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Technical Bulletin

9CFR AVA Testing of Bovine Sera

SAFC Biosciences is regulated by the Food and Drug Administration (FDA) and must follow the practices and procedures outlined in the United States Pharmacopeia (USP). The USP designates how raw materials should be tested before they are used in the manufacture of finished products; however, it does not provide specific rules for adventitious viral agents (AVA) testing of products of animal origin, namely sera products.

Title 9 of the Code of Federal Regulations (9CFR) includes the standard sampling and testing requirements for animal sera used in the manufacture of biologics. SAFC Biosciences performs the entire battery of AVA tests listed in the 9CFR, Part 113, Section 53(c), on every lot of serum, where applicable.

Specifically for bovine sera, 9CFR, Part 113, Section 53(c), requires that 2 prescreened cell lines, Vero and a line of bovine origin, typically Madin-Darby Bovine Kidney (MDBK), be subcultured in the presence of test and control sera. After at least 2 subcultures over 21 days, the monolayers are examined for the presence of AVA by 3 industry-accepted methods: visualization of cytopathic effect (CPE), a hemadsorption assay (HA) and fluorescent antibody (FA) techniques.

CPE

Many viruses cause a noticeable change in the physical appearance of the cells they infect. The cells may become abnormally large, grainy, have inclusion bodies or may lyse altogether. These cytopathic effects, commonly called CPE, can be observed when viewing an infected cell monolayer under a microscope and are dependable indicators of the presence of AVA. A cytological stain is used to enhance the visual differences between cells with and without CPE.

HA

Some viruses do not cause a noticeable change in the cellular appearance, but can be identified by a hemadsorption assay (HA). Cell monolayers are washed and covered with a suspension of guinea pig and chicken red blood cells (RBCs). After an appropriate incubation period, uninfected cells will appear normal, while cells that contain hemadsorbing agents will take up the RBCs and appear dark.

FA

One of the most sensitive methods for detecting AVA is labeling with fluorescently tagged antibodies (FA). Antibodies against various viral agents are first tagged with a fluorescent marker. If the monolayers are infected, the antibodies will specifically adhere to the viral particles or infected cells and will glow under a microscope emitting ultraviolet light. The antibodies are easily washed off of uninfected cultures, which will not exhibit the same fluorescence under the UV light.

The combination of these 3 techniques provides a powerful tool that is used for the detection of the following adventitious viral agents:

- Bovine Viral Diarrhea (BVD) Virus
- Parainfluenza Type 3 (PI_3) Virus
- Bovine Parvovirus
- Rabies Virus
- Reovirus
- Infectious Bovine Rhinotracheitis (IBR) Virus
- Bovine Respiratory Syncytial Virus (BRSV)
- Blue Tongue Virus
- Bovine Adenovirus
- Vesicular Stomatitis Virus

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