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# Animal-Derived Agents in Disposable Systems

## Growing Concern Over the Use of ADCs in Polymeric Materials

Polymeric materials have been widely used in bioprocessing for more than a decade. Disposable processing products manufactured from plastic materials include flexible tubing, sanitary fittings, cylindrical tanks, carboys, powder-handling bags, capsule filters, and flexible film-based containers used for storage and mixing of process fluids. Polyethylene (PE) and polypropylene (PP) are the most common polymers employed for surfaces that come into direct contact with solid or liquid process materials.

Although polymers are manufactured from petroleum feedstock, plastics manufacturers often use additives of animal origin to improve material properties and/or to aid in processing of raw polymers.

The principal animal-derived components (ADC) used today are various salts of stearic acid, a long-chain (C18) fatty acid. Derived from the rendering of beef fat (tallow), stearates comprise approximately 100200 ppm in typical raw polyethylene. When added to polymer formulations, calcium and aluminum stearate salts (among others) impart lubricity, preventing the polymer from sticking to metal surfaces during extrusion or mold release. These additives are often referred to as "slip" agents.

In addition to lubrication, stearates bind to and inactivate trace polymerization catalysts remaining in the polymer blend. Stearates applied directly to molds and extruders provide lubricity. Stearate additives have become part of the culture of polymer processing because they are inexpensive and work well.

### Concern Over Prion Diseases

Recent outbreaks of bovine spongiform encephalopathy (BSE; "mad cow disease") and related human spongiform illnesses, generically known as transmissible spongiform encephalopathies (TSEs), have raised concern over the safety of ADCs. The trend toward serum-free media is largely due to concerns over TSEs. This group of diseases includes BSE, scrapie (which affects sheep), chronic wasting disease (deer and elk), and Creutzfeld-Jakob disease (CJD; humans).

Cases of BSE have been sporadic, with the majority limited to Great Britain and Northern Ireland. Significant isolated outbreaks have arisen in other European countries. In North America, five cases of BSE were confirmed between 2002 and 2004. Although the number of animals affected has been in the hundreds of thousands (98% from the U.K.), fewer than 150 cases of the human form of BSE, CJD, have been confirmed worldwide between 1995 and 2002.

BSE and CJD are caused by a prion, an infectious, abnormally shaped, self-replicating protein that is much smaller than viruses or bacteria. CJD is believed to arise from ingestion of tissues, primarily nerve and brain, from infected animals.

Despite a mostly successful effort at eradicating BSE in food animals and the small number of human cases of CJD worldwide, bioprocessors have expressed concern over the use of ADCs in the manufacture and processing of polymeric materials that come into direct contact with bioprocess fluids.

Their apprehension is due to the small size and difficulty in detecting prions, and the fact that most biotech products are injected. Safety standards for injectible drugs are significantly higher than for ingested therapeutics due to the potential for direct infection.

Recently, bioprocessors have developed orthogonal infectious agent removal and inactivation schemes, as add-ons to normal viral clearance, which purportedly remove prions. However, a growing number of biotech experts believe that the unpredictability of BSE/CJD outbreaks, and the seriousness of the human form of prion disease (100% fatal), represent an unnecessary risk.

In response to this perceived risk, many bioprocessors now request fluid-handling products that are free of materials of animal origin. Animal-free materials eliminate unnecessary risk as well as the need to trace materials of construction back to raw materials.

Interest in animal-derived product-free polymers is strongest in Europe, where BSE has been in the news for more than a decade. However, there has been a discernible increase in attention to ADC status from North American and Asian bioprocessors as well.

Increasingly, bioprocessors are asking suppliers to document that construction materials are either ADC-free or, if they employ stearates from animal sources, that the additives were prepared in accordance with standards that guarantee inactivation of any and all infectious agents, including prions.

Since they operate in the epicenter of BSE incidence, regulators in the European Union have a keen interest in the causes and prevention of TSEs. In 2004, the Official Journal of the European Union published a guidance on minimizing risk of transmitting animal spongiform encephalopathy agents through veterinary medicinal products. This document states:

"Tallow derivatives, such as glycerol and fatty acids, manufactured from tallow by rigorous processes, are thought unlikely to be infectioussuch materials manufactured under the conditions at least as rigorous as those given below shall be considered in compliance for this note for guidancetrans-esterification or hydrolysis at not less than 200C for not less than 20 minutes under pressure (glycerol, fatty acids, and fatty acid esters production)"

Generally, processes used to manufacture tallow-based derivatives exceed these specifications.

