



WORLD
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Advances in Disposable Diatomite Filter Aid Systems for cGMP Bioseparations

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Session – Pretreatment in Bioseparations

AFSS Annual Meeting

Valley Forge, Pennsylvania

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Presentation Outline

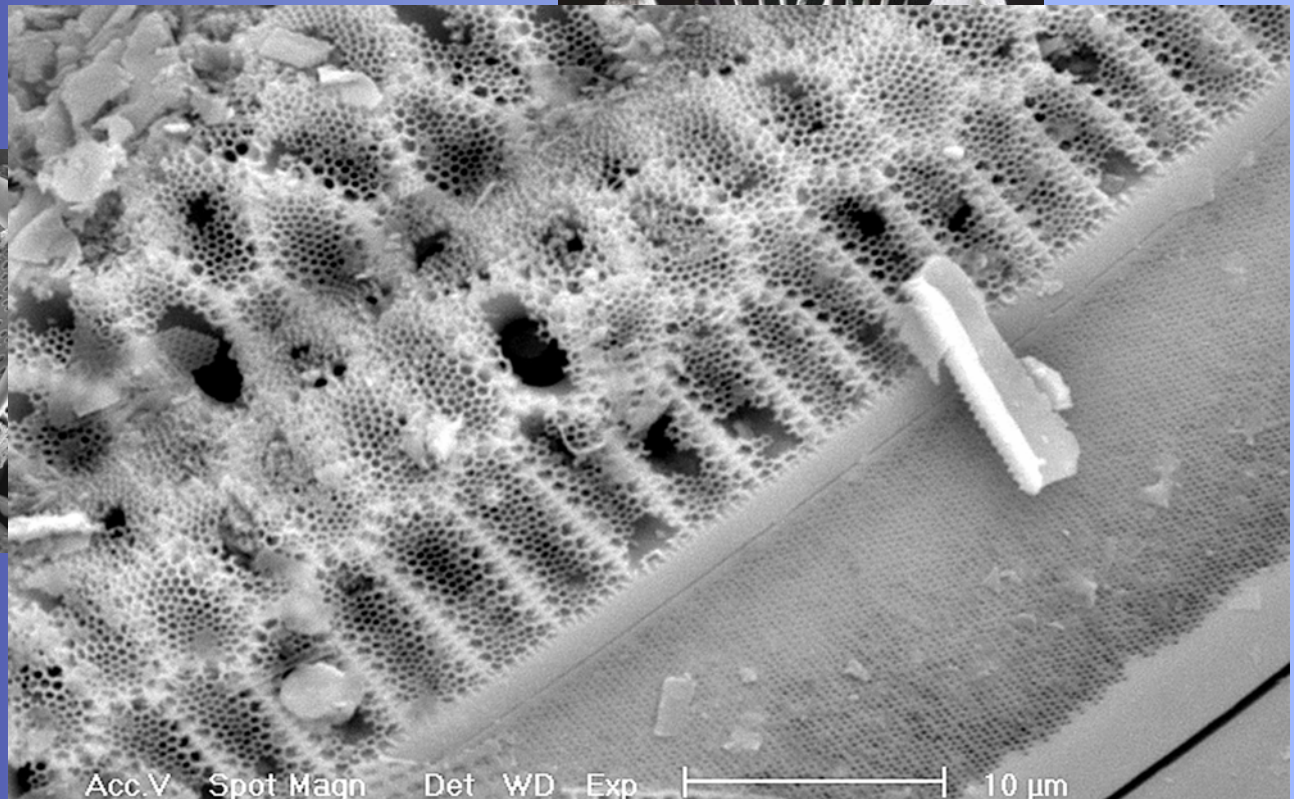
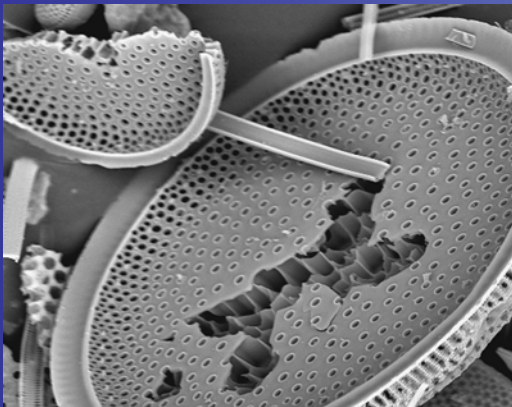
- Introduction to filter aid and cGMP concepts
- Requirements of filter aid in cGMP bioseparations
- High purity USP-NF filter aid
- Disposable body feed components and system
- Proof of principal trial of system

Diatomite Filter Aids for Non-GMP Bioprocess Clarification

- > Well demonstrated and extremely robust for nearly any biological solid/liquid separation challenge
- > Readily available food grade products
- > Extremely low cost compared to other solid-liquid separations technologies

Brief Definition of Diatomite (DE) Filter Aids

Fossilized silica remains of
marine plankton



What is Current Good Manufacturing Practices (cGMP)?

