the globe due to vaccine preventable diseases. The disease burden is significant in the developing world. Introduction of important vaccines in the immunization programs of various developing nations has assisted in the prevention from several deadly diseases. However, few very important vaccines are still affordable by countries with a high incidence of respective diseases. Conjugate vaccines are one of such a class of high cost but important vaccines. Several diseases can be prevented by conjugate vaccines e.g. *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Salmonella* typhi etc. Globally, infections due to Hib and multiple serogroups of *N. meningitidis* (Men) are the leading causes of bacterial meningitis, pneumonia and septicemia. Various effective plain polysaccharide and conjugate vaccines have been developed against both Hib and Men infections utilizing bacterial capsular polysaccharides. The multivalent vaccines including Hib and Men conjugates can cover significant proportion of respective diseases but with high costs. Hilleman Labs is working on development of cost effective conjugate vaccines against Hib and Men with an additional target to achieve optimal immunogenicity through use of novel processes. A significant part of the cost of conjugate vaccine production is attributed to the complex steps in production of bacterial capsular polysaccharide (Men PS) and its conjugation to the carrier protein. We have identified the optimum polysaccharide chain length of Hib capsular PS for the generation of the best immune response among different chain lengths. We have also developed very short polysaccharide production processes and high yielding conjugation processes for serogroup A, C, Y, W and X of *N. meningitidis*. The polysaccharides could be produced in as little as 6 hours of downstream processing and the optimized conjugation reactions could yield up to 45% of conjugated polysaccharide. The conjugates were tested for immunogenicity in the rat and mouse model for Hib and Men, respectively. All the conjugates were found to elicit IgG and functional antibody titers comparable or better than those elicited by a licensed vaccine for Hib, and Men Serogroups A, C, Y and W. The Men X conjugates also gave rise to more than 10-fold antibody titers as compared to the vehicle control. The multivalent vaccine formulations are under evaluation for immunogenicity. The results point to the possibility of developing an affordable Men conjugate vaccine and possibly low dose Hib conjugate vaccine. Hilleman Labs is seeking partnership opportunities with like-minded developing country manufacturers for both affordable Hib and meningococcal conjugate vaccines.

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Simple Manufactured Microbial Platform as Rapid and Low-cost Modular Capsomere Vaccine for Poultry Vaccination

402

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Avian influenza (AI), commonly known as bird flu, is a severe respiratory tract infection of birds. A highly pathogenic avian influenza (HPAI) outbreak could cause potential economic and social impacts. The increasing number of human cases and the growing outbreak of HPAI in domestic birds underline the need for sophisticated capabilities to effectively respond to the rapid spread of influenza virus. Vaccination of poultry remains effective in reducing virus spreading in animals and transmission to humans, preventing pandemic development. However, existing vaccine bioprocesses could not respond to a new virus outbreak rapidly, or at a cost and scale that is commercially viable for mass poultry vaccination. Here, we have developed a microbial platform to produce a low-cost modular capsomere vaccine candidate for poultry vaccination. Modified murine polyomavirus (MuPyV) VP1 capsomere was engineered to present structural-based designed Hemagglutinin (HA1) antigenic module from influenza virus. Stable modular capsomeres presenting HA1 (CapHA1) were successfully produced in *Escherichia coli*, without the need for protein refolding. The highly purified CapHA1 (cCapHA1) and crudely purified CapHA1 (nCapHA1) were evaluated for use as poultry vaccine candidates. The alhydrogel adjuvanted cCapHA1 induced a high level (almost 105 endpoint titre) of HA1-specific antibodies when administered into chickens. These strong HA1-specific antibodies conferred full protection when challenged with HPAI virus. Adjuvanted nCapHA1, which contains some cellular contaminants, induced a strong antibody response, similar to the titre obtained with cCapHA1 containing pure CapHA1. Based on our process simulation, modular capsomere vaccines can be produced up to 320 million doses per 2.3 days at a cost less than 1 cent per dose. The results presented here suggest that this microbial platform for modular capsomere manufacture could contribute to a rapid-response and low-cost vaccine suitable for poultry vaccination.

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Status of Chinese Vaccine Industry for Moving into International Main Stream

403

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The goal of world vaccine product and technology development is to improve human health and life quality through the most economic way. China is expected to play a key role in developing vaccines and making more vaccines available to the world and especially developing countries in the near future. This presentation will update the status of China vaccine industry, the overall strategy of China vaccine development, the challenges of moving into world market, and the readiness in making good quality and low cost vaccines for those who need them.

