

# A Risk-Based Approach to Establishing Animal-Component-Free Facilities

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**B**ovine spongiform encephalopathy (BSE) and its potential to affect humans emerged as a concern in the 1990s. So suppliers of many essential animal-sourced components used in cell culture and fermentation processes became concerned about the potential for material contamination with prions. Viruses also can be present in raw materials derived from animal origins. Many important drug and vaccine products are made by mammalian cell culture or bacterial fermentation, so their biological safety is paramount. However, it is very difficult to ensure that any material from an animal source carries no infection. Even the rigorous cleaning methods designed to minimize carry-over of biohazards from one batch to the next is no guarantee of safety.

Because it's difficult to identify and purify components made from animal sources, the safest way to minimize risks from associated pathogens is to, whenever possible, use raw materials of nonanimal origin. However, eliminating animal-sourced products from a manufacturing facility requires that all its suppliers provide animal-component-free (ACF) products — and that all those suppliers' suppliers do too. Even if one company uses no animal components itself, a danger remains of possible contaminant carryover from the processing steps of its suppliers.

**PRODUCT FOCUS:** ALL BIOLOGICS

**PROCESS FOCUS:** UPSTREAM AND DOWNSTREAM (MANUFACTURING)

**WHO SHOULD READ:** QA/QC, FACILITY DESIGN/ENGINEERING AND MANAGEMENT, OPERATIONS, AND MANUFACTURING PERSONNEL

**KEYWORDS:** ANIMAL-FREE, TSEs, VIRAL SAFETY, VALIDATION

**LEVEL:** BASIC

## REGULATORY GUIDELINES

The EMEA guidance document for minimizing the risk of transmitting transmissible spongiform encephalopathy (TSE) agents states that great care must be taken when using materials sourced from TSE-susceptible animals (e.g., cattle, sheep, and goats) to ensure that such materials are fit for use (1). All possible measures should be taken to minimize the risk of transmission. Ideally, manufacturers should use either materials of nonanimal origin or those derived from animals that are not susceptible to TSEs (1).

SAFC Biosciences defines animal-component-free products as those manufactured from raw materials that are free of animal components at both the primary and secondary levels. The primary level includes the finished raw material itself and the manufacturing process that produces it. No ACF raw material is directly derived from animal tissues, nor are any animal components used in processes used to manufacture such materials. The secondary raw materials level includes starting material(s) used to manufacture a primary raw material. The tertiary raw material level would include starting material(s) and manufacturing process(es) used to generate those secondary raw materials. A raw material can have animal-derived materials at the tertiary level if they are classified as very low risk: category IV as defined by the European Medicines Evaluation Agency, category C as defined by the World Health Organization (1, 2).

Many raw materials used in cell culture are neither regulated nor licensed by government agencies. The suppliers of these raw materials have no regulatory requirements to provide materials free of such contaminants. But they have to meet strict standards set by the biopharmaceutical companies that use them. Although the raw materials



The SAFC Biosciences ACF powder media production facility in Lenexa, KS, has controls established to monitor production processes, material flows, and personnel traffic throughout all processes, to ensure that facility integrity is maintained.

themselves may not be regulated, the authorities do require biomanufacturers to manage their suppliers and ensure that all raw materials they use in their processes are fit for their intended use. All sourced ingredients have to meet a company's own quality standards and be consistent from lot to lot.

Likewise, no regulatory requirements are specified for raw materials to be declared ACF by a supplier, but industry best practices require that such raw materials — and the processes in which they are used — are free from materials either derived from or processed using materials of animal origin wherever possible. Consistency of supply and batch quality reassure customers that TSEs and viruses will not be introduced into their facilities and processes.

## STEP BY STEP

The first step to creating an ACF facility — whether designing it from scratch or converting an existing plant — is to assess its overall TSE risk. The procedure begins by identifying the critical points at which TSE material might be introduced into a

manufacturing process. Then controls are established to ensure that facility integrity is maintained. These include

- Sourcing of raw materials and starting materials
- Thoroughly researching the raw material supply chain
- Controlling receipt of all raw materials and processing aids
- Controlling the manufacturing process
- Controlling material flows throughout all processes
- Identifying appropriate personnel flows.

**Quality Systems:** A well thought-out quality system is vital. An effective system will provide measures to assess and monitor the entire supply chain, including receipt and confirmation of raw materials. It will also monitor all production processes and ensure proper batch delineation: from defining what constitutes a lot to the separating different lots and the cleaning processes that must be carried out between them. Without an effective quality system in place, breaches in an ACF system are inevitable.

Perhaps the most important part of the process is ensuring traceability of raw material right through to the finished product, with provisions made for self auditing and assessing critical suppliers. SAFC Biosciences relies on its suppliers to provide all necessary material-origin documentation and also notification if they make any substantive changes to their products or processes. A controlled and completely transparent raw material supply chain is essential if a truly ACF operation is to be established and maintained.

In addition to evaluating risks proactively, it is also important to identify potential gaps in the existing quality system. This is best achieved by forming a cross-functional team that includes members from quality, production, engineering, supply chain, and technical departments. These team members work together to pinpoint and then rectify gaps in the system through a paper-based gap analysis. They first determine all the different elements of a process as well as

associated material flows, then look for points where the system could get out of control. SAFC Biosciences has developed a check list of important areas that are necessary to address in establishing ACF production at other sites. The “Checklist” box shows it in an abbreviated form.