Increasingly, polymer manufacturers will document that their stearate additives meet or exceed EU standards for tallow-based products. Moreover, many suppliers source stearate additives exclusively from North American sources, which greatly reduces prion contamination risk.

Normally this would be enough to assure biopharmaceutical manufacturers that product-contact surface areas in disposable plastic components pose no risk. However, despite the FDA's recent emphasis on risk-based and science-based manufacturing, biotech remains a highly risk-averse industry. As a result, interest in ADC-free polymers is growing.

### Staying Ahead of the Curve

Biotech's awareness of ADC additives in polymer processing is reminiscent of the industry's concern over leachables and extractables a decade ago, when disposable polymeric process products were just gaining market acceptance.

Interest in leachables/extractables began as a scientific curiosity but eventually grew into a set of regulations and practices, which today are generally recognized as prudent measures for protecting public health. Today, suppliers of plastic disposable components use only materials for which adherence to regulatory standards for leachables/extractables can readily be demonstrated.

Similarly, if concern over ADCs and prion diseases persists and grows, a product or material's ADC status may become an issue for biotechnology. It is not inconceivable that, at some point in the future, standards for ADCs formulated into product surface areas will evolve from today's acceptance of components that were processed according to reasonable standards, to zero tolerance.

Although substitutes for ADC-based polymer additives are not difficult to find, plastics containing these replacement additives are uncommon. Silicone oils can serve as lubricating agents, as can stearates

derived from nonbovine animals, or even nonstearate-based plant-based long-chain fatty acids and waxes. In some situations polymer processors can eliminate slip agents altogether.

The major issue is sourcing and supply. Polymer resins are the prototypic commodity product. About 60 million tons of polyethylene are produced worldwide each year, according to a study by petroleum giant BP. Even specialty or niche PE markets have become commoditized, to the point where suspending production to switch to a new additive involves significant expense.

This added cost is probably not an issue for users motivated to use ADC-free materials. However, the issue is not so much cost as availability, which depends on market forces, principally polymer processors' perception of the value in continuing to produce and sell ADC-free base materials. Today, few PE or PP manufacturers offer ADC-free raw materials; this is unlikely to change soon.

In our experience, most bioprocessors prefer ACD-free materials. While the majority are satisfiedfor nowsimply to be apprised of a material's ADC status, some have already decided to source products produced from ADC-free polymers exclusively.

At the very least, bioprocessors' concerns have increased and the burden is on suppliers of plastic process equipment to demonstrate ADC status for all relevant ingredients.

From the perspective of plastic fabricators and vendors like TC Tech (Maple Plain, MN), establishing and certifying ADC-free status is preferable to demonstrating to each customer, through an exhaustive supply chain analysis, that animal-based ingredients were processed according to reasonable, accepted prion inactivation standards.

To this end, TC Tech has established a line of disposable fluid handling products that are certified to be free of materials of animal origin (Figures 1 and 2). In all cases, certified products carry written documentation from the raw material supplier and the molder/extruder stating that materials and production processes are free of animal-derived agents.

### ADC-Free Material

At some point, if worldwide regulatory bodies adopt stricter controls over ADC-derived materials, manufacturers may be required to demonstrate ADC-free status. Or, in the absence of formal guidance, biotech firms may decide simply to switch to ADC-free materials as a prudent measure to reduce risk, validation, and paperwork.

As biotechnology adopts more disposable polyethylene and polypropylene products, there will be a growing need to source single-use containers, tubing, valves, and other equipment from vendors who have been ahead of the curve with respect to the ADC issue.

As with leachables/extractables, where FDA does not outright prohibit new materials, the burden will be on bioprocessors to demonstrate that their processes "do no harm." In our experience, a straightforward certification that components are ADC-free is simpler to achieve than re-inventing the proverbial wheel for each material.