NOTES

A Glance at the Global Regulatory Landscapes for Biological Products

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NOTES

Virus Clearance Validation from Western and Eastern Perspective

501

BPA BioProcessing Asia

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The origin of potential impurities is host cell and media derived components, adventitious agent, endotoxins, leachables and excipients. The risk management goes along with the process chain in an overlapping and redundant control strategy for risk mitigation. MCB, WCB and EPB have to be characterized and validated according to bacterial and fungal sterility, mycoplasma, adventitious and endogenous viral contaminants and tumorgenicity. In downstream processing the host cell protein and DNA removal should be shown in consecutive chromatography or filtration steps with a host cell specific ELISA and DNA hybridization assay. Bacterial endotoxins derived from raw materials or water can be removed by Sarbind Q. For removal of adventitious viruses derived from host cell, raw materials, employees and HVAC systems, different clearance steps such low pH, nano filtration and chromatography steps have to be validated for the individual, product specific downstream process by spiking of model viruses. For nano-filtration highly purified and high titer virus spikes are recommended. Single stranded and double stranded RNA and DNA viruses have to be selected according to their size, enveloped and non - enveloped structure and resistance to heat, pH and detergents. The number of step and viruses required for virus clearance validation varies in Eastern and Western regulatory requirements. All these clearance steps have already to be considered in early process development and validated in downscale models. In case of viral clearance preferentially single use material should be used.

NOTES

United Against the Bioburden Threat

502

Anders Ljunglöf, Anna Grönberg, Elin Monie, Tomas Björkman and Magnus Wetterhall*

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Bioburden can enter into the biopharmaceutical process through different routes and can negatively affect the safety and efficacy of the biopharmaceutical drug. Therefore, regulatory authorities put increasing demands on biopharmaceutical producers. To be successful in the accomplishment of a bioburden free process, biopharmaceutical companies and their suppliers must fight this battle side by side. It begins with the supplier developing products and operational routines that enable aseptic procedures in the biopharmaceutical process. Furthermore, the biopharmaceutical producers must develop control strategies, implement aseptic procedures and training to prevent bioburden entering their processes. This paper will focus on the commitment from suppliers and will describe the continuous improvement in delivery of aseptic chromatography media, further chromatography resin development for sustainability at harsh sanitization conditions and investigation of new sporicidal agents for sanitization.

NOTES

Development Pathways for Advanced Therapy Medicinal Products – Challenges and Regulatory Perspectives

503

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Advanced therapy medicinal products (ATMPs), include gene therapy medicinal products, somatic cell therapy medicinal products and tissue-engineered products. These products offer significant hope for a number of diseases for which there are limited or no therapeutic options, such as skin regeneration in burns victims, Alzheimer disease, cancer or muscular dystrophy. ATMPs are at the cutting edge of innovation and as such they have been subject to considerable interest and debate. European authorities have established a consolidated regulatory framework for ATMPs, but there are still many challenges that have to be overcome. In many instances, standard GMP requirements need to be adapted given the unique nature of the start materials (e.g. stem cells) or new cell culture additives developed and validated. The challenges presented by ATMPs and regulation thereof are wide and varied, and from a bioprocessing perspective there are many factors that need to be considered. This presentation will focus on the regulatory and bioprocessing challenges faced by companies looking to develop ATMPs.

NOTES

The Dynamics of Contract Plasma Fractionation

601

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Plasma Derived Medicinal Products (PMDPs) are an essential component of the modern therapeutic armamentarium. They are differentiated from most other medicines in several ways, particularly the unique nature of the raw material used for their manufacture. Human plasma has been fractionated to PDMPs for the past 75 years, and the economics of manufacturing requires currently that as many products are harvested from each litre as is feasible and reflective of clinical needs. PDMPs may be purchased on the open market from the various commercial and not-for-profit manufacturers. They may also be produced under contract from plasma supplied by government and similar agencies as a product of blood transfusion services. The global capacity for fractionation generally exceeds the supply of plasma available for the commercial supply of PDMPs. Hence, contract manufacture (CM) is offered by most fractionators. Clients for CM aspire to make full use of donated plasma, hence maximizing the donors' gift after the standard components of transfusion have been harvested. Many such countries also aspire to making their national clinical needs self-sufficient in PDMPs, attempting to acquire strategic independence from the vagaries of the commercial open market. The increasing commercial imperatives operating in the PMDP sector generate a tension with such ethical aspirations which are not easily resolved. In particular, the need to harvest as many proteins as possible may generate products which are surplus to national needs, necessitating an ethical paradigm for the optimal provision of such products. In addition, traditional relationships between blood services and domestic fractionation agencies may come under stress as a result of the competitive processes underpinning such transactions, which are now subject to international norms of free trade. Blood services engaged in the supply of hospital transfusion components are detached from the pharmaceutical GMP culture needed for the production of plasma for CM, while the generation of such plasma through extraction from whole blood donations deflects the focus from that of a dedicated raw material for CM to a by product of the donation process. We review the field of CM, assess the current tensions within the sector, and offer suggestions for the strategic positioning of governments and other clients so as to ensure optimal outcomes for all the stakeholders involved.

