PDA
An International Association For Pharmaceutical Science And Technology

FDA

Viral Clearance Forum

October 1-3, 2001
Bethesda, Maryland
WELCOME!

The Program Committee, under the direction of ***Kurt Brorson, Ph.D., and Richard Levy, Ph.D., Program Chairs,*** *looks forward to your contribution to the success of the conference.*

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Mei-Ying W. Yu, Ph.D., CBER, FDA
Leslie Zeck, PDA

Speaker Presentation Abstracts

(in order of presentations in the agenda)

Overall Process Validation: What are the Regulatory Requirements for Viral Clearance Methods?

Monday, October 1, 8:10 a.m. - 9:00 a.m.

European Regulatory Requirements for the Virus Safety of Biologicals

Hannelore Willkommen, Ph.D., Paul-Ehrlich-Institut

The European Commission and the Committee of Proprietary Medicinal Products (CPMP) established a regulatory framework for approval of biological medicinal products, like plasma derivatives, cell derived products, animal sera and vaccines. New strategies in the development of medicinal products, such as the use of transgenic animals or transgenic plants for manufacture of medicinal products, as well as new strategies in the treatment of patients, such as human somatic cell therapy, xenogenic cell therapy, gene therapy, require specific considerations with regard to product quality and safety.

The presentation will provide a short overview about the current regulations and thoughts on this field. The presentation will focus on the requirements and the current considerations with respect to the virus safety of the biological medicinal product.

Overall Process Validation: Current Industry Perspectives

Monday, October 1, 9:00 a.m. - 10:00 a.m.

Virus Safety of Plasmaderived Biologicals and Blood Components: Overall Process Validation - Industry Perspective

Albrecht Groener, Ph.D., Aventis Behring GmbH

Virus safety of plasmaderived biologicals for human use has been demonstrated by the application of three principal complementary approaches:

- Selecting and testing source material for the absence of undesirable viruses which may be infectious and/or pathogenic for humans;
- Assessing the capacity of the production steps to remove or inactivate infectious viruses including the evaluation of the robustness of these steps to withstand fluctuations in operating conditions;
- Testing the product at appropriate stages of production for the absence of contaminating infectious viruses.

These three principles and their application during manufacturing will be discussed for human and non-human plasmaderived products and for blood components. Tor testing blood/plasma as source material, the focus will be on validation of nucleic acid amplification tests for the detection of blood borne viruses. The validation of the manufacturing procedure to inactivate and/or remove viruses will be addressed by the following key topics: appropriate downscaling of

bovine or porcine adventitious agents by performing IFA analysis on infected host cells. The production lots from the Master Seed Stock and Working Seed Stock are qualified for use after a similar set of IFA tests are performed.

We have recently been studying the ability to inactivate parvoviruses, which are often used as models for one of the more difficult viral types to inactivate. While this virus has traditionally been described to be highly resistant to many common agents for inactivation, we had detected some partial inactivation using HCl and NaOH. However, these studies also demonstrated some apparent resistant virus. To further examine this complex kinetics of inactivation, we have initiated our own testing with low and high pH inactivations for porcine parvoviruses. Some of the parameters to be discussed include characterization of the 'resistant' population, concentration of the inactivating agent, the presence or absence of population, concentration of the inactivating agent, the presence or absence of test samples, and the purity level of the initial virus. The level of purification of the viral agents can have some effect on the amount of virus inactivated or removed. Serum contamination can directly influence a process validation: for example, some preparations decrease the flow rates for columns and viral membrane filtrations. This can often be addressed by generating the viral preparation with reduced or no serum present. Additionally, the performance of column purified viral agents in viral clearance studies is being examined.

In summary, while the selection of the model viruses has in the past been highly dependent on the clinical trial phase and the source of the biopharmaceutical, there are other optimizations that one should consider in order to achieve higher log reduction values. We have seen that using well characterized agents and employing different methods for purification and detection can be critical to optimize the different processing steps for biopharmaceutical development.

Some Basic Procedure for Preparation and Qualification of Viral Challenge Cultures in "Spiking" Experiment

Daniel L. Prince, Ph.D., Gibraltar Laboratories, Inc.

Viral clearance studies incorporate either assays for viral inactivation or virus removal. The use of model viruses from various physicochemical groups has proven useful. As examples, methods for laboratory production of high-titered pools of poliovirus, myxoviruses, parvovirus, herpes virus (HSV), Coxsackie or encephalomycocarditis virus (EMC) as derived from at least three taxonomic groups, and others will be described including host range and quantal ($TCID_{50}$) vs. quantitative (PFU) infectivity assays. Data on the use of duck hepatitis virus as a substitute for human hepatitis B virus will be discussed in our current state of knowledge. The chemical inactivation of hydrophilic and lipophilic viruses will be reviewed in terms of a "scale of disinfection". Comments on a basic safety screening of biologics for viruses and Mycoplasma is part of the presentation.

