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# First Annual: Conference on Neutralizing Antibody Assays

**26-27 January 2015**

**Palm Springs, CA**

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## Neutralizing Antibody Assays

Finally a meeting dedicated to helping you develop Neutralizing Antibody Assays! Find out about regulatory expectations, industry standards, how companies are handling their rare reagents, setting cutpoints, and improving sensitivity without increasing their false positive rates. Come hear the thought leaders in the field, and understand the expectations for your NAB assay

### *Keynote Presentations*

- **Regulatory Perspective on Nab Assays & Assessment of Neutralizing Activity of Anti-drug Antibodies** presented by Dr. Joao Pedras-Vasconcelos, of the FDA
- **Reporting of Clinical Immunogenicity Data to Support Therapeutic Protein Development: A Review of the AAPS Sponsored White Paper** presented by author Dr. Steve Swanson



### *Over 12 Case Studies including:*

- Isolation of Nabs from Samples Containing High Concentrations of Therapeutic
- Development of an Enzyme Activity-Based Neutralizing Antibody Assay
- Validating Cell-based Toxin Neutralisation Assays
- Development of Nab Assays for Antibody Therapeutics with Effector Functions
- Robust Cell-Based Assays for Detection of Neutralizing Antibodies to Follow on Biologics like Insulin, GLP1 and Avastin
- A Neutralizing Antibody (NAB) Assay Based on a Reporter of Antibody Dependent Cell-Mediated Cytotoxicity

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# BEBPA's First US NAb Conference

## Neutralizing Antibody Assays Conference

Day 1

**8:30-9:00: Open of Workshop: Comments by organizer**  
**Dr. Laureen Little**, Principle Consultant, **Quality Services**


### Key Note Speaker: Regulatory Perspective of Nab Assays

**9:00-10:00: Regulatory Perspective on Nab Assays & Assessment of Neutralizing Activity of Anti-drug Antibodies**

Biologics are a class of drugs of growing importance in the treatment of human diseases. The cost to the biotechnology industry of developing a biologic from early stage all the way to licensure is very high, and many factors can impinge upon approval. One potential obstacle impacting product development is the occurrence of neutralizing antibodies (NAb) against the biologic in treated patients. NAb are a subset of the total anti-drug antibodies induced by the biologic, and are functionally defined by the assay that detects them. NAb can impact both efficacy and safety of the product depending on patient-related and product-related factors. This presentation will provide an overview of two FDA guidances pertaining to immunogenicity risk management for biologics including risk assessment and mitigation, and neutralizing antibody detection and assay selection. We will discuss the importance of NAb assays to a well thought out immunogenicity plan.

**Dr. Joao Pedras-Vasconcelos**, Visiting Scientist, **FDA**


### Non-Cell Based Nab Assays

 **10:00-10:30: Development and Implementation of a Neutralizing Antibody Assay: Comparing Cell-Based versus Ligand Binding Formats**

Immunogenicity is well recognized by both the biopharmaceutical industry and health agencies as a safety concern, and it is thus a requirement and expectation that appropriate assays are employed to evaluate immunogenic responses to protein therapeutics throughout the drug development process. Neutralizing antibody (Nab) assays are secondary characterization assays designed to determine whether anti-therapeutic antibodies specifically neutralize drug activity. Nab assays are designed to mimic the drug mechanism of action, and can be formatted either as a cell-based (CBA) or ligand binding assay (LBA). In this case study of a Fab directed against a soluble growth factor, we compared two CBAs and one LBA in terms of their suitability to detect Nabs. Based upon relative sensitivity, the LBA was determined to be a more appropriate assay, and was implemented to support phase III clinical trials. A low percentage of Nab-positive patients was detected, with no apparent clinical impact.

