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Gamma irradiation is routinely used by FBS companies to sterilize or clear FBS of potential contaminants, as requested by "end user" clients and as required by USDA and EU regulations. Currently, each serum company has its own irradiation procedures and standards, depending on client requests, yet this information is not published or shared throughout the industry. The standard irradiation dose for most US and EU customers is 25 kGy, but biopharmaceutical companies generally require a minimum of 30-35 kGy or higher. Some companies require that FBS bottles be packed on wet ice during irradiation, while others require the serum to be frozen on dry ice. There are also differences in the geometry of how boxes to be irradiated are positioned, as well as the number and placement of dosimeter verification devices. Some companies irradiate raw FBS before it is tested for BVD to avoid testing positive to BVD, while other companies prescreen individual jugs of FBS for BVD, making sure the entire lot is negative to BVD before irradiation for the other potential adventitious viruses. The lack of standardization of these procedures for the irradiation of FBS, often leads to doubt, mistrust, and in some cases, deceptive practices within the industry.

We believe that standardized irradiation guidelines need to be developed, validated, and published for inactivating potential virus contaminants of animal sera, just as validated guidelines have been developed and published for eliminating pathogens in human tissues and implants, and for microbial contaminants in meat products and for plant pests for fruits and vegetables.
The 9 CFR 113.46-53 requires that potential contaminants in the serum be inactivated by heat sterilization or other sterilization methods acceptable to the USDA (APHIS), or that the serum tests negative for each specific pathogen of concern. Since heat sterilization destroys many growth factors of FBS, irradiation is widely used to inactivate pathogens of concern, especially the BVD virus, which is always present in non-irradiated and non-prescreened lots of raw pooled FBS. Most biopharmaceutical companies want raw FBS to test negative for BVD before it is irradiated, as required by the EU regulation (EMEA-CPMP-BWP-1793-02). However, to avoid problems, some FBS companies irradiate raw FBS prior to testing for BVD, without disclosing this information to the biopharmaceutical company, and choose tests for BVD that do not detect the presence of inactivated virus or that are less sensitive. Again, the lack of standardized procedures for the irradiation of FBS and for testing for BVD sometimes leads to deceptive practices within the industry.

During the last 25 years, a tremendous amount of published and unpublished work has been done on virus inactivation in human and animal tissues by gamma irradiation. Today, producers of FBS and biopharmaceuticals are not only concerned about proper doses of irradiation needed to inactivate the viruses listed in 9 CFR 113.46-53, and 9 CFR 94 regulations, but are also concerned about doses high enough to inactivate other smallest-sized viruses (not mentioned in the 9 CFR 113), without adversely affecting the quality of the serum.

We believe that transparent and verifiable standards should be developed jointly by a "FBS Irradiation Working Group", made up of interested FBS companies, biopharmaceutical companies, and experts from academia and regulatory agencies like the USDA and FDA. The purpose of the Working Group would be to share irradiation procedures and research relating to:

- Irradiation doses and protocols.
- Standards for irradiation facilities.
- Preservation of serum quality.
- Testing and inactivation protocols for BVD and other viruses of concern, including the small-sized viruses and other viruses not mentioned in 9 CFR 113.

We believe that the harmonization of irradiation standards and guidelines must start within the industry itself and include the input and participation of government regulators and academia. Having such standards in place for raw and for finished FBS will result in a much-needed positive transparency and perception of the FBS industry as a whole, and at the same time, an increased assurance in the safety of FBS products in general.

REFERENCES
1. USDA 9 CFR 113.46-53
2. EMEA-CPMP-BWP-1793-02
7. Circoviridae, Parvoviridae, Picornaviridae, and Polyomaviridae

NOTE
This position paper was written with input from: GE Life Sciences (HyClone Laboratories), SAFC (Sigma Alrich), and Biowest.

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