PDA/FDA Viral Clearance Forum
October 1-3, 2001
Hyatt Regency
Bethesda, Maryland
AGENDA

66

MONDAY, OCTOBER 1 — *MEETING LOCATION*

7:00 a.m. - 5:00 p.m. REGISTRATION — *Ballroom Foyer*

7:30 a.m. -8:30 a.m. COFFEE SERVICE — *Ballroom Foyer*

8:00 a.m. – 8:10 a.m. WELCOME AND OPENING REMARKS
Edmund M. Fry, President, PDA
Kurt Brorson, Ph.D., CBER, FDA
Richard V. Levy, Ph.D., Millipore Corporation

8:10 a.m. - 9:00 a.m. OVERALL PROCESS VALIDATION: WHAT ARE THE REGULATORY REQUIREMENTS FOR VIRAL CLEARANCE METHODS? — *Haverford/ Baccarat*
Moderators: Mei-Ying W. Yu, Ph.D., CBER, FDA
Gail Sofer,, BioReliance Corporation

U.S. Regulatory Requirements for the Virus Safety of Biologicals
Christopher Joneckis, Ph.D., CBER, FDA

European Regulatory Requirements for the Virus Safety of Biologicals
Hannelore Willkommen, Ph.D., Paul-Ehrlich-Institut

9:00 a.m. – 10:00 a.m. OVERALL PROCESS VALIDATION: CURRENT INDUSTRY PERSPECTIVES — *Haverford/ Baccarat*
Moderators: Mei-Ying W. Yu, Ph.D., CBER, FDA
Richard V. Levy, Ph.D., Millipore Corporation

Virus Safety of Plasma-Derived Biologicals and Blood Components: Overall Process Validation: Industry Perspective
Albrecht Groener, Ph.D., Aventis Behring GmbH

Viral Security Strategies for Biotechnology Products
Judith Sernatinger, Biogen, Inc.

Poster: *(to be presented at 5:00 p.m. reception)*

Salient Points for Design of Viral Removal Studies for Mammalian Culture rDNA Biotechnology Processes
E.J. Brandreth, BioMarin Pharmaceuticals

Chromatographic Membranes for Nanometer-Sized Bioparticles
Mark R. Etzel, Ph.D., University of Wisconsin

Enveloped Virus Inactivation by Caprylate: a Robust Alternative to Solvent-Detergent Treatment
Marina Korneyeva, Ph.D., Bayer Corporation

Viral Inactivation Utilizing Depth Filter Media Containing a PVPP-Iodine Complex
Michael Skladanek, SeitzSchenk Filter Systems

4:45 p.m. – 6:30 p.m.	**RECEPTION AND POSTER SESSION**	*Waterford/ Lalique*

WEDNESDAY, OCTOBER 3

7:00 a.m. - 3:00 p.m.	**REGISTRATION**	*Ballroom Foyer*
7:30 a.m. -8:30 a.m.	**COFFEE SERVICE**	*Ballroom Foyer*
8:15 a.m. – 9:45 a.m.	**NEW VIRUS INACTIVATION TECHNOLOGIES: APPLICATIONS AND VALIDATION** *Moderators: Kurt Brorson, Ph.D., CBER, FDA*	*Haverford/ Baccarat*

Inactivation of Infectious Pathogens and Leukocytes in Labile Blood Components
Laurance Corash, M.D., Cerus Corporation

Stabilization of Proteins for Application to HTST Heat Inactivation of Virus
Joachim K. Walter, Ph.D., Boehringer Ingelheim Pharma KG

Gamma Irradiation of Circoviruses in Animal Origin Products
Mark Plavsic, DVM, Ph.D., ACVM, Q-One Biotech, Inc.

Validation of Broad Spectrum Pulsed Light (BSPL) as a Virus Inactivation Step
William Cover, Ph.D., PurePulse

1:30 p.m. – 3:00 p.m. — VIRUS CHALLENGES: PREPARATION AND STANDARDIZATION — *Haverford/ Baccarat*

Moderators: Arifa Khan, Ph.D., CBER, FDA
Carol Marcus-Sekura, Ph.D., Biotechnology Assessment Services, Inc.

Standardization and the Viral Clearance Industry
Kenneth Hughes, Ph.D., Microbix Biosystems, Inc.

GMP Production of AAV Vectors: Challenge and Clearance Studies
E. Morrey Atkinson, Ph.D., Targeted Genetics Corp.

Low pH of Feed Solutions Significantly Increases Porcine Parvovirus (PPV) Aggregate Formation and Affects Virus Clearance Capacity of Nanofilters
Henry Li, Ph.D., Bayer Corporation

Influence of Well Characterized Model Viruses for Clearance Studies
Joseph Hughes, Ph.D., AppTec Laboratory Services, LLC.