NOTES

A New Modular Approach to Plasma Fractionation

602

BPA BioProcessing Asia

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Conventional plasma fractionation is carried out by Cohn fractionation using ethanol precipitation at various pH and temperature combinations. Plasma proteins are further purified by multiple chromatographic steps and tangential flow filtration. The limitations associated with the conventional method, combined with strict regulations on product efficacy and safety have always demanded a new and improved approach for the purification of plasma proteins. PrIME is a membrane based, tangential flow electrophoresis technology used primarily for separation of biological molecules. PrIME Biologics has developed an integrated, orthogonal PrIME+ manufacturing process for the purification of Albumin and IgG with high yield and safety. Unlike the conventional process, this process does not involve the use of Cohn fractions or cryoprecipitate. Furthermore, using the Singapore fractionation plant as a footprint, PrIME Biologics has developed a modularized mini fractionation plant PrIMODTM for emerging nations. PrIMODTM is a standardized, pre-engineered modular solution with full cGMP compliance that can be rapidly configured to the desirable commercial scale and deployed globally. It delivers a fractionation facility fully equipped, installed on site and validated through to PQ completion. This new modular approach has lowered investment cost by minimizing need for re-engineering and reduced time, risks and complexity associated with establishment of a plasma fractionation plant. The PrIMODTM allows for the introduction of a state of the art plasma fractionation technology for low volume processing of plasma in emerging nations where safe raw material is not easy to obtain. This may revolutionize plasma fractionation in emerging countries.

NOTES

Global Manufacturing Technology Transfer: the R & D Contribution

603

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CSL Behring Australia received FDA licence approval for the manufacture of CSL Behring's leading commercial intravenous immunoglobulin G therapeutic (Privigen®) in October 2015. This followed the successful like-for-like technology transfer of the manufacturing process from CSL Behring, Switzerland. The transferred process has a capacity of 3.7 million litres of plasma equivalent and encompasses bulk production, filling, visual inspection, labelling and packaging. The R&D department in Australia played a key role in the development and technology transfer of the Privigen process. There was initial collaboration with the R&D department in Switzerland over a decade earlier for the development of the Privigen manufacturing process. A subsequent secondment of an R&D employee to Switzerland to be actively involved in process development and commissioning activities, aimed to train a subject matter expert (SME), who upon returning to Australia would provide local expertise and facilitate cross-site communication. The SME took the lead in a cross-site R&D team collaboration, which during execution of the initial facility engineering test batches, was responsible for observing the process, advising manufacturing operators and supporting in-process testing requirements. The aim was to identify any issues and devise corrective actions to ensure successful execution of the subsequent validation batches. The SME subsequently played a pivotal role in compiling and interpreting data for regulatory submissions and providing technical support for on-site inspections. With routine manufacture now established in Australia, R&D activity is focused on enhanced analytical testing to support comparability protocols associated with continuous improvement activities requiring regulatory submission and manufacturing support. There is an ongoing requirement for further process optimisation to reduce costs, increase yield and enhance product attributes. A key strategy in addressing these requirements is the development of a scale-down model of the process. Ongoing collaboration between global R&D departments is being fostered to ensure a wide range of inputs and to achieve optimum utilisation of resources.

NOTES

Plasma Derived Medicinal Products Scene in India

604

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India is highly import dependent market for plasma products, which are considered to be life saving medicines. At this point in time, India produces mainly two plasma products Albumin and IVIG from Indian plasma and rest of the products are imported. Because of changing disease pattern, improved clinical diagnostic facilities, affordability, medical tourism, patient advocacy groups, and many other factors the demand of these products are increasing day by day and they are usually in short supply. Hyper-immune plasma proteins (Anti D, Tetanus Immunoglobulin Hepatitis-B Immunoglobulin, and Rabies Immunoglobulin are also 100 % imported or prepared from imported bulk, as India does not produce any hyper-immune plasma. This creates a huge demand and supply gap and many patients loose the battle of life because of non-availability of these products.

A decade ago scene was very different than now. In the last 5 years, India has made a significant progress on various fronts, including change in the public health policy on availability of plasma products. "Make in India" is catching up in India and Government is very receptive to new ideas and hopefully this will help plasma industry to grow in India.

NOTES

Do Manufacturing and Meeting Clinical Needs Go Together in Asia?

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The plasma protein market in Asia will soon be one the fastest growing markets for a variety of reasons including economic improvements (and thus healthcare spending), increased diagnostics and increased awareness of the genetic disorders that require plasma protein therapies. Growth is also influenced by other factors such as the recent change of the one-child policy in China. That in itself will lead to more patients. A quick calculation shows that as a result of this, there will be an increase of than 2,500 persons with hemophilia A in China over the coming years. In order to meet this clinical need, enormous efforts need to be made on all levels to produce sufficient starting material to manufacture these lifesaving therapies. That is where the problems start to surface. We see differences in the collection of source versus recovered plasma. We see countries that solely use recovered plasma, others do not allow recovered plasma to be used. Something needs to change here. The production of immunoglobulins is another area of challenge. Exposure to pathogens is reflected in the antibody spectrum in the manufacturing pool. Is it still justifiable to have regional pools or, with the globalization of our world, does it make sense to start thinking out of the box and think about other pools? Last but not least, the cost of fractionation is dependent on multiple factors and, especially in a cost sensitive environment, an area that requires much attention. Short cuts at the expense of quality and/or safety cannot be tolerated while at the same time, insufficient access to lifesaving therapies is equally unacceptable. This presentation will cover all these aspects.

