Introduction and Workshop Summary: Advanced Technologies for Virus Detection in the Evaluation of Biologicals—Applications and Challenges

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The November 2013 workshop was organized by the Parenteral Drug Association (PDA) and U.S. Food and Drug Administration (FDA) to provide an open scientific dialogue between industry and regulators based upon data presentations and discussions regarding considerations for the use of advanced virus detection technologies for the characterization of biological materials used in the production of vaccines and recombinant, therapeutic products. This was initiated by the Advanced Virus Detection Technologies Users group that was formed in October 2012 [Duncan, P. Summary of the Advanced Virus Detection Technologies Users Group Efforts - 2013. *PDA J. Pharm. Sci. Technol*, 2014, DOI: 10.5731/pdajpst.2014.01018] in response to the need for openness and sharing of non-proprietary information between technology users and to generate critical data for further regulatory applications [Khan, A. S.; Lubiniecki, A.; King, K. PDA/FDA Adventitious agents and novel cell substrates: Emerging technologies and new challenges. *PDA J. Pharm. Sci. Technol*, 2012, 66 (6), 502–511]. It was recognized that although there has been no known case of a human infection due to the presence of an adventitious virus in a biological product, adventitious agents have been detected in biological materials used in product manufacturing. Such reports emphasized the need for broad-spectrum and sensitive assays to detect adventitious viruses and other microbial agents in biological products. Advanced virus detection methods such as massively parallel or deep sequencing, broad range PCR with mass spectrometry, and virus microarrays have demonstrated success in identifying novel viruses in some research, biological, and clinical samples. However, there are a number of factors to consider for using these methods to characterize biological materials used in manufacturing. Approaches to address some of the critical issues related to sample processing and bioinformatics were presented in this meeting. Additionally, an expert panel including representatives from industry and regulatory agencies discussed the novel detection assays, their strengths and limitations, and how they can be used to enhance the characterization provided by conventional assays.

The meeting was opened by welcoming remarks from Arifa Khan, Center for Biologics Evaluation and Research (CBER), FDA.

Session 1 on the “Needs and Challenges for Using New Technologies” was moderated by Michael Wiebe (Quantum Consulting) and included presentations on regulatory and industry perspectives on use of the new technologies for virus detection. This session started with a presentation from Glyn Stacey (National Institute for Biological Standards and Control, Medicines and Health Care Products Regulatory Agency), who summarized the World Health Organization Cell Substrate Study Group meeting on current issues for cell substrates and DNA-based detection of adventitious agents using current and new methods, held May 2013 in Beijing, China (publication in progress); Phil Krause presented CBER, FDA perspective on the role of advanced technologies for virus detection in the development and regulatory of vaccines; and Laurent Mallet (Sanofi Pasteur) concluded the session with a presentation on the industry perspective for need of new technologies for detection of adventitious agents in vaccine and biotech products.

Session 2 was moderated by Mark Plavsic (Genzyme) and focused on “Performance Evaluation” of the current and new methods: Siemon Ng (Sanofi Pasteur) presented results from preliminary evaluation of next-generation sequencing performance relative to PCR and in vitro cell culture tests, and Jens Modrof (Baxter BioSciences) presented data from parallel evaluation of broad virus detection methods.

Session 3 continued talks on “Performance Evaluation” with focus on the technical considerations. This session was moderated by Kathryn King (CDER, FDA) and included presentations by Christopher Wang (Merck) on a sample preparation workflow for systematic evaluation of next-generation sequencing performance relative to PCR and in vitro cell culture tests, and Jens Modrof (Baxter BioSciences) presented data from parallel evaluation of broad virus detection methods.

Session 4 was moderated by Jean-Pol Cassart (GlaxoSmithKline) and included talks on “Development and Optimization of Data Analysis Pipelines”. John
Thompson (Merck) presented on an approach to a viral detection pipeline using existing imperfect viral and non-viral sequence resources, and Robert Charlebois (Sanofi Pasteur) presented on cataloguing the taxonomic origins of sequences from a heterogeneous sample using phylogenomics for adventitious agent detection.

On day 2, Session 5 focused on improving quality and standardization of viral and bacterial databases as a key component of bioinformatics pipelines. This session on “Bioinformatics and Databases” was moderated by Laurent Mallet (Sanofi) and included talks by Tom Slezak (Lawrence Livermore National Laboratory) on bacterial genome database efforts, and by Carolyn Wilson (CBER, FDA) on CBER efforts toward database standardization.

Session 6, on “Applications of New Analytical Technologies”, was moderated by Paul Duncan (Merck). Marc Eliot (Institut Pasteur and PathoQuest) presented on using high-throughput sequencing as a virus safety test for biotech products, and Paul Shabram (PaxVax) presented jointly with John Kolman (BioReliance) on evaluation of A549 as a new vaccine cell substrate using massively parallel sequencing.

Session 7 on “Novel Virus Discoveries and Detection” was moderated by Dominick Vacante (Janssen) and included a talk by Arifa Khan (CBER, FDA) describing her laboratory’s experience with the challenges of novel virus detection. Paul Duncan (Merck) presented a summary of the background, initiatives, and ongoing efforts of the Advanced Virus Detection Technologies Users Group.

At the end of the day, there was an expert panel discussion (Session 8) moderated by Arifa Khan (CBER). This panel included experts on the technologies and bioinformatics to discuss the potential implementation of the advanced virus detection methods in biologics. Discussions were based upon current knowledge and the identification of issues that remained to be addressed scientifically. The panel included J. Rodney Brister (National Center for Biotechnology Information, National Institutes of Health), Jean-Pol Cassart, Robert Charlebois, Kostantin Chumakov (CBER, FDA), Paul Duncan, Jens Modrof, and Tom Slezak.

The meeting concluded with a summary from Dominick Vacante (Janssen):

- Advanced virus detection technologies are currently used for investigations of potential contaminants and characterization of novel cell substrates.

In the near term, these methods could be used as supplemental to conventional methods.

- The methods may not be ready for Quality Control release or in-process control assays for unprocessed bulk testing due to additional need for improving the limit of detection (LOD) and for method validation. However, they may be considered for use as an additional endpoint assay to currently used assays.

Some ongoing challenges:

- Since technology platforms are evolving, there is a need for flexibility in data generation and formats, and a need to consider standards.

- Although, pipeline analysis works well, scalability may be an issue.

- Method standardization is needed.

- Confident reference databases are needed, including community efforts for curation, annotation, and maintenance for updating.

The need for continued efforts to address any regulatory challenges for applications of the new technologies for characterization of cell substrates and evaluation of biological products was recognized. Some current activities of the Advanced Virus Detection Technologies Users Group includes:

- A multicenter spike recovery study to evaluate detection limits and specificity of next generation sequencing platforms
- Generation of reference materials to determine effectiveness of test systems
  - Viruses and/or nucleic acids for spiking
  - Simulated data sets to evaluate pipeline analysis
- Complete virus database for obtaining confident results

This edition of the PDA Journal of Pharmaceutical Science and Technology contains papers based on the talks given in the meeting. We hope these will be useful for further discussions and decision-making regarding applications of the new virus detection technologies.

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