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Bioassay Development: Validation & Maintenance

25-27 September 2013 Basel, Switzerland

Hear from the following Organizations:

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CSL Behring
DiscoveRx Corporation
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Quotient Bioresearch
Roche Diagnostics GmbH
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Stratum Medical Corporation

Conference Topics

Main topics include:

- **Use of DOE During Bioassay Development**
- **Novel Read-out Systems for Bioassays: qPCR and Beyond**
- **How to Set Equivalence Limits with Limited Historical Data**
- **Biological Characterization of Follow-on Biologics**
- **Establishing Assay Monitoring Practices to Satisfy Regulators**
- **Host Cell Protein Assay Update: USP update and QC Practices**
- **Validation Using DOE Paradigms**
- **Stability Indicating Properties of Bioassays: a Critical Quality Attribute**

Plus! 2 Pre Conference Workshops

Workshop #1: **Neutralizing Antibody (Nab) Assays**
Attend the first ever BEBPA workshop on Nab Assays. Be part of the in-depth discussions about how to really determine sensitivity and learn about new approaches to establishing cutpoints. Case studies, tutorials and novel solutions to existing problems. It is our plan to jump start a new white paper of these critical assays, come and be heard about what works and what doesn't.

Workshop #2: Bioassay Basics Mini-Course
This course is designed for those new to bioassay development or those wishing to revisit the basics. It provides a solid base to understand the complexities of a relative potency assay and the practical tips to allow you to go back to your laboratory and implement the new ideas you will hear about in the conference. This is also the perfect place to meet your colleagues and become part of the bioassay community.

★ **Don't miss our special main conference mini-tutorial: Establishing Analytical cell banks.**

Join Us Wednesday Evening for a Covance Sponsored Reception

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BEBPA's 6th Annual Biological Assay Conference

Pre Conference Workshop #1 25 September 2013

NAB Workshop

Neutralizing antibody assays (Nab assays) are one of the most challenging biological assays to develop. They are typically cell-based assays, based upon the CMC potency release method, but are by definition designed for maximum sensitivity and used to analyze serological samples. All these characteristics present severe analytical challenges for the scientists tasked with their development. This workshop is BEBPA's first concerted effort to bring together a group of scientists and statisticians to openly discuss the challenges and approaches for smoothing out optimisation of these critical assays. It is our hope to emerge from this workshop with ideas on how to reshape our approaches to improving assay precision, establishing different approaches to establishing statistically and clinically relevant cut-points and utilizing modern Quality by Design tools to improve overall assay robustness.

Schedule

9:00-9:10: Opening remarks
Chaired by Drs. Jane Robinson and Janka Ryding

9:10-9:50: Development & Validation of Assays for Therapeutic Drug Monitoring of Anti-TNF Biologic
Dr. A. Ann Gils, Professor**, KU Leuven**

9:50-10:30: Nab Assays
Craig Stavold, Quotient Bioreasearch

10:30-11:00: Morning Break

11:00-11:40: Statistical Definitions of Sensitivity and How it Pertains to Cut-off Assays
Dr. Stanley Deming, President, **Statistical Designs**

11:40- 12:20: Use of DOE & Z-Factor to Optimize Cells for Development of a More Sensitive Nab Assay
Dr. Laureen Little, Principal Consultant, **Quality Services**

12:20-1:40: Lunch

1:40-2:20: Development of a Nab for BioSimilar Product
Dr. Camille Dycke, Manager, **Covance Laboratories**

2:20-3:00: Evaluation of Dried Blood Spots for the Quantification of Therapeutic Monoclonal Antibodies & Detection of Anti-Drug Antibodies
Denise Sickert, Novartis

3:00-3:30: Afternoon Break

3:30-4:10: Case Study: Validating a Functional Nab Assay for Change of Species
Dr. Sue Charlton, Team Leader**, Public Health England**

4:10-4:50: New Technologies to Detect Neutralizing Anti-Drug Antibodies During Immunogenicity Testing
Dr. Abhi Saharia, Sr. Product Manager, **DiscoveRx Corporation**

4:50-5:30: Nab Question and Answer Session: After the workshop there will be time for an "open microphone" session to discuss current Nab issues in the industry.

