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# Biological Assays Conference

Preliminary Brochure

**29 September – 1 October 2010, Barcelona, Spain**

**Hear from the following Organizations:**

- Ablynx
- BCG
- Biogen-Idec
- BioAnaLab Ltd.
- Bureco AG
- Covance
- DDL Diagnostic Lab
- EMA
- Global Cellular Analytics
- HPA
- Institute Andre Lwoff
- MedImmune
- NIBSC
- Novartis Biologics
- Paul-Ehrlich Institut
- Premas Biotech Pvt. Ltd
- Precision Bioassays
- Protagen AG
- Quality Services
- Statistical Designs

## *Main Conference Topics*

- **EMA Speaker Provides an EU Regulator's Perspective on Bioassays**
- Industry Authors Summarize Soon to be Published White Paper on ADCC Assays and How to Replace Them
- Practical Advice for Determining Reference and Test Article Similarity
- Developing and Validating Multiplex Bioassays
- Bioassays to Support Product Release: Beyond Potency
- Tips on How to Correlate Functional and Binding Assays

## *Plus! Pre-Conference Bioassay Tools Workshop*

Be sure to attend this interactive and practical Workshop. If you are struggling with implementing the new USP recommendations, or want to learn about the array of useful statistical tools to speed up assay development and validation be sure to attend this workshop.


**…….and Cases Studies!**

- Cell-Based Potency Assays
- Functional Surface Plasmon Resonance Assays
- One Step Neutralizing Antibody Assays
- Report Gene Assays
- Using DOE to Develop a Cell-Based BioAssay
- Validating a Difficult NAB Cell-Based Assay
- Replacing ADCC Assays

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# BEBPA's 3rd Annual Biological Assay Conference

## Pre-Conference Workshop: Practical Tools for the Bioassay Scientist

**8:15—8:30 Open of Workshop:** Organizers' Comments
**Laureen Little**, **PhD,** Principal Consultant, **Quality Services**

**8:30—9:30 Primer for the Statistical Design of Experiments (DOE)**
Simply put, experiments are carried out to obtain unknown information. Statistical concepts applied to the design of experiments can make the experiments more efficient, more effective, and therefore more productive—that is, statistically designed experiments can obtain the required information with a minimum expenditure of resources (a desirable business goal!). This brief introduction will discuss the important topics of replication to measure and minimize the effects of purely experimental uncertainty: factor interaction; and the use of broad designs to minimize uncertainty in the results. Various classical experimental designs will be introduced.
**Dr. Stanley Deming,** President, **Statistical Designs**, USA

**9:30-10:15 Design of Experiments in the Framework of a Cell Based Potency Assay**
Biological assays for measuring the potency of a therapeutic drug candidate are critical components to monitor its quality and stability. These potency assays should describe the specific ability or capacity of a product to achieve a defined biological effect. In the given example this biological effect is measured in a virus neutralization assay. In particular, for the development of this assay, accuracy, precision and window of the virus neutralization curve had to be optimized as a function of seven potentially critical factors. The design and the analysis of these experiments are discussed. For the design of experiments (DOE) part, some important issues concerning the randomization scheme, blocking and hard-to-change variables are highlighted. Additionally, the impact of changing the design settings before and during experimentation is discussed. For the analysis part, multiple responses that should be optimized together if possible are dealt with. The problem of missing data is also tackled by using multiple imputation techniques. Finally, the resulting optimal factor settings together with the final model are tested through additional experiments.
**Dr. Katrien Verschueren,** Biostatistician**, Ablynx,** Belgium

***10:15—10:45 Morning Break***

**10:45-11:30 Application of DoE in Bioassay Development: A One Day Simplified Muli-Factorial DoE Approach Addressing Bioassay Robustness**

**Dr. Hyun (Jun) Kim**, Associate Scientist II, **MedImmune**, USA

**11:30-12:15 Validation of Relative EC50 ELISA Assays**

We will discuss a case study for the validation of these types of ELISAs. The design and outcome for all ICH parameters will be reviewed together with lessons learned. We will also briefly discuss the statistical design of the assay and the analysis of validation data.
**Matthew Trickett**, Experimental officer, **Covance Labs,** UK

**12:15-1:00 Strategies to Reduce Noise-Dependant Censoring Bias in Bioassays**
Bias, like relative potency, can be most efficiently estimated within-assay. A common result is attenuation of estimated potency that increases with differences between sample and reference potency. This is also seen in computer simulation experiments where attenuation also increases with noise around the fitted lines or curves, often acting via similarity failures. In linear model bioassay the noise-induced bias partially depends on the strategy used to select near-linear portions of the response curves. Potency bias depends on the assay design, the potency range, the analysis method, and the variation in the assay. Careful study of how these combine can inform many strategic choices in bioassay design, analysis, and use.
**Dr. David Lansky,** President, **Precision Bioassay**

