ADVANCES IN DISPOSABLE DIATOMITE FILTER AID SYSTEMS FOR CGMP BIOSEPARATIONS

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Tom Sulpizio and Jeff Taniguchi, Advanced Minerals Corporation
A Member of Imerys
130 Castilian Way, Santa Barbara, CA 93117

ABSTRACT

Filter aid and associated filter media are well suited to address the growing need for robust, disposable separation technology in current Good Manufacturing Practices (cGMP) bioseparations. These products must meet these requirements:

- Low and well characterized extractables;
- Auditable production facilities operating under full ISO or near GMP conditions for pharmaceutical raw materials or components;
- Process containment of powdered materials;
- Disposable components utilizing permanent hardware with minimal cleaning validation.

Advanced Minerals pharmaceutical filter aid products (Celpure® USP-NF grades and Acid Washed Celite® NF grades) and the companion filter media and hardware meet these requirements.

INTRODUCTION

The growing trend in bio-processing is increased cell culture efficiency through better cell lines with greater titer and cell density. This makes first stage clarification increasingly difficult with existing solid/liquid separation equipment or techniques. Many pilot and small scale production sites are constrained by the lack of expensive, sophisticated equipment and the physical space to process these more advanced cell culture broths. The result is unexpected capital equipment costs, the need for greater processing space in a GMP or clean room suite, and potential for product recover losses (1).

An equally growing trend is the use of disposable or single-use processing components in biopharmaceutical drug development and manufacturing. There are numerous recent bioprocess journal reviews of this trend and various solutions

for therapeutic protein, vaccine and monoclonal antibody process systems with disposable unit operations (2, 3, 4, 5).

There are two disposable technologies which will help to improve the industry cost effectiveness. Those are depth filter media and diatomite filter aids which can be used as the body feed[a] in combination with the lenticular depth filter modules. While lenticular filter modules are well established in downstream processing and purification, the use of filter aids is not as widespread.

There are several groups in a cGMP biopharmaceutical or biotech company which must approve any solid/liquid separation technology.

Process development – Concerned with the function of the solid/liquid separation technology.
Manufacturing – Concerned with the cost and adaptability of the solid/liquid separation technology and its impact on the production suite.
Quality and regulatory affairs – Concerned with the suitability of the solid/liquid technology to meet the GMP standards of the pharmaceutical company.

The overwhelming efficacy of filter aid in various types of cell culture systems has been demonstrated (6). The main reasons recited for not adopting this technology more universally in GMP bioseparations are powder handling, inappropriate quality of the process aid, and perceived limitations in hardware to handle the process aid. Advanced Minerals, working with several filter media manufacturers and hardware consolidators, has addressed and overcome those limitations with a unique range of filter aids, depth media, and integrated hardware solutions.

ADVANCES IN FILTER AID TECHNOLOGY

Advanced Minerals has presented papers at the AFSS annual meetings in 1999 and 2001 to introduce a new range of diatomite filter aids suitable for use in cGMP pharmaceutical manufacturing (7,8). Conventional filter aids available today are produced in huge mineral processing plants and are Food Chemicals Codex standards or lower in quality, which is perfectly suitable for many large industrial or food industry users. Process aids used in the production of pharmaceuticals must meet the standards of raw materials for cGMP processes, as defined in 21CFR211.84(d)(2), and ICH Q7A (GMP for Active Pharmaceutical Ingredient, 2001), which requires that the impurity profiles of process additives be well characterized and implying that if a compendium standard exist for the process aid, then that quality should be employed. There is a U.S. Pharmacopoeia (USP) National Formulary (NF) compendium for Purified Siliceous Earth. Products used

[a] Definition: Body Feed is filter aid suspended in the feedstock during filtration.

in the biopharmaceutical industry must meet the manufacturing standards and specifications of this monograph at the very least.

Pharmaceutical grade filter aids are available which meet these requirements and more. They are Acid Washed Celite® NF products and Celpure® NF filter aid products from Advanced Minerals. There are typically seven specifications controls for purity and extractables measurement with these cGMP suitable products. Most heavy metals have a limit of 10 mg/kg or lower in the finished product. These purity specifications include:

Iron
Aluminum
Arsenic
Lead
Conductivity and pH
Total acid soluble substances
Total water soluble substances

It is not enough to characterize and control the impurities in a process aid. The USP preamble specifies that for a process additive to be considered UPS-NF quality, it must be made in a facility which is operated under full ISO and near-GMP conditions and is properly registered with the U.S. Food and Drug Administration (FDA). Long distance or on-site audits by pharmaceutical company end-users should establish the specific quality and cGMP requirements which each company establishes. It is simply not acceptable anymore to evoke precedent as the basis for using lower quality filter aids in a cGMP process licensed by the U.S. FDA, the EU's Medicines Evaluation Agency (EMEA), or other competent health agencies or authorities.

PROCESS CONTAINMENT

The availability of suitable quality filter aids solves a huge limitation in the past and addresses the needs of QA and regulatory affairs, but it is not enough to address the needs of manufacturing in a cGMP or clean room suite. The normal packaging for USP-NF filter aids must eliminate paper packaging and use polyethylene containers, but also must eliminate any dust or worker exposure to the powder. This same restriction applies to powdered salts and buffers used in pharmaceutical processes.

A) Set Up

The use of disposable polyethylene transfer containers from several manufacturers offers the desired containment. The charge of a 25-liter process container is 4 kg

of filter aid (depending on the loose weight of the powder) which is filled in the filter aid manufacturing plant. That powder is then transferred via a 8-cm opening and using clamp fittings to a larger disposable polyethylene container (typically 150 or 200 liters) in which water, buffer, or the actual broth is in place with agitation. The proper set up must be according to the biopharmaceutical company standard operating procedures (SOP) and cGMP guidelines. The attached process diagram shows a disposal body feed (DBF) system as developed by ManCel Associates (1). Their process uses a disposable reciprocating mixing system. Other processes use constant recirculation to maintain the filter aid in suspension.

B) Filtration Hardware

The heart of the system is the lenticular depth filter modules in a stack which allow for the accumulation of the body feed solids. The modules and flexible tubing are disposable, but the housings are stainless steel which can be reused if desired. The concept of body feed over filter sheets is one which has been presented previously (8, 9).

There are producers of advanced filter media using the pharmaceutical quality filter aid ingredient from Advanced Minerals.

C) Demonstration

This disposal system has been recently demonstrated in two full GMP production trials.

1) Mammalian cell culture clarification
2) Diagnostic serum processing.

These trials eliminated the use of a centrifuge and demonstrated that the number of filtration steps could be reduced by 50%, resulting in cutting processing time and the use of thousands of liters of high purity water and buffers for rinsing and cleaning.

Cell culture example:

- 25 kg of Celpure P1000 added to 150 liter of cell culture buffer (16.7% slurry) in a disposable diatomite mixing container.
- The addition of typically 10 to 50 grams per liter of Celpure P1000 directly to the cell culture broth.
- Solids collected on a lenticular cartridge stack.
- Rinsing of cake is an option as is nitrogen to evacuate the cake of the target protein.

CONCLUSIONS

The use of body feeding of filter aid over filter media modules is a concept which fits perfectly with the trend to the use of disposables in bioprocessing. Diatomite filter aids suitable for cGMP pharmaceutical processing are available. The development of powder handling containment options solves one remaining obstacles and clears the way for greater use of this versatile and robust solid/liquid separation technology.

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