Once risk analysis has taken place, the next step is to introduce necessary engineering design/controls, develop appropriate operating procedures, and then carry out a comprehensive decontamination process to ensure that a facility is free from TSEs and viruses at the outset. All raw materials must have the necessary ACF documentation from their suppliers before they are allowed into the facility. In addition, a one-way material flow process will allow material to move from ACF areas to non-ACF areas to allow for flexibility in the management of inventory while ensuring that material cannot move back in the other direction, which would put the ACF facility at risk. Similarly, personnel movement and gowning procedures must be implemented to ensure no possibility of cross-contamination.

**Validation:** Usually, no validation studies are required on procedures for removal/inactivation of TSEs. The EMEA guidance document recognizes that the nature of these studies makes them difficult to construct and interpret. Introducing a prion into a production facility to test its cleaning procedures is an unnecessary risk. Scaled-down cleaning procedure test models are well documented in the referenced literature. Because of the nature and risk posed by prions, more research is needed to establish a better method for carrying out future validation studies.

SAFC Biosciences worked with a technical consulting service — Cleaning Validation Technologies of Kodak, TN ([www.cleaningvalidation.com](http://www.cleaningvalidation.com)) — to develop a decontamination process for use in all equipment and facilities that are being converted for ACF manufacturing. To qualify for ACF decontamination, equipment cannot have been previously exposed to high-risk raw materials. Two

separate cleaning methods were used one after the other, both having been demonstrated as effective at decontamination. The first cleaning process uses CIP 100 cleaner, an alkaline agent based on potassium hydroxide from Steris Corporation ([www.steris.com](http://www.steris.com)), and the second uses CIP 150 cleaner, another alkaline cleaning agent from the same company (this one containing sodium hypochlorite). Concentrations and conditions for both are based on data from their manufacturer, which proves their effectiveness in decontaminating both prions and viruses.

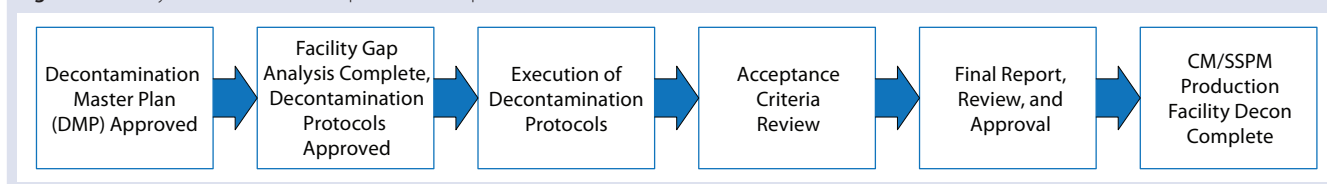
## CHALLENGES AHEAD

Only when all that cleaning, raw material documentation, and process evaluation are complete can a facility be declared animal component free. Only ACF components may then be used in such a facility. Alternatively, nonanimal-sourced equivalents may have to be sourced, or replacement raw materials may need to be developed for use in ACF facilities. Some animal-derived materials for cell culture processes are more difficult to replace than others. Multiple modifications may need to be made to a cell culture medium formulation to make it entirely animal component free but still perform as well as a traditional medium.

In particular, finding a substitute lipid source for a cell culture medium can be very difficult. One traditional lipid source is a fatty acid methyl ester (FAME) synthesized by the transmethylation of cod-liver oil. Creating an animal-free FAME alternative with the same fatty-acid profile is neither simple nor inexpensive, but we used experimental analysis to determine which of its lipid components are critical in the cell culture. By replacing those lipids derived from cod-liver oil with a defined set from various nonanimal sources, an ACF culture medium can be created. Our company now uses that defined set of lipid sources in a number of cell culture products.

**With Supplier Help:** Once a facility has been declared animal component

**Figure 1:** Facility decontamination implementation plan



free, it is important to ensure that it stays that way — and that it can be proven. The supplier quality assurance and supply chain management departments must work alongside suppliers to ensure that only ACF raw materials are used. Quality, not price alone, is of paramount importance in supplier selection.

SAFC Biosciences carries out both on-site and paper-based quality audits of its suppliers to ensure that they are aware of the company's requirements. Working alongside suppliers in this way is more effective than merely giving them a set of quality standards that they are expected to meet. Change-notification agreements are an important tool to inform a manufacturer of alterations in process or quality that have been made by its suppliers. In some cases, we also use formalized quality agreements that list expected quality parameters and agreed-on responsibilities. To ensure that the whole system works, a verification process is an important part of the company's raw material delivery and acceptance procedures.

Minimizing the risk of introducing prions and viruses into a manufacturing process relies heavily on the willingness of suppliers to be transparent about their own processes and supply chains — and to provide accurate information. Once the risk has been assessed, an appropriate process to minimize that risk can be developed. Risk can be measured in terms of potential impacts on product quality and end-user safety. Risk is inherent and unavoidable in all processes, and the role of quality assurance is to establish effective systems that manage and mitigate it in an appropriate manner.

SAFC Biosciences believes that the demand for ACF media will grow 12–15% per year in the foreseeable future. The cost and requirement for revalidation and relicensing if manufacturing processes for existing products are changed are barriers to changing the formulations of biologics that are already on the market. But whenever possible, new products are likely to be made by processes that require ACF raw materials. As a result, the importance of ACF cell culture media will increase in coming years. Only by setting out formal quality standards and procedures for ACF manufacturing — and through careful adherence to them — can this demand be met.

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