***1:00—2:15 Luncheon***

**2:15-3:15 Primer: USP Approaches to Similarity and Modeling for the Bench Scientist**

**Presenter to be Determined**

***3:15—3:45 Exhibit/Poster and Refreshment Break***

**3:45-4:30 Parallelism Testing of Four-parameter Logistic Curves for Bioassay: A Case Study for Implementation of USP Bioassay Guidance**

**Dr. Hyun (Jun) Kim**, Associate Scientist II, **MedImmune**, USA

**4:30-5:15. Detecting "Non-Parallelism" using Residual Sums of Squares from a Parameter Logistic Model.**
Making the reasonable assumption that all wells on a bioassay plate have been prepared uniformly, it is then reasonable to fit a four-parameter logistic (4PL) model that has a single upper asymptote parameter, a single lower asymptote parameter, and a single slope parameter (common parameters) for reference standard, control, and test samples applied to the plate; each sample has it's own "C" parameter (related to its log [ED50]) in the model. For individual samples that behave similarly, their average sums of squares of residuals (SSR) are expected to be approximately the same; for a non-similar (non-parallel) sample, its SSR is expected to be inflated. Experience with real samples shows this to be true. The average SSR is also useful for detecting what appear to be sequential pipeting errors and "bad" wells on a plate.
**Dr. Annemarie King**, **HPA,** UK

***5:15 End of Workshop***

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# BEBPA's 3nd Annual Biological Assay Conference

## *Main Conference, Day 1: 30 September 2010*

**8:00-8:15 Open of Conference:** Welcome and BEBPA Update
**Laureen Little**, **PhD,** Principal Consultant, **Quality Services**

### Functional Assays for Antibodies: ADCC and Beyond

**Session Chairs: Hans-Joachim Wallny, PhD, Novartis and Xu-Rong Jiang, Ph.D., M.D., MedImmune, LLC**

### Keynote Address

**8:15-9:15 Development, Validation and Real-life Experience of a Potency Assay for an Anti-Cytokine mAb**
A potency assay was developed to support release and stability testing of GMP drug substance and drug product of a fully human monoclonal antibody targeting a cytokine. The potency assay is based on inhibition of a transcription factor essential for biological function of the cytokine. The presentation will focus on assay development and validation, the establishment of procedures to monitor assay performance, as well as issues that became apparent during routine use of the assay and how these were addressed.
**Dr. Thomas Millward,** Group Head Bioanalytics, **Novartis Biologics,** Switzerland

**9:15-10:00 A Strategy for Assessment of Effector Functions of Therapeutic Monoclonal Antibodies (this is an overview of the Fc effector function characterization whitepaper co-authored by experts from Amgen, Genentech, Biogen Idec, Merck, Eli Lilly & MedImmune)**
The Fc region of therapeutic monoclonal antibodies can play an important role in safety and efficacy. Although much is known about the structure-activity relationship of antibodies and the factors that influence Fc effector functions, it remains unclear how manufacturers should assess and control Fc functionality. We present a control strategy.
**Dr. Xu-Rong Jiang,** Associate Director, **MedImmune,** US

***10:00—10:30 Morning Break***

**10:30-11:15 Correlation Between Binding and Cell-based Functional Potency Assays**
**Dr. Svetlana Bergelson,** Associate Director**, Biogen Idec,** US

**11:15-12:00 Functional Analysis of Therapeutic Monoclonal Antibodies Using Surface Plasmon Resonance (SPR) and Flow Cytometry (FC)**
ADCC is an important mode of action for many monoclonal antibodies but these assays are challenging to develop. We showed binding of the prototypic humanised antibody alemtuzumab to the critical Fc gamma RIII receptor, measured by SPR and FC, correlates with physiological activity measured by ADCC. Glycoengineered antibodies with different levels of binding activity were used to show the sensitivity and specificity of the method. The Fcgamma RIII ligand binding assays provide a functionally relevant indicator of product quality for batch release and stability testing.
**Dr. Alice Harrison,** GMP Services Manager, **BioAnaLab,** UK

### BioAssay Statistical Tools

Chair: **Dr. Stanley Deming,** President, **Statistical Designs**

**12:00-12:45 Specifications and Fundamental Statistics**
As ICH clearly points out, the only rational basis for setting specifications is based on fitness for use, considerations usually involve safety and efficacy. From Q6B: "Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies.." The common practice of setting specifications based on current performance of an existing process without evaluating fitness for use carries two risks: risk to the customer, and risk to the manufacturer. Further, the common use of arbitrary numbers of "sigmas" to set simple specifications (for example, in batch release testing) often involves risks that are inappropriately large for the business application. "Specifications for the Chemical and Process Industries...", ISBN 0-87389-351-4, is recommended.
**Dr. Stanley Deming,** President, **Statistical Designs**, USA