Briefly...

Quality management and manufacturing system defined by 21CFR211 and administered by the US FDA and international equivalent agencies.

There are numerous guidance documents and opinions which define the “current” part of cGMP.

Levels of GMP as it relates to raw materials and process components

Function → Application ↓	Active Ingredient	Key Constituent	Inert or Excipient
Sterile Pharma	4 (Highest Level)	4	3
Non Sterile Pharma	4	3	2
Cosmetics Health Aids Dental	2	2	1 (Lowest)

Challenges to the Use of Diatomite Filter Aid and Body Feed in cGMP Bioseparations

- > Inappropriate quality of products available
- > Powder handling
- > Limitations in hardware to handle the technology

cGMP Bioseparations – Applications for Body Feed or Filter Aid over Filter Media

Solids →	< 10 g/L (1%)	10 – 50 g/L (1 – 5%)	> 50 g/L (> 5%)
Scale ↓			
Lab: 1 – 10 L	Polishing of mammalian or pichia supernatant	Microbial: supernatant	Microbial: extracellular expression
Pilot: 10–100L	Polishing of phytopharma	Mammalian or pichia: whole cell broth filtration	Cell debris after lysis
Production: 100 – 10,000L		Phytopharma: supernatant	Phytopharma: filtration of bulk extracts

Requirements of Diatomite Filter Aid and Filter Media for cGMP Bioseparations

- > **Low and well characterized extractables**
- > **Auditable filter aid production facility**
 - > **Near-GMP conditions for raw materials**
- > Process containment of powder
- > Disposable components

High Purity Filter Aids for cGMP

- > US Pharmacopoeia – National Formulary (NF) defines standards for pharmaceutical compendium “Purified Siliceous Earth”
- > Must be produced under full ISO and preferably near-GMP conditions.
- > Acid Washed Celite[®] NF and Celpure[®] NF products meet these criteria.
- > Fully characterized impurity profiles and release specifications based on purity metrics and frequently conducted.
 - > As, Pb, Fe, Al (each <10 mg/kg)
 - > Total acid and water solubles
 - > pH and conductivity

Requirements of Diatomite Filter Aid and Filter Media for cGMP Bioseparations

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- > **Process containment of powder**
- > **Disposable components**