**Dr. Eric Wakshull**, Senior Scientist, **Genentech**

**10:30-11:00: Morning Break**


 **11:00-11:30: Development of an Enzyme Activity-Based Neutralizing Antibody Assay**

The drug product of interest is a protein that possesses enzymatic activity. The drug catalyzes the attachment of amino acid (His) to its cognate tRNA. The neutralizing antibody assay is therefore a non-cell based in vitro assay which measures the ability of patient sera to inhibit this enzymatic activity. The potency release assay for this drug measures the spe-

cific activity of the drug by measuring incorporation of radiolabeled His into tRNA. Development of the neutralizing antibody assay based upon this release assay necessitated optimization in a serum matrix, as well as optimization of drug concentration and incubation period to improve ease of execution and thus accuracy and precision of the assay.

**Dr. Esther Chong**, Scientist, **Atyr Pharma**

### Good Development Practices for Nab Assays

 **11:30-12:00: Optimizing Cell-Based Assays for the Quantification of Neutralizing Anti-Drug Antibodies** Regulatory guidelines recommend cell-based assays for the detection of neutralizing anti-drug antibodies (NADAs). Conventional cell-based assays are subject to serum-matrix effects, have low drug tolerance, and are unsuitable for detection of NADAs against therapeutic monoclonal antibodies administered at high doses and with prolonged washout rates. We have developed fully validated assays for a number of biopharmaceuticals based on innovative engineered cell lines that quantify both functional drug levels and NADAs with a high degree of precision within 2 to 4 hours in the same sample without drug interference or serum matrix effects. Case studies will be presented for biopharmaceuticals ranging from novel forms of human insulin and FGF-21 to structurally diverse TNF- $\alpha$  and IL-6 antagonists.

**Michael Tovey**, Laboratory of Biotechnology & Applied Pharmacology

**12:00-1:15: Lunch**

 **1:15-1:45: Technical Focus: Case Studies on Nab Assay Development**

**Renuka Pillutla**, Director, **BristolMyersSquibb**

 **1:45-2:15: Isolation of Nabs from Samples Containing High Concentrations of Therapeutic**

Dosing of biologicals to produce a clinically beneficial effect present a significant challenge for the detection of drug-induced neutralising antibodies (NAb) using a cell based system. Concentrations of monoclonal antibody therapeutics are often present at such high levels in clinical matrix taken to assess an immunogenic response that assessment of NAb presence is made impossible because of the interfering effect of the residual drug on the cell system. Here we look at our approaches to overcome this problem, the challenges faced and results achieved.

**Dr. Stu Dunn**, Sr. Study Manager, **Covance**

**2:15-2:45: Afternoon Break**

**2:45-3:15: Challenges of evaluating drug tolerance for neutralizing anti-drug antibody (NAb) assays for immunogenicity assessment of therapeutic biologics**

**Dr. Xiao-Yan Cai**, Merck Research Lab

**3:15-3:45: Minimum Detectable Amounts and Neutralizing Antibody Assays**

**Dr. Stanley N. Deming**, President, **Statistical Designs**

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# BEBPA's First US NAb Conference

## Neutralizing Antibody Conference

Day 2

### Establishing Assay Sensitivity & Cutpoints

#### 3:45-4:15: Defining Positive Samples. What if the Cut Point Doesn't Cut It?

The process of defining positive and negative clinical samples for the presence of neutralising antibodies often follows the methodology of the ADA analysis. This generally involves assigning a cut point to determine positive and negative samples. The nature of cell based assays means that they are intrinsically more variable than the ADA analysis and therefore applying a cut point may not be appropriate. Data will be presented using different methods of determining positive and negative samples showing that defining a cut point might not always be the best approach.

**Dr. Paul Caldwell**, QC Scientist, Covance

### Live Survey

#### 4:15-5:15: Interactive Current Practices Survey

**Dr. Lauren Little**, Principal Consultant, Quality Services

### Day 2

#### 8:45-9:00: Opening Remarks by Chairperson

### Clinical Aspects of Nab Assays

#### 9:00-10:00: Reporting of Clinical Immunogenicity Data to Support Therapeutic Protein Development: A Review of the AAPS Sponsored White Paper

Therapeutic proteins have the potential to elicit an immune response when administered to patients. An important aspect of developing these medicines is to understand the immunogenicity and to be able to communicate this information to patients, prescribers, and regulators. A group of AAPS scientists representing regulatory agencies and industry recently published a white paper including recommendations on ways to best communicate immunogenicity information. A goal of the white paper was to harmonize reporting of key concepts describing a therapeutic protein's immunogenicity including incidence, kinetics, magnitude, effects on pharmacokinetics of the drug, ability to neutralize the biological effect of the drug, and cross reactivity with endogenous proteins.