***12:45-2:15 Luncheon***

**2:15-3:00 Characterization of Effector Functions of Monoclonal Antibodies**
The characterisation of biotech/biological products by appropriate techniques is necessary to guarantee their efficacy and to establish relevant specifications. Methodologies include physicochemical and immunochemical methodss, and biological activity. All functional properties of a biological product should be addressed during characterisation. It is important, therefore, to develop reliable and sensitive assays to detect putative differences in the biological properties. Furthermore, standardized assays to address certain characteristics, e.g. Fc function of monoclonal antibodies, allow comparison of: pre- and post changes, products with the same target. or even biosimilar products.
**Dr. Steffen Gross,** Laboratory Head, **Paul-Ehrlich Institut,** Germany

***3:00—3:30 Exhibit/Poster and Refreshment Break***

### Multiplex Assays

*Increased pressure on researchers to gain greater understanding of products, protein interaction, identification of markers etc has led to a number of emerging technologies offering 'multiplexing' of assays. Multiplex assays are designed to generate simultaneous measures from a single sample against multiple analytes. This session will describe the promises and pitfalls of 'multiplexing' and describes two case studies on the development and validation of multiplexed assays.*
**Session Chairs: Bassam Hallis, PhD, HPA and Thierry Pascal, PhD, GSK**

**3:30-4:15 Promises and Pitfalls of multiplexing!**

**Dr. Annemarie King,** General Project Manager, **HPA**, UK

**4:15-5:00 Validation of a Multiplex Luminex ImmunoAssay (MLIA) for Assessment of the Immunogenicity of Bordetella Pertussis Vaccines**

**Dr Nathalie Durant**,**GlaxoSmithKline Biologicals**, Belgium

**5:00-5:45 Validation of the HPV Genotyping Assay**

**Bernhard Kleter, DDL Diagnostic Laboratory**

**5:45** ***No Host Networking Reception in Bar***

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# BEBPA's 3rd Annual Biological Assay Conference

## *Main Conference, Day 2: 1 October, 2010*

**8:00-8:05 Chairperson's Opening Remarks**
**Dr. Laureen Little,** Principal Consultant, **Quality Services**

**8:05-9:00:** ***Opening Address:***

**Recent EU Regulatory Experiences with BioAssays**

**Dr. Peter Richardson,** Head of Biologicals, Quality of Medicines Sector, **European Medicines Agency**

**Neutralizing Antibody Assays**

**9:00-9:45 A Novel One-Step BioAssay for the Quantification of Neutralizing Antibodies**
A unique one-step bioassay was developed that overcomes limitations of conventional cell-based assays. This technology allows both drug activity and anti-drug neutralizing antibodies (NAbs) to be quantified rapidly and precisely in the same sample simply by adding reporter cells. Reporter cells express a reporter gene under control of a drug-responsive promoter, and express the drug normalized relative to an internal standard. Assay results are independent of cell number or differences in cell viability.
**Dr. Michael Tovey,** Director, **Instit. Andre Lwoff**, France.

**9:45-10:30 Development and Validation of a Difficult Neutralizing Antibody (NAB) Assay: A Case Study.**
We developed and validated a cell based assay for determining neutralizing antibodies (NAB) directed against a molecule with endocrine activity. The assay was developed based on a potency assay with a cAMP read out. Most critical parameters were low signal-to noise ratio, high variability, and a tremendous influence of the matrix. By optimizing assay conditions and parameters a satisfactory NAB assay was established, validated and implemented.
**Dr. Gisela Peraus**, **Bureco AG,** Switzerland

***10:30—11:00: Break***

**11:00-11:45 Dilutional Linearity (DL) for NAB Assays**
Neutralizing antibody (NAB) serological assays routinely proceed without assessing similarity among specimen dose-response curves. This lack of similarity can manifest as specimen-specific dilution bias. Test samples typically have activities several folds wider than the dynamic range of the assay, which further narrows acceptable bias. These two features make DL assessment essential for NAb assays. The DL study documents sample effect dilution on assay precision and bias. Sources of error can be categorized into five distinct types. Care must be taken to measure and account for each.
**Dr. David Lansky,** President, **Precision Bioassay,** USA

**Beyond Potency—Cell-based Bioassays in Quality**
**Session Chair: Dr. Nadine Ritter,** Consultant**, BCG, USA**

**11:45-12:30 Modifications in Therapeutic MAb Products: Isoforms or Impurities?**
Therapeutic Mabs are complex molecules and are prone to several modifications during production process and storage. Potency assays play a key role in determining whether these modifications are impurities or product related isoforms. Real life case studies will be presented.
**Dr Venkat Mukku**, **Global Cellular Analytic Solutions** US