NOTES

Qualification of Single Use Technology for Next Generation Manufacturing at Amgen

701

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Amgen's Next Generation bioprocessing facility in Singapore relies on several emerging technologies as enablers to increase efficiency in bioprocessing. High deployment of single use implementation is one of those enablers to our flexible design. The presentation will provide an overview of some of the single use benefits realized to date including the following: flexible facility design that allows easy adaptation of emerging technologies or new biological modalities, closed processing with extensive use of aseptic connections, and reduced reliance on SIP/CIP. The presentation then focuses on Amgen's qualification of the high deployment of single use systems at the Next Generation facility. Amgen's qualification program will be reviewed in the context of existing guidance documents such as PDA TR 66, ASTM-2500, and ASTM E3051.

NOTES

Facility of the Future

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Sub-title: A new pharma reality drives innovation in the manufacturing strategies of tomorrow's vital biopharmaceutical products The healthcare sector requires more and more specialised products, which might only be used by a small group of patients. These products are typically made through complex biological processes and require highly controlled supply chain management, as well as sophisticated devices to ensure well controlled administration of the products to the patient. Fortunately, regulatory authorities support this trend by offering various accelerated approval processes for a broader range of more specialised pharmaceuticals. This reality – coupled with an increased focus on reducing manufacturing costs amid less predictability of future products in the increasingly expanding product portfolio – demands more flexible and agile facilities. Successful supply of those life-changing or even lifesaving pharmaceuticals, leaves the healthcare industry with the fundamental question of which production supply option to choose: outsourcing, in-house manufacturing or a combination of these strategies. This is a complex question with a potentially compelling financial impact for pharmaceutical companies. Not only do facilities need agile and flexible operations to navigate these financial implications, but they also require an agile and flexible design and construction approach. A broad range of tools must be activated to meet this requirement, which include a modular approach, single use technologies, continuous processing and new operational models. This presentation will examine this new pharma reality, as well as other predominate trends in the pharmaceutical industry. Additionally, the presentation will cover the implication this reality has on manufacturing strategies, cost implications with focus on the development of new technologies.

NOTES

Strategies for Enhancing Manufacturing Efficiency while Saving Time and Money

703

BPA BioProcessing Asia

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As companies enter the biopharmaceutical sector and competition increases, pressure will be placed on development and manufacturing organizations to streamline process transfer and routine drug substance manufacturing. Multiple levers can be utilized to drive efficiency, increase flexibility and reduce costs. These include process design, raw material selection, facility design, and process implementation. However, often not all levers are available, especially when transferring mature products. Additionally, using certain levers such as a raw material change may increase complexity and incur costs elsewhere, such as regulatory complexity. Discussion will occur on experiences gained in recent process transfers of mature biopharmaceutical products to different plants in Asia, including green field facilities. Further, the talk will discuss strategies to reduce process transfer timelines and costs. Lessons learned will both inform the design of future lean manufacturing facilities and drive increased manufacturing excellence.

NOTES

Samsung Biologics: Transforming the Landscape of Biopharmaceutical Manufacturing and Its Impact in Economics in Asia

704

BPA BioProcessing Asia

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As economic pressure of the biologic medicines grows with emergence of biosimilars, utilizing a CMO that can provide competitive pricing with its know-how and experience in designing, building, and operating highly optimized facilities can be more attractive solution than building own manufacturing plant. Since its inception in 2011, Samsung Biologics has been expanding their biopharmaceutical manufacturing capabilities rapidly in Incheon, South Korea. With FDA and EMA approval of three DS products this year, Samsung Biologics is changing strategy of many large pharma companies. This presentation will reveal Samsung's unique ability of building and starting up cost competitive large scale manufacturing facilities and how it's changing manufacturing economics in Asia.

NOTES

Design and Realization of a Worldwide Biomanufacturing Facility

705

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Let's design a facility that can be deployed everywhere around the world. Should we follow the most stringent interpretation of the GMPs to ensure compliance? How can we enhance simplicity to favor quick and in-time construction? Following a current industry response to Annex 2 of the EU GMPs, the presentation will develop key characteristics that make KUBio from GE Healthcare a worldwide biomanufacturing facility and the first of its kind. We will listen from the lessons learned after the first KUBIo project executed in China.

NOTES

Summing up BioProcessing Asia 2016 and looking ahead

Keynote 2

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NOTES

Characterization of Xcellerex™ Single-use Mixing and Bioreactor Systems

801

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Single-use mixing and bioreactor systems are widely used in biomanufacturing due to the many advantages that come with disposables, including reduced cross-contamination risk and shorter batch changeover time. The main challenge, however, when transferring biotherapeutic production processes from stainless-steel to single-use vessels is insufficient knowledge about the physical performance of the equipment. Data on oxygen transfer capacity, power input, and mixing time is essential for effective process transfer. To define ranges for efficient process control and to establish a scalable design space, Xcellerex XDR bioreactor systems were characterized with respect to volumetric oxygen transfer, mixing time, heat transfer, and power input. Additionally, Xcellerex XDM single-use mixing systems were characterized with regard to mixing time for solids and liquids as well as heat transfer. The resulting data provide the information required for process transfer to Xcellerex single-use systems, and will also facilitate transfer between larger and smaller process scales.