**Dr. Steve Swanson**, Consultant

#### 10:00-10:30: Morning Break

### Product Specific Nab Assays

#### 10:30-11:00: Neutralizing antibodies to TNF blockers: a clinical perspective

Millions of patients have been successfully treated with biological agents, particularly in the autoimmune diseases. However, long-term treatment with therapeutic monoclonal antibodies can induce anti-drug antibody (ADA) formation, also known as immunogenicity, which is asso-

### Day 2

ciated with lower drug levels and clinical non-response. Biologicals may be recognized by the human immune system as 'non self' and induce an immune response. Therapeutic antibodies, even those that are fully human, carry unique stretches of amino acids, which form the antigen-binding site and determine their specificity. These sequences are frequently seen as foreign by the immune system of the patient and induce the formation of ADA. By forming a complex with the drug, ADA can neutralize drug activity, which can result in treatment failure. To understand the impact of immunogenicity on treatment response and potential adverse effects we made a detailed analysis of the antibody response to adalimumab and infliximab, including the relationship between ADA, drug levels and clinical impact in various rheumatic disease settings. Furthermore, patient-derived monoclonal antibodies were obtained and analyzed for their binding and neutralizing capacities. Our results indicate that antibody responses to therapeutic monoclonal antibodies predominantly target the antigen binding site thereby neutralizing the drug. Nevertheless, even for a fully human therapeutic antibody such as adalimumab there may be multiple determinants that contribute to immunogenicity.

**Dr. Theo Rispens**, Sanquin Blood Supply



#### 11:00-11:30: Development of Nab Assays for Antibody Therapeutics with Effector Functions

Monoclonal antibodies with mechanisms of action involving effector functions have been used successfully in treatment of a variety of malignant diseases. This presentation will describe development of a cell-based neutralizing antibody (NAb) assay for a humanized therapeutic antibody that is designed to deplete target tumor cells via effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). A general guidance on selection of NAb assay format for antibody therapeutics will also be presented.

**Dr. Shan-Chung**, Senior Scientist, Genentech

#### 11:30-12:00: A Neutralizing Antibody (NAb) Assay Based on a Reporter of Antibody Dependent Cell-Mediated Cytotoxicity (ADCC)

**Dr. Yuling Wu**, Principal Scientist, MedImmune

#### 12:00-1:30



#### 1:30-2:00: Robust Cell-Based Assays for Detection of Neutralizing Antibodies to Follow on Biologics like Insulin, GLP1 and Avastin

One of the major bottlenecks in the development of biosimilars is the need for good bioassays to create potency, stability and neutralizing antibody (NAb) assays. With innovator companies patenting their bioassays, those developing biosimilars are left with few commercially available options for rapid development of NAb & potency assays. The requirements of these assays for sensitivity, precision, robustness, reproducibility and the need for matrix (serum/plasma) tolerance make this an even more challenging task. We have developed over 30 cell-based assays for biosimilar targets that rely on the native biology of the

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# BEBPA's First US NAb Conference

## Neutralizing Antibody Assay Conference

### Day 2

receptor. These assays are highly specific, linear, scalable, robust and have a homogenous mix-and-read protocol, which facilitates rapid transfer to any location worldwide. Data will be presented on assay optimization in 96-well format, reproducibility, serum tolerance and sensitivity, for three assays, namely Insulin, GLP1 and Avastin (Bevacizumab). Performance comparisons will also be drawn on the use of these assays in convenient "thaw-and-use" format and in continuous culture systems.