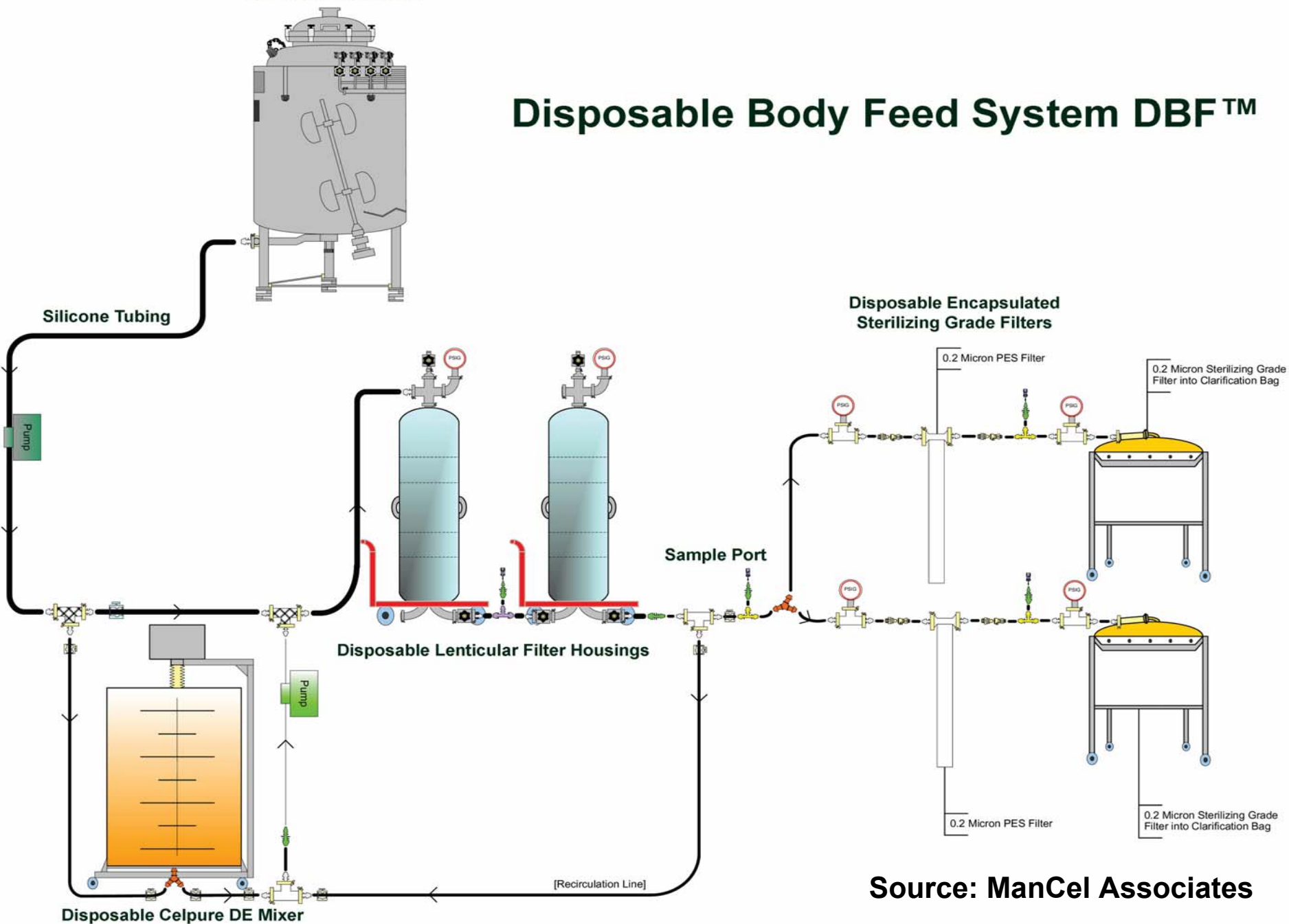
Process Transfer Device

- > 25-liter polyethylene Hyclone “Transfer-tainer”
- > 4 kg of Celpure NF Diatomite