NOTES

CaptureSelect™ Affinity Purification and Detection; Enabling Development of Next Generation Biotherapeutics

802

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CaptureSelect ligands are based on the variable domain of heavy chain-only antibodies of Camelidiae. The ligand technology enables rapid identification of highly stable and specific affinity ligands using immune antibody libraries. Process conditions to bind and subsequently elute the protein of interest are implemented in this screening process to meet customer requirements. The identified lead ligands are efficiently expressed and produced at large scale as 12-15 kD ligands in the yeast *S. cerevisiae*, completely free of animal derived components. The CaptureSelect ligand technology was used to develop a generic platform for the purification and detection of high quality Fab fragments and methods to purify gene therapy vectors. In addition, ligands and affinity resins have been developed for a variety of biotherapeutics, including Fc and albumin fusion proteins, biosimilars, biobetters and viruses, all offering unprecedented specificity to the target protein.

NOTES

Continuously Improving Bioprocess: A Highly Productive and Scalable Continuous Chromatography Approach

803

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Currently enabling technologies are being developed by Pall to increase productivity and flexibility along with reducing footprint and cost of manufacture of biotherapeutics. As a test bed to realize this vision Pall has developed a laboratory dedicated to continuous end to end downstream processing. Our current work focuses on the chromatography steps of the process. Here we demonstrate a scalable multi column chromatography approach to process bioreactor volumes from 20L to 200L using the Cadence BioSMB PD and up to 2000L with the Cadence BioSMB GMP. At the 200L (1g/l titer) scale we have demonstrated an integrated continuous chromatography process. The capture step involves eight Protein A columns that are loaded continuously and sequentially. Four columns are always being loaded two in parallel and two in series. The system that performs the capture step is also employed to operate the low pH hold for viral inactivation. After the viral inactivation step turbidity is lowered using depth and sterile filtration. The polishing steps are operated on a single system. AEX is loaded in flow through mode directly onto two mixed mode cation exchange columns arranged in series and operated in bind and elute mode. By operating these four process in a continuous and integrated way we achieve increased productivities and can produce up to 150g of polished mAb product in 20 hours. By operating continuously we can reduce the resin volume required for processing by 95% whilst still achieving high levels of purity, single digit parts per million of host cell proteins and 1% aggregate. Additionally, the continuous process requires 44% less buffer than batch operation. These chromatography steps are critical for the development of a complete continuous downstream process. In the long term this will be key to delivering a highly economical and flexible approach to both clinical and full scale manufacturing of biotherapeutics.

NOTES

Acoustic Wave Separation – A Scalable Disruptive Technology for Continuous Clarification of Fed Batch Cell Culture Prior to Capture Chromatography

804

BPA BioProcessing Asia

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With advances in fed batch cell culture leading to higher cell densities and higher product titers there is a drive to improve the efficiency and speed of the cell harvest and clarification stage to generate Harvested Cell Culture Fluid (HCCF) for capture chromatography and subsequent downstream processing. This is further driven by the evolution of continuous processes where there is a preference for a continuous feed of HCCF available for direct load to the continuous multicolumn capture chromatography step. Existing cell culture clarification using either centrifugation or depth filtration are typically operated in batch mode and require bulk storage of feed or HCCF during the process. In the present work we report on a novel disruptive and scalable single-use technology for cell culture clarification based on an acoustophoretic separation. Acoustic Wave Separation (AWS) technology involves the use of low frequency acoustic forces to generate a 3 dimensional standing wave across a flow channel. Cell culture from a fed batch bioreactor enters the flow channel and as the cells pass through the 3D standing wave they are trapped by the acoustic forces. The trapped cells migrate to the nodes and clump till such time as their buoyancy decreases and they settle out of the suspension by gravity. This yields a partially clarified HCCF which can be polished using a small area depth filter. We have not seen any demonstrable adverse effects on the quality of the HCCF or the cell viability following AWS clarification. We report the continuous clarification of fed batch culture of a CHO-S based cell line expressing a humanised IgG1 MAb. At process development (PD) scale we demonstrate the ability to clarify CHO cell culture at cell densities of 30 - 100 million cells/mL, in a continuous manner at flow rates of up to 3.6 L/h. Furthermore we have shown the technology to be scalable and using prototype systems have demonstrated clarification flow rates of 50 L/h that when configured in parallel. This enables the technology to be applicable for 2000L bioreactors and allows the AWS technology to be positioned for clinical manufacture. The partially clarified HCCF is polished in a continuous mode using depth filtration but typically requires 3-5x less depth filter area than used for a traditional depth filtration process. This offers economic benefits in terms of footprint and depth filter costs, but also significant reductions in the volume of Water for Injection (WFI) used in depth media conditioning and post-harvest buffer wash following clarification as well as reduced waste disposal costs and significant set-up time savings. The economic benefits of the AWS approach will be discussed in more detail. AWS technology enables the continuous clarification of cell culture from bed batch bioreactors in a single-use operation. The technology has been shown to perform well at cell densities of up to 100 million cell/mL and so is well positioned to meet the clarification demands of emerging higher cell density fed batch processes currently in development as well as perfusion applications that are gaining momentum in the biotech space.