***12:45—1:45 Lunch***

**1:45-2:30 Protein Microarrays in Combination with Cell Based Bioassays are More Reliable for Stability Testing**
Stability a major concern for quality, efficacy and safety of therapeutic active monoclonal antibodies. Reliable and fast evaluation tools are required for screening during product development and ICH compliant stability testing. The combination of well accepted cell based bioassays, modern protein microarrays and classical structure characterization techniques allows a unique and comprehensive view on mAB degradation pathways and characteristics. Advantages and disadvantages of different analytical approaches as well as synergetic effects due to method combination will be presented.
**Dr. Katja Aschermann**, Manager, **Protagen AG**, Germany

**Session Title: Hands On Session - Case Studies**
**Session Chair: Dr. Jane Robinson, NIBSC, UK**

**2:30-3:15 Preclinical Development of Nanobodies® : Challenges in Potency Assay Development**
Nanobodies® are a novel class of therapeutic proteins based on the smallest functional fragments of heavy chain antibodies, which occur naturally in the *Camelidae* family. This platform has lead to a wide range of Nanobody formats, including unique multivalent, biparatopic, and bispecific compounds. Such flexibility provides a challenge in the development of stability indicating potency assays. This case study discusses the development of various potency assays for release and stability testing. Examples demonstrate how assays were optimized to discriminate between the multivalent or biparatopic Nanobody formats and their monovalent analogues.
**Dr. Hans Ulrichts,** Sr. Scientist**, Ablynx,** Belgium

**3:15-3:45 Poster Talks**
Back by popular demand! Two posters will be selected for 15 minute presentations in the main conference. This is great opportunity for students and junior analysts to present.
**Presenters to be selected day 1 of the conference.**

***3:45—4:15 Exhibit/Poster and Refreshment Break***

**4:15-5:00 Development of a Whole Blood Cell Depletion Assay for Characterization of Therapeutic Antibodies Directed Against Lymphoid Targets**

**Dr. Roger Grau**, **Novartis Biologics,** Switzerland

**5:00-5:45 Case studies from India: Development of Cell Based Reporter Gene Assays for Biosimilars.**
Bioassays are the only non-clinical tests that indicate a biosimilar product is biologically active. Cell based reporter gene assays are the benchmark to prove functional similarity of a biosimilar to the originator molecule. We present a case study on the development of an in vitro reporter gene assay using luciferase to determine the potency of a biosimilar erythropoietin (EPO).
**Dr. Rajeev Soni,** President and COO, **Premas Biotech**

***Chairperson's closing comments and selection on next year's meeting venue***

***5:45 Conference Adjourns***

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# BEBPA's 3rd Annual Biological Assay Conference

## Assay Monitoring Round Table Discussions

**Wednesday, 29 September 2010 7PM**

Come join us for the first white paper discussion group. Last year, in Rome, workshop attendees learned about various problems associated with maintaining cell-based potency assays for routine use. This year ideas from this workshop and any others you bring to the table will be included in BEBPA's first non-concensus white paper.

**The Topic:**

Assay Monitoring for cell-based assays is a critical activity for maintaining and using assays for routine product release. Currently there are no standardized terminology or practices. Regulatory guidance is non-existent and industry standards are vague and highly variable.

**The Approach:**

This round table will focus on proposing terminology and various parameters for monitoring as well as explore statistical approaches for setting action limits. Dr. Michael Sadick will facilitate the discussion while a note taker records suggestions and comments. All suggestions will be complied into a publicly available white paper to be posted on the BEBPA web page. Attendees are encouraged to bring ideas, slides, handouts or any other form of notes they are interested in having included in the white paper. No companies or individuals will be identified with specific recommendations unless they specifically request recognition.

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**Roger Grau**
**Steffen Gross**
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**Alice Harrison**
**Xu-Rong Jiang**
**Hyun (Jun) Kim**
**Annemarie King**
**Bernhard Kleter**
**David Lansky**
**Laureen Little**
**Thomas Millward**
**Venkat Mukku**
**Gisela Peraus**
**Peter Richardson**
**Nadine Ritter**
**Jane Robinson**
**Rajeeve Soni**
**Michael Tovey**
**Matthew Trickett**
**Hans Ulrichts**
**Katrien Verschueren**

## Meeting Organizers:

**Laureen Little**
**C. Jane Robinson**
**Hans-Joachim Wallny**
**Stanley Deming**
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## BEBPA: Who are We? What Do We Aim to Accomplish?

The Biopharmaceutical Emerging Best Practices Association (BEBPA) is a not-for-profit association, founded in 2008, managed by and for the benefit of the biopharmaceutical scientific community. BEBPA provides an open forum for the presentation and discussion of scientific issues and problems encountered in the biopharmaceutical community.