Pre Conference Workshop #2: 25 September 2013

Bioassay Basics Mini-Course ★ Plus: Technical Group Meeting

Although sometimes challenging, and (incorrectly) associated with high %CV, biological assays can actually be precise and robus. This bioassay development workshop will begin with an overview of the basic tools required for success: analyst training, critical reagent maintenance, laboratory/equipment set-up, assay formats, cell maintenance, propagation and banking, as well as regulatory expectations for Phase I/I/III clinical trials. Practical approaches to designing assay formats, system suitability, and preparation for bioassay transfer will be discussed, as well as approaches to working with a CRO. The following topics will be covered in this short, intense course:

Workshop hours: 9:00 to 5:30

- **Bioassay-Characterizing a "Well Characterized" Product**
- **Basic Tools: Analyst Training, Documents, Equipment, Reagents, Assay Formats, Cells**
- **Designing Bioassays**
- **Regulatory Expectations**
- **Data Analysis**
- **Setting Acceptance Criteria/System Suitability**
- **Bioassay Transfer**
- **Why Team with a CRO?**
- **Lessons Learned**
- **Questions & Discussion**

Instructors: Dr. Michael Sadick *is the Senior Manager in Biopharmaceutical Characterization at Catalent Phamra Solutions.* ***Dr. Michael Merges*** *is Director of Analytical Development Solutions at Catalent where he oversees Biopharmaceutical and Biophysical Characterization, Extractables and Leachables and Organic & Inorganic Spectroscopy.*

Technical Group Meeting

The last 45 minutes of the Bioassay Basics Mini-Course will be an "open microphone" session of short case studies. If you bring a current technical problem to share with the group we will waive your fees for the workshop! Here is your chance to attend a day of training and get free technical advice from your peers. Please contact us at bebpa@surewest.net and reserve your 10 minute spot at the microphone.

Technical Group Meeting Chaired by Dr. Mette Willer Ollenborg, Sr. Research Scientist, **Novo Nordisk**

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BEBPA's 6th Annual Biological Assay Conference

Main Conference, Day 1, 26 September 2013

9:00-9:10: Open on Conference: Welcome and BEBPA Update
Dr. Laureen Little, Principal Consultant, **Quality Services**

Session 1: Assay Development

9:10-9:40: Selecting the "Right" Assay for GMP During Early Development
Effective selection of the right assay for functional assessment of potency early in product development can eliminate time-consuming and costly bridging and equivalent studies during late phase, and also promote data continuity. This presentation will use a case study to demonstrate how early stage 'research' assays can be converted with minimal effort into precise, reliable GMP assays that can be used throughout the lifecycle of the product.
Dr. Nicola Crawford, Scientist II, **MedImmune Ltd**

9:40-10:10: NFAT-Luciferase Bioassay; a GMP-capable Surrogate for ADCC Effector mAb
In response to a client's need to establish an ADCC-like bioassay with sufficient accuracy, precision and robustness to support both qualification and later validation, we adopted and adapted the Jurkat cell-based NFAT-luciferase reporter gene bioassay from Promega. Data will be presented as to how the assay was optimized to be used as a full-plate 96-well assay, with a reference standard, assay control and 2 samples per plate.
Dr. Mike Sadick, Senior Manager**, Catalent Pharma Solutions**

10:10-10:40: Troubleshooting on Performance When Developing Bioassay for mAb's
An in vitro reporter gene assay was developed for measuring potency of a receptor blocking antibody. The assay was validated and found fit for purpose for NN1 and for NN2, a back-up candidate, since NN1 and NN2 have the same mode of action. For NN1 the bioassay is robust, for NN2 the method generated challenges with regards to critical reagents. This talk focuses on these challenges and how problems were tackled, for example using DoE.
Dr. Maria Melander, Senior Scientist, **Novo Nordisk A/S**

10:40-11:10: Morning Break

11:10-11:40: Case Study: The Experimental Approaches Used to Optimise & Control A Cell-based Potency Assay
We present a cell-based assay testing potency of a live attenuated Dengue vaccine. This includes i) assay deconstruction to understand parameters that may impact the assay's behaviour ii) distillation of these parameters for evaluation using risk management approaches iii) screening studies that examine controllable parameters iv) assay optimisation exploring Design Space to improve robustness.
Dr. Lee Smith, Principal Consultant, **GreyRigge Associates Ltd**

11:40-12:10: Design of Experiment: Building Quality Into the Cell Based Assay
A design of experiment (DOE) approach has the potential to facilitate a more thorough assessment of assay variables over a reduced period of time whilst providing scientific understanding of the effects of multiple assay variables. Here we look at our experience of using DOE as a systematic approach to cell-based assay development from a scientific and practical point of view.
Stuart Dunn, Senior Study Manager**, Covance Laboratories**