NOTES

The Use of Extractables Data from Silicon Tubing for Toxicological Risk Assessment

805

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Single Use Technologies are now established as a suitable alternative to stainless steel as well as emerging within hydrid facilities. Silicon tubing is an important transfer component in SUT. Within the expanding SUT industry, intense debate between suppliers and end users of SU components remains on extractables. To this end, BPOG have published a detailed protocol on extractables testing. This presentation will describe the extractables studies undertaken on different types of platinum cured silicon tubing following the BPOG protocol, it will describe the methodology taken, and detail the range of analytical techniques used to provide a comprehensive extractables package for platinum cured silicon tubing. Discussion points will also include the differences in the extractables profile between sterilisation methods and the effect that post curing of silicon tubing has on the presence of cyclosiloxanes. There will be a section on how to use extractables data for toxicological assessment and presenting detailed risk assessment to regulatory bodies.

NOTES

Selecting the Right Sterile Connector for Your Single Use System

806

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The presentation will be an unbiased view point on the various options for sterile connectors in the market place today. Designed to give the audience a more comprehensive overview of the various options in the market.

NOTES

Scale-up in the Single Use Age: Design Matters

807

BPA BioProcessing Asia

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Single use bioreactors (SUBs) are becoming standard work horses in the biopharmaceutical industry. These SUBs are supplied by vendors as off-the-shelf designs, limiting the cell culture engineer's ability to match the design of the SUB to that of their existing stirred tank reactor (STR) capacity. The first generation of SUBs departed from conventional stirred tank bioreactor (STR) geometry in terms of impeller number and orientation and sparger hole diameter. Moreover, one marked feature of SUB bioreactors was that they could be operated at lower volumes than conventional STRs, bringing considerable operational flexibility. This practice, however, further negated the principle of geometric similarity. This presentation considers the implications of changing reactor design on scale-up of mammalian cell culture processes using multivariate data analysis to compare different geometries and different fill volumes. This approach uncovered a surprising result when working at half volume, which may not have been spotted using conventional data analysis methods. Mass transfer studies were performed with two manufacturing-scale SUB systems and a miniature SUB system, using the gassing-out approach. The results have been compared to results generated using Lonza's proprietary STR design from 10 to 20,000 L. Vessel design is shown to have a substantial impact on mass transfer. Cell culture evaluations were performed with a model cell line in all three systems. The results were compared to historical data obtained in 10 L STR and airlift vessels. Multivariate analysis of the data showed that there were substantial differences in cell culture performance between different STR vessels. The impact of operating at half volume was investigated for one vessel design at two different vessel volumes. Multivariate data analysis showed that there was considerable difference in behavior of the cultures performed at half volume when compared to cultures performed in the conventional scale-down model. Furthermore, the analysis indicated that there was also a difference in behavior of the half-volume cultures in different size vessels. This indicated a lack of scalability between half-volume cultures performed in different scale vessels, which was not apparent when the same vessels were run at full volume. Product characteristics were comparable between all cultures. This demonstrates that for Lonza's Version 8 process critical quality attributes are robust to substantial differences in reactor design – even when these differences can be shown to affect the growth and metabolism of the culture performed in them. It was concluded that SUB design does matter when scaling processes up and should be a key consideration in a quality by design approach to minimizing differences in culture behavior during cell culture process scale-up. Moreover, multivariate data analysis can provide useful supplemental insights in bioreactor process performance comparisons.

NOTES

Breaking Through Current Chromatography Operating Barriers: Integration of a Novel Modular Chromatography Scaffold and Resin Design to Achieve a Hyper-productive Capture and Fow Thru Processes

808

BPA
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Much attention has been focused on the recent proliferation of protein A resins. Coincidentally, there has been an increased focus on operating modes including continuous, SMB and multi-column operations. Each of these possesses various attributes that can affect Mab purification, operations and costs. However very little innovation has been made on the chromatography bed itself and how that can enhance productivity or affect resin usage. The combination of two new developments, Chromasette™ chromatography device with a supported lattice bed design, and Ampshere ™ resin, have demonstrated 5-10 X productivity gains over current proceedures. Process modeling was used to elicit the optimal design point for both bead properties as well as peak productivity operating velocities. The novel 3D printed Chromassette™ bed design will be reviewed along with results for Amsphere Mab capture. Future direction and possibilities of this new technology will also be discussed.

NOTES

Manufacturing Technologies to Enable Process Intensification

809

BPA
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The biopharmaceutical industry is adopting a more strategic view toward manufacturing, seeking solutions that offer increased productivity and improved economics without sacrificing process robustness. The industry addresses these challenges through process intensification efforts including unit operation optimization, linked and continuous processing. This presentation provides insight into upstream and downstream intensification approaches to improve processes. Examples include high producing and stable cell lines, column size reduction, product purity improvement and enabling a continuous process.