Some Basic Procedures for Preparation and Qualification of Viral Challenge Cultures in "Spiking" Experiments
Herbert N. Prince, Ph.D., Gibraltar Laboratories, Inc.

3:00 p.m. – 3:30 p.m. — BREAK — *Ballroom Foyer*

3:30 p.m. – 5:00 p.m. — VIRUS CHALLENGES: CHOICES — *Haverford/ Baccarat*

Moderators: Carolyn Wilson, Ph.D., CBER, FDA
Kathryn Martin Remington, Ph.D., Bayer Corporation

The Choice of Viruses for Validation of Viral Clearance
Mahmood Farshid, Ph.D., CBER, FDA

Heat Resistance Patterns of Different Hepatitis A Virus Clones during Pasteurization of Albumin
JoAnn Hotta, Ph.D., Bayer Corporation

Differences in Viral Inactivation of Three Serotypes of Influenza with Different Cleaning Agents
Joseph V. Hughes, Ph.D., AppTec Laboratory Services, LLC

Applicability of Bacteriophages as Surrogates for Mammalian Viruses in Filter Validation Studies
Hazel Aranha, Ph.D., Pall Corporation

10:30 a.m. - 12:00 p.m. — VIRUS ASSAYS: POINTS OF VIEW ABOUT NEW AND EXISTING TECHNOLOGIES, CONT. — *Haverford/ Baccarat*

Moderators: Rebecca Sheets, Ph.D., CBER, FDA
Yuan Xu, Ph.D., Genentech, Inc.

Viral Clearance Validation: Approaches Based on DNA Microarray Technology
Konstantin Chumakov, Ph.D., CBER, FDA

Validation Issues in Oligonucleotide Microarray Technology
Rolf E. Taffs, Ph.D., CBER, FDA

Evaluation of a Quantitative Product-Enhanced Reverse Transcriptase Assay to Monitor Retrovirus in mAb Cell-Culture
Kurt Brorson, Ph.D., CBER, FDA

12:00 p.m. – 1:00 p.m. — LUNCH — *Waterford/ Lalique*

1:00 p.m. - 2:30 p.m. — FILTRATION: TECHNOLOGY AND PERFORMANCE — *Haverford/ Baccarat*

Moderators: Paul Stinavage, Ph.D., CDER, FDA
Jerry Martin, Pall BioPharmaceuticals

Virus Validation of Filtration Procedures
Hannelore Willkommen, Ph.D., Paul-Ehrlich-Institut

Outstanding Performances of Planova™ Virus Removal Filters: Membrane Structure, Mechanism and Actual Performances
Hiroo Nakano, Ph.D., Asahi Kasei America, Inc.

Filtration for Viral Clearance: Performance Evaluation and Process Considerations
Hazel Aranha, Ph.D., Pall Corporation

Ensuring Predictable Viral Filter Capacity and LRV: Effects of Fluid Properties, Operating Conditions, and Membrane Quality
Marty Siwak, Ph.D., Millipore Corporation

Poster: ***(presented at previous evening's reception)***

Quantitative PCR as a Measure of Retrovirus Clearance by Multiple-Use Protein A Resins
Janice Brown, CDER, FDA

12:00 p.m. -1:00 p.m.	LUNCH	*Waterford/ Lalique*
1:00 p.m. - 2:30 p.m.	GENERIC APPROACHES TO VIRUS REMOVAL AND INACTIVATION *Moderators: Janice Brown, CDER, FDA* *Hannelore Willkommen, Ph.D., Paul-Ehrlich-Institut*	*Haverford/ Baccarat*
	Viral Clearance Design - Small Changes...Big Consequences? Jeri Ann Boose, Ph.D., BioReliance Corporation	
	Generic Validation of Virus Removal and Inactivation Yuan Xu, Ph.D., Genentech, Inc.	
	Factors Affecting the Kinetics of Xenotropic Murine Leufemia Virus Inactivation by Low pH: the Role of pH Range, Temperature, Protein Concentration and Product Amin Abujoub, Ph.D., Biogen Inc.	
	Generic Approaches to Virus Removal and Inactivation Karl Reindel, Protein Design Labs	
2:30 p.m. – 3:00 p.m.	BREAK	*Ballroom Foyer*
3:00 p.m. – 4:30 p.m.	IMPLEMENTATION AND FUTURE DIRECTIONS CLOSING PLENARY SESSION	*Haverford/ Baccarat*
	Kurt Brorson, Ph.D., CBER, FDA Richard V. Levy, Ph.D., Millipore Corporation	
4:30 p.m.	ADJOURN	