**Dr. Abhisek Saharia, Director, DiscoverRx**

#### **2:00-2:30: Characterization of Anti-Drug Neutralizing Antibodies: Navigating the Analytical Challenges**

Development of anti-drug antibodies (ADA) to protein therapeutics results in a wide range of clinical sequelae from no clinical effect to some clinically meaningful effect. Although impact of ADA on pharmacokinetics and pharmacodynamics is more commonly seen, dampening of efficacy due to neutralization of drug activity by neutralizing ADA (nADA) is also observed infrequently. In rare cases, development of nADA can lead to a reduction in the function of the endogenous human protein counterpart resulting in fatal outcomes. Development of appropriate analytical methods to understand the clinical risk of immunogenicity is essential. This talk will discuss strategies for selection of cell-based versus non-cell based assay formats to characterize nADA and will present case studies on challenges encountered in the design and development of neutralizing ADA assays to detect clinically meaningful antibodies.

**Dr. Meena Subramanyan, Biogen Idec**



#### **2:30-3:00 Implementation of USP Development & Validation Approaches to CMC Bioassays & Neutralizing Antibody (NAB) Assays**

Potency is a critical quality attribute for biopharmaceuticals. To this end, ligand binding and cell-based assays are generally used to accurately determine the biological activity of protein based drugs. Those assays applied for chemical and manufacturing control (CMC) frequently serve as the basis of studying also neutralizing antibody (NAB) response, which may lead to unwanted side effects or counteract the drug activity. We will present practical examples of how CMC bioassays can be translated into NAB assays and review the development and validation best practices for both, CMC and NAB bioassays, respectively. Furthermore, we will demonstrate classical validation strategies versus new approaches as described in the USP chapters 1106 and 1032/1033/1034 for CMC assays.

**Dr. Gael Debaue, Group Leader, UCB Pharma & Nadja Prang, CEO, TECObiosciences**

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

### **NAb Assays for Vaccine Products**

**3:30-4:00: Development and validation of a multi-species antibody neutralising assay.**

A cell based toxin neutralisation assay (TNA) has been developed and validated to assess the ability of antibodies in mouse sera to neutralise *Bacillus anthracis* lethal toxin. This presentation will describe the approach to the adaptation and validation of this assay for use with other species including human sera.

**Dr. Bassam Hallis, Public Health England**

#### **4:00-4:30: Challenges during Development and Validation of Functional Antibody Assays to measure Vaccine Immunogenicity**

**Dr. Rocio Marchese, Merck Research Lab**

#### **4:30-5:00: Validating cell-based toxin neutralisation assays.**

A toxin neutralisation assay has been developed and validated to measure the functional neutralising activity of antibodies following vaccination. This presentation will walk through the development and validation stages. Optimisation of assay conditions and determination of system suitability will be described as well as validation criteria.

**Dr. Bassam Hallis, Public Health England**

#### **5:00-5:30: Scientific Rationale for Stability Testing of Anti-Drug Antibodies (ADA)**

Long- and short-term stability testing of the analyte is one of the key parameters in bioanalytical method validation in support of pharmacokinetics. However, for immunogenicity testing the scientific rationale for long- and short-term stability testing on quality control (QC) samples most often spiked with polyclonal antibody raised in a different species should be questioned. Therefore, the European Bioanalysis Forum (EBF) formed a Topic Team (TT) to discuss the scientific rationale for stability testing of anti-drug antibodies (ADA). A review of EBF member companies' experience on ADA stability and on anti-vaccine antibodies (AVA) from vaccine projects was the basis of this discussion. EBF recommends to perform short-term stability testing of the positive control but not to perform long-term stability testing of ADAs in non-clinical and clinical studies.

**Dr. Janka Ryding, Research Scientist, Ferring Pharmaceuticals**

**5:30: Conference Adjourns**

Are you interested in presenting at one of our conferences in the future? Please email Cori Schrader at [bebpa@surewest.net](mailto:bebpa@surewest.net) or fill out the abstract form at [BEBPA.org](http://BEBPA.org). BEBPA has 2 upcoming events:

1. Host Cell Protein Workshop, May 14-15, 2015, San Francisco, CA
2. BEBPA Annual Bioassay Conference, September 23-25, 2015, Budapest, Hungary

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