NOTES

Designing Mammalian Cell Culture Facilities with Adventitious Agent Barriers

810

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Novel organisms have presented biologics manufacturing with challenges that prove to be significantly disruptive to operations as well as challenging to implement corrective actions. Early adoption of a comprehensive and systematic broad-spectrum barrier for adventitious agents in conjunction with enhanced detection methods is critical to ensure consistent, uninterrupted supply of safe, quality product to patients. This talk will discuss the experience with novel contaminants that has influenced the industry to adopt additional adventitious agent barriers in mammalian cell culture operations, a discussion of the relative merits of a selection of barriers, and the challenges associated with retrofitting existing facilities to include these barriers.

NOTES

Selective Exclusion of Hepatitis B Virus-like particle in Negative Chromatography Using Polymer Modified Ion Exchange Adsorbents: Adsorbent Size and Grafted Polymer Architecture

811

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Negative chromatography (NC) is an alternative to the bind and elute mode of chromatography for the purification of large biomolecules from either cell cultures or fermentation fluids. Selective exclusion of hepatitis B virus-like particles (HB-VLPs) while adsorbing smaller size *Escherichia coli* host cell proteins (HCPs) was achieved by employing anion exchange adsorbents grafted with poly(oligo(ethylene glycol) methacrylate) (POEGMA), as described in our previous study. The current study aims to evaluate the effect of adsorbent size and POEGMA branch chain length on the recovery of HB-VLP. POEGMA was polymerized via free radical polymerization using anion exchange adsorbents of different sizes. Variable lengths of POEGMA branch chains were achieved by manipulating the ratio of monomers (MEO2MA, OEGMA300 and OEGMA500) used in the polymer grafting reaction mixture. Modified adsorbents Q200, Q300, Q400 and Q500, from shortest to longest branch chain length, were produced. The larger adsorbent [SEPHAROSE Q FF (Q), 90 microns] has significantly improved the flow-through recovery of HB-VLP from an *E. coli* homogenate, when compared to a smaller adsorbent [High Performance Q (HPQ), 35 microns]. Further modification of Q with short branch chain POEGMA grafted Q200 adsorbent showed better flow-through recovery of HB-VLP (89.33%) from an *E. coli* homogenate when compared to unmodified Q (79.08%). This was mainly contributed by lower HB-VLP adsorption in the polymer grafted adsorbent. The improvement in flow-through recovery of POEGMA modified adsorbents compared to unmodified Q is still modest howeverand is most likely caused by convective entrapment of proteins within the grafted polymer layer. In summary, the larger 90 micron adsorbent, modified with moderate branch chain length (POEGMA300) was found to provide optimal performance with 89.7% HB-VLP recovery and a purification factor of 1.53. It was also found that varying the branch chain of POEGMA did not have a significant effect on the flow-through recovery of HB-VLP.

NOTES

Production of Mycophenolic Acid by Penicillium brevicompactum in Solid State Fermentation Using Various Agro-waste as Substrate

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Mycophenolic acid (MPA) is a secondary metabolite produced by many fungal species including Penicillium. MPA and its derivatives are commercially used as frontline immunosuppressive agents to prevent rejection of transplant organs as well as in the treatment of various autoimmune disorders. Other than its use as a immunosuppressive agent, it is also used as the anti-inflammatory, antiviral, antipsoriasis and antifungal agent. Commercial immunosuppressants based on MPA include CellCept (mycophenolate mofetil; Roche) and Myfortic (mycophenolate sodium; Novartis). To meet the ever increasing demand of industries, efficient alternatives to the currently used submerged fermentations need to be explored. Solid-state fermentation based on the cheap agricultural substrates are especially suited for the growth of fungi because of their low moisture requirements. Solid-state fermentations are simple to implement, cost-effective, afford easier downstreaming steps and often provide a more concentrated product compared to submerged cultures. Production of mycophenolic acid (MPA) using the microfungus Penicillium brevicompactum by solid-state fermentation is reported here. Of the initial substrates tested (whole wheat; cracked wheat; long grain Basmati rice; and short grain Parmal rice), Parmal rice proved to be the best in producing a higher concentration of mycophenolic acid. Under the optimized conditions, using Parmal rice with 80% initial moisture content at an initial pH of 5.0, a maximum MPA concentration of 3.4 g/kg substrate was achieved in 12 days of fermentation at 25°C. The moistened substrate was supplemented with the following additional nutrients (g/L packed substrate): glucose 40.0; peptone 54.0; KH_2PO_4 8.0; $MgSO_4.7H_2O$ 2.0; glycine 7.0; and methionine 1.65 with a small amount of a specified trace element solution. The final MPA concentration was found to be to nearly 4 g/kg substrate when glucose was replaced by molasses. Replacing Parmal rice with rice bran as substrate further improved the MPA concentration to nearly 4.5 g per kg of the dry substrate.