12:10-1:30: Lunch

Afternoon Sessions Chaired By:
Dr. Hans Joachim Wallny, Leading Scientist, **Novartis**

1:30-2:00: In Silico Simulation Applied to Bioassay Development
Development of in vivo assays to demonstrate immunogenicity of vaccines is complex and time consuming. A well designed validation study of an in vivo potency assay for a vaccine under development was executed and variance component estimates were obtained. They were then used to build a simulation model of an in vivo assay. Applications such setting equivalence limits in absence of historical data and defining the best mathematical model for relative potency estimation will be presented and discussed.
Sara Franceschi, Biostatistician, **Novartis V&D**

Session 2: PCR Read Out Systems

2:00-2:30:qPCR Testing of Retroviral Gene Transfer Vectors for Development, Release Testing & Patient Monitoring
Many gene therapy trials rely on retroviral vextors to deliver therapeutic genes into patients' cells. Quantitative real-time PCR (qPCR) is the method of choice to qauntify retroviral vector specific nucleic acids. This presentation will focus on the different requirements for such qPCR methods and give examples from gene therapy approaches using gamma or lentiviral vectors.
Dr. Carsten Lindemann, Head of Analytical Development & Validation, **Eufets GmbH**

2:30-3:00: Quantification of Gene Expression As A Readily Available & Rapid Method to Measure Bioactivity
The measurement of gene expression in responsive cell lines by qRT-PCR offers an alternative to late-stage functional bioassays that is rapid, has the potential to be automated and does not require the development of transfected cell lines. We examined the induction of gene expression in response to erythropoietin (EPO) in the EPO-sensitive cell line, UT-7/EPO and identified that the immediate early gene, EGR1, is rapidly induced in response to EPO in a dose-dependent manner and the response is inhibited by the inclusion of patient serum containing anti-EPO neutralising antibodies.
Dr. Jackie Ferguson, Senior Scientist, **NIBSC**

3:00-3:30: ***Afternoon Break***

Mini-Tutorial: Cell Banking for Cell Based Assays

Well behaved cells are critical for the development of an accurate, precise and long term reliable and reproducible bioassay. Unlike cell banks used for a therapeutic product, there are no regulatory requirements or guidances on cell banks used for assays. This mini-tutorial will discuss using cell banks to maintain well behaved cells. Issues with sourcing cells, documenting their history, defining passage number, developing cell banks for assays, qualifying them, testing them for adventitious agents, and changing cell banks will be presented. The recent white paper in Bioprocess International on this subject will be discussed

3:30-4:30: Mini-Tutorial: by Dr. Sally Seaver, President, **Seaver Associates LLC**

4:30-5:00: Case Suty: Characterization and Storage of Cells in NAb Assays by Dr. Janka Ryding, Research Scientist, **Ferring PharmaceuticalsA/S**

5:00-5:30: Case Study: Controlling Cell-based Bioassay Performance through Controlled Preparation of Bioassay-ready Cells by Dr. Teresa Surowy, Research Manager**, Promega**

5:30: Conference Adjourns

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Main Conference, Day 2: 27 September 2013

8:50-9:00: Welcome by Chairperson
Dr. Stan Deming, President**, Statistical Designs**

Bioassay Development Case Studies

9:00-9:30: Monitoring the Performance of Commercial Bioassays & Health Authorities Expectations
Monitoring of bioassay performance and trending of results is not only good GMP practice within a QC environment, but is a "must have" when it comes to health authorities expectations. This talk presents a case study of a commercial bioassay for which a product control was newly introduced for routine assay performance monitoring (and SST) on specific health authority request.
Dr. Till Konig, Laboratory Head**, Novartis**

9:30-10:00: Potency Assays and Biological Characterization Assays for Follow-on Biologics: Rituximab as a Case Study
As patent expiration is approaching, follow-on biologic versions of Rituximab are slowly making inroads worldwide. This presentation will give an overview of state-of-art technologies used for these cell-based assays for Rituximab.
Dr. Venkat Mukku, President**, GCAS USA**

10:00-10:30: Automation of QC potency Assays sing a Flexible Multi-project ELISA Platform
Potency assays are project-specific by definition since they reflect mode of action of the biopharmaceutical. We developed a robot-based binding ELISA platform for potency determination of therapeutic proteins. The automated system was qualified using three QC binding ELISAs of project currently in clinical development.
Dr. Markus Wendeler, Functional Lead Analytics, **Novartis**