50-5000 Liter Reactor

Disposable Body Feed System DBF™

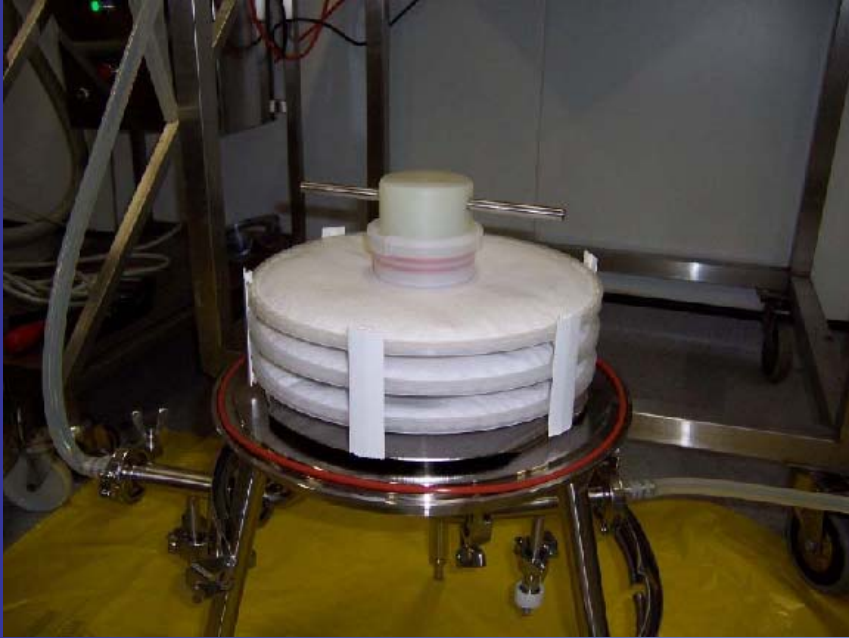


Source: ManCel Associates

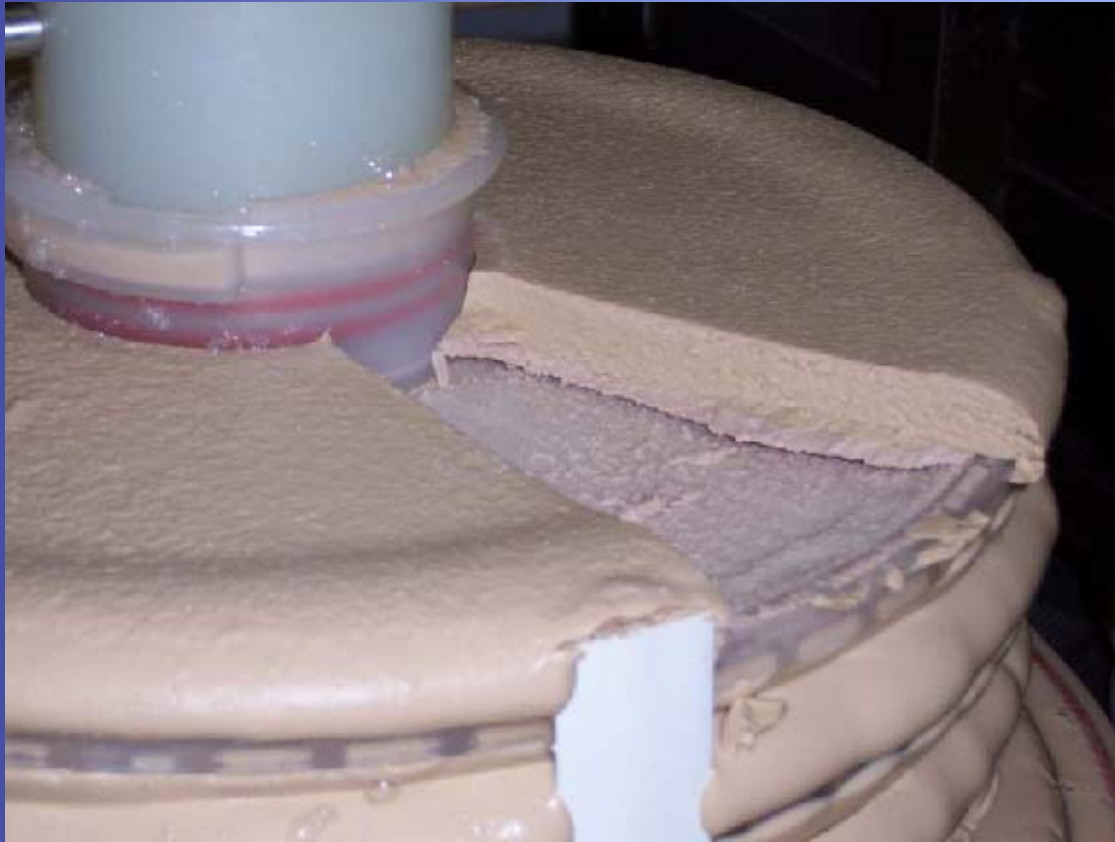
Bioprocess Container Plus Reciprocating Mixer



Lenticular Filter Media Showing Body Feed Spacing and Housing Hardware



Lenticular Filter Media Showing Cake Solids after Filtration





Proof of Principal Trial Using the DBF™ System from ManCel Associates

Cell culture expression system

- > 17% slurry of Celpure P1000 (NF) in cell culture broth in disposable mixing container.
- > Body feed over Celpure-based advanced filter media (disposable).
- > Final addition amount ranged from 10 to 50 g/L (1 – 5 wt %).
- > Incumbent solid/liquid separation technology – centrifuge.

Results

- > Cut filtration time by 50%.
- > Filter aid increased V_{max} of filter media without body feed by >10X.
- > Greater yield of target therapeutic protein.

Conclusions

- > **Diatomite filter aid – Well demonstrated and robust in bioseparations.**
- > **Limitations of previously available products and systems constrained widespread use in cGMP bioprocessing.**
- > **Advanced filter aids made in auditable, near-GMP production facility now available.**
- > **Viable, disposable powder handling and hardware system now demonstrated to enable greater use of this versatile solid/liquid separation technology.**

ACKNOWLEDGEMENTS

Special thanks to ManCel Associates for their work on the Disposable Body Feed (DBF™) hardware configuration and their permission to use their flow diagram and photos.

Thanks also to Carl Stuart Ltd. for the use of their photos of lenticular modules.

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