NOTES

Developing Down-stream Processes for Producing Recombinant Proteins Suitable for Clinical Trials. CSIRO Working With the Biotechnology Industry – Two Case Studies

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CSIRO is Australia's national science agency. Our Biomedical Manufacturing group work with biotechnology clients to develop innovative solutions for advancing their product development pipelines. Many laboratory based discoveries rely critically on innovation to succeed, yet much of that innovation requires capital-intensive infrastructure and multi-disciplinary scientific capabilities that are often beyond the reach of university departments and individual companies. At CSIRO we provide biology and chemistry capabilities, infrastructure and equipment to universities and fledging biotech companies through partnerships that are focused on sharing risk and returns or simply fee-for-service arrangements. Our Recombinant Protein Production Facility can provide optimization, scale-up, production and purification of recombinant proteins and antibodies in quantities large enough to support pre-commercial investigations and trials. Two case studies will be presented detailing the development of environmentally-friendly and economically feasible down-stream processes to produce high purity recombinant proteins with minimal endotoxin, host cell protein and DNA contamination that are suitable for large scale production by Contract Manufacturer Organizations (CMOs) using protocols approved by regulatory authorities. Both proteins are required for clinical trials to evaluate their effectiveness and suitability as: a novel bio-therapeutic to treat inflammation and fibrosis, and conjugation to polysaccharides for use as a cancer vaccine.

NOTES

Broadening Clarification Solutions for Vaccines

814

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Vaccine production is a complex process due to various production systems. The clarification step of vaccine processes is important due to its direct impact on downstream purification. Diverse technologies have been used for vaccine harvest clarification. Historically, centrifugation and microfiltration have been employed as primary clarification. Normal flow filtration technologies are becoming more commonplace due to their ease of use and single use implementation. Membrane and depth filtration have established themselves as promising options for viral and bacterial vaccine clarification. Flocculation/ precipitation has also shown to be an evolving technology in vaccine clarification, especially when used with new and novel depth filters which have gradient design structures specific for the particle size distributions of pre-treated feed streams. Sufficient product recovery and debris removal were observed in such applications and warrants further attention in this area. This poster aims to share certain successful adaptation of flocculation/ precipitation with such depth filters and offers an alternative to simplify vaccine clarification processes.

NOTES

Quality by Design (QbD) to Tangential Flow Filtration (TFF) Operations

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Quality by design (QbD) is a modern, scientific approach to formalize the quality of a product that is being promoted by regulators. It ensures the quality of the products produced are consistent by keeping critical process parameters (CPP) within a design space. In the QbD concept, quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured, along with a knowledge of the risks involved in manufacturing and an appropriate risk response plan, i.e., the control strategy. Industry is gradually embracing the quality by design concept. Tangential flow is an important operation in the downstream processing of a recombinant protein, since it is the last step prior to the sterile filtration when the protein is concentrated and changed to the formulation buffer and the final drug product is constituted. To establish QbD for a unit operation such as formulation using tangential filtration (ultrafiltration), parameters and attributes need to be identified and prioritized, a series of experiments using a qualified scale down model are then required to identify sensitivities for a given molecule, and finally a control strategy is required for critical process parameters. Protein loading, cross flowrate, transmembrane pressures (TMPs), different cassette lots were identified as process parameters in this study. Process attributes (Process time, achievable final concentration, retention) and product attributes (Aggregate level, buffer exchange, and final concentration) were evaluated. In this poster, the impact of cross flowrate, TMPs and loading on process time and aggregate level will be discussed. From the study, TFF process operating in the polarized region of the flux curve led to no significant impact of TMP parameter changes on the quality attributes. Process time attribute increased with decreases in the crossflow rate and increases in product loading on the membrane. Size-exclusion high performance liquid chromatography (SEC-HPLC) result showed the increases in the aggregate content attribute were not significantly correlated with changes in any parameter. Slight increases in aggregates during diafiltration is attributed to increasing pump passes causing stress on the protein with each pass through the pump. In conclusion, TFF unit operation is a robust operation that delivers consistent process performance with proven engineering principles and mass transfer equations. Process (process time) and quality attribute (aggregate level) may be managed within the design space with well controlled key parameters. Result obtained at small scaled studies may vary with different molecules and with scaled up hardware. Further tests with a product molecule are required at large scale (qualification runs) to complete the understanding of parameter changes on attributes.

NOTES

Novel Protein L-based Chromatography Resin for Affinity Purification of Antibodies and their Fragments

816

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Therapeutic monoclonal antibodies have become a major product class in the biopharmaceutical industry, and much recent interest is also directed towards antibody fragments (eg. Fab, scFv and diabody). We have developed a novel affinity chromatography resin with a recombinant Protein L ligand, which has an affinity for the antibodies and their fragments containing kappa light chains. Fundamental features of the resin, such as binding characteristics for immunoglobulin G and Fab, alkaline stability and applicability for the Fab purification, will be discussed in this presentation.

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Fast Trak Your Molecule to Market

817

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Whether you're looking to launch a new molecule, enhance existing capacity or bring biosimilars to emerging markets, process development and cGMP manufacturing support will be critical to the long term success of the product. This presentation will focus on a key case study converting a process from stainless steel to single-use while at the same time ensuring the product is of the same quality and is manufactured in a reproducible manner. Fast Trak services support you in optimizing key process steps upstream and downstream and can produce cGMP product suitable for Phase I and II clinical studies. Our expert team of global technical scientists with over 30 years of experience can assist you in solving specific process challenges for manufacturing at scale and using state of the art enabling technologies.

Author list

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