10:30-11:00: Morning Break

11:00-11:30: In-vivo Bioassay Validation: The Estimation of the Intermediate Precision %CV – a Case Study
Intermediate precision estimates should capture influence of factors such as operators, analytical sessions, batches of mice etc. This validation used variance decomposition to estimate sources of variability imputable to the factors.
Barbara Pomili, Biostatistician**, Novartis V&D**

11:30-12:00: Equivalence Testing: Establishment of Evidence Based Equivalence Limits
Until recently, assessment of comparability was achieved by statistical hypothesis tests. These procedures often yield unsatisfactory results. Therefore, alternative test procedures such as equivalence tests or intersection union tests often are used. We suggest a meta-analytic predictive approach based on past assay results for establishing equivalence limits
Dr. Thomas Gsponer, Senior Statistician**, CSL Behring**

12:00-12:30: Optimization of an Amino Acid Based Bioassay Method to Support the Development and Regulatory Submission of a Drug/Medical Device Combination Product
Product characterization of an investigational combination device included elucidation of loading and release kinetics and absolute peptide quantity (dose) per implanted device. An amino acid analysis (AAA) method which takes advantage of the non-natural amino acid constituent, amino hexanoic acid (Ahx) of the FGF peptide analogue was optimized and allowed quantitation in a high background of other amino acids stemming from the collagen carrier.
Juerg F. Tschopp, CEO**, Stratum Medical Corporation**

12:30-1:45: Lunch

Session Chaired by Dr. Bassam Hallis, Public Health England
1:45-2:15: Comparison of Different Bioassays for Stability Studies with Membrane Target Binding mAbs
Two monoclonal antibodies mAb1 & mAb2 specific for the same epitope were analyzed with 4different bioassays: (i) direct binding ELISA (ii) FACS binding, (iii) functional bioassay and (iv) ADCC. Different potencies were observed with ELISA, FACS and ADCC at temperature stressed conditions. Characterization suggest differences correlate with a post-translation modification.
Dr. Petr Obrdik, Functional Lead**, Novartis Biologics Process**

2:15-2:45: Development & Validation of a Cell-based Potency Assay Using DOE Approach
A cell-based potency assay was developed on the xCELLigence platform using a multi-factorial design of experiment approach to achieve required sensitivity, accuracy and precision. The xCELLigence system monitors cellular events by measuring the impedance of the cells, providing quantitative information on cell viability and morphology.
Dr. Tinnke Denayer, Sr Scientist Pharmacodynamics-Pharmacology, **Ablynx NV**

2:45- 3:15: Assessing Goodness-of-Fit of Non-Linear Models During Calibration Inference in Biological Assay
This paper discusses a statistical method to assess a goodness-of-fit of non-linear models during calibration inference in immunoassays using a chi-square test. Empirical examples are given and are shown to yield better outcomes. Also, the impact of the selection of variance function on goodness-of-fit test is also addressed. . **Dr. Eloi Kpamegan**, Director**, Novavax, Inc**

3:15-3:45: Poster Presentations

3:45-4:15: Afternoon Break

4:15-4:45: Summary of USP HCP meeting
Dr. Laureen Little, Principal Consultant**, Quality Services**

4:45-5:15: Characterization of CHO Host Cell Proteins by 2D-LC Immunofractionation
Host cell protein (HCP) impurities are a lead parameter in evaluating production of biopharmaceuticals from CHO cells. To monitor HCP removal, we use electrochemiluminescent and ELISAs combined with prior 2D-ion exchange/size exclusion chromatographic fractionation. Comparing batches at different purification steps and different products help us identify generic and product-related HCP and evaluate process capability.
Oxana Pester, Group Leader, **Roche DiagnosticsGmbH**

5:15-5:45: Characterization of CHO HCP and Corresponding Specific Antibodies by 2D-DIGE and Western Blot Techniques
Dr. Monika Meier, Post Doc**, Roche Diagnostics GmbH**

5:45-6:15:ELISA Based Impurity Testing In Quality Control: Let's face facts
This talk focuses on the use of ELISAs to control the depletion of process related impurities during downstream purification such as Host Cell Proteins (HCPs). Several case studies are shown to discuss strength and limitations of ELISA based impurity testing by considering the scientific andregulatory requirements.
Dr. Thomas Waerner, Associate Professor**, Boehringer Ingelheim Pharma GmbH & Co.KG**

6:15: Conference Adjourns

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