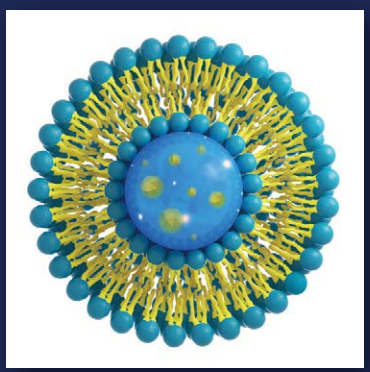
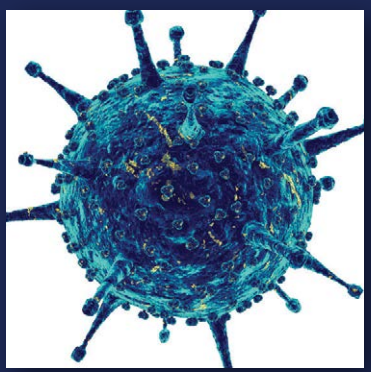
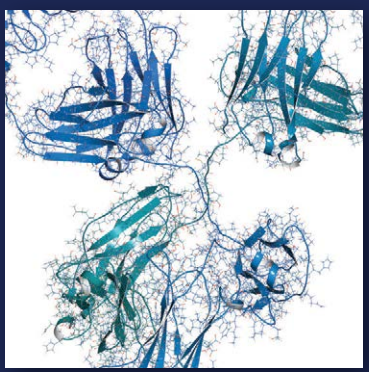
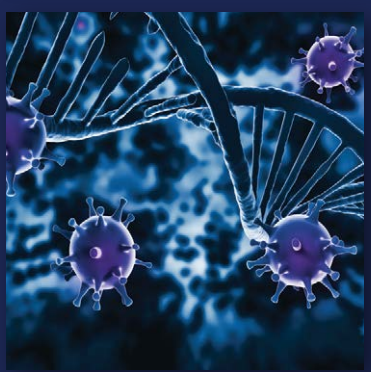
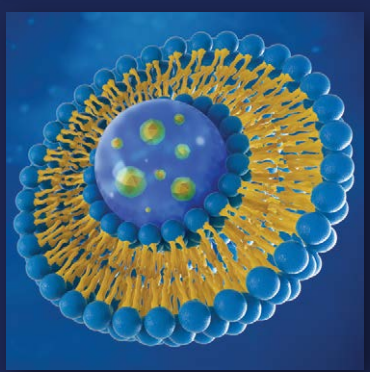
New Sterile Filtration Challenges in the Changing Landscape of Drug Formulations

BioProcess International
SPECIAL REPORT

PALL Biotech

New Sterile Filtration Challenges

in the Changing Landscape of Drug Formulations

Tom Watson

A growing number of the new parenteral drug products under development are "complex formulations" that can make them markedly different from traditional drug types. Here, Pall Biotech discusses several challenges associated with sterile filtration of three types of drug product that are considered to be nontraditional or complex: high-concentration monoclonal antibodies (MAbs), liposomes, and lentiviral vectors.

Sterilizing-Grade Filtration of Drug Products

US Food and Drug Administration (FDA) aseptic processing guidelines require that a filter, when used to sterilize drug product, will "reproducibly remove all viable microorganisms from the process stream, producing a sterile effluent" (**1**). A filter's ability to do that in a drug product application is confirmed through filter validation based on bacterial challenge testing with *Brevundimonas diminuta* (*B. diminuta*) or an indigenous bioburden in laboratory experiments that simulate process conditions (**1**).

Other important aspects of process-specific filter validation are studies confirming that (in parallel with producing a sterile effluent) a filter will not impede the ability of a process to yield product that meets other critical quality attributes (CQAs).

Typically, 0.2-µm "industry standard" sterilizing-grade filters will be selected for sterilization of parenteral drug products. Those filters should be validated by their manufacturers to produce a sterile effluent when challenged with a minimum level of 1×10^7 *B. diminuta* colony-forming units (CFU) per cm^2 of filter area. Filter selection for complex parenteral formulations may not be as straightforward as it is for traditional formulations.

Considerations for Complex Formulations

High-Concentration MAbs: Intravenous (IV) infusion has been a common administration route for MAbs, but subcutaneous delivery (sub-C) in 1- to 1.5-mL doses now is preferred for patients who require a frequent-dosing regimen. Sub-C provides them the possibility of self-treatment using prefilled syringes (**2**). To accommodate such small-volume doses, MAbs typically need to be prepared at concentrations >100 g/L — up to 250 g/L (**3, 4**).

In fluids containing high MAb concentrations, the potential for molecular interactions can create complications. Understanding those interactions and how they affect downstream processing and drug product sterilization remains a challenge (**5**). Notably, at concentrations >100 g/L, interactions between MAb molecules can increase fluid viscosity

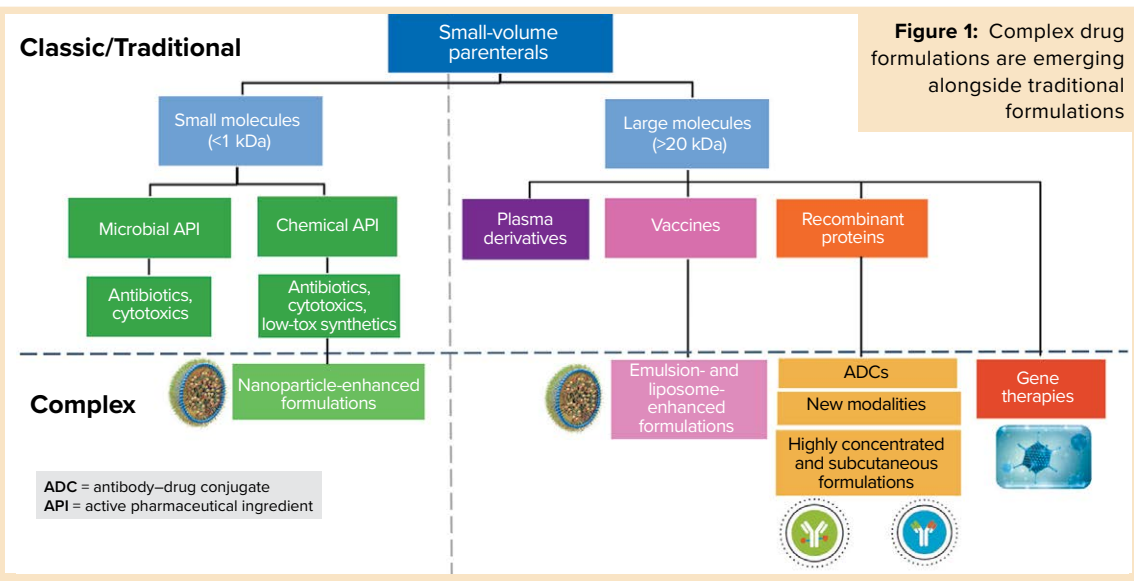


Figure 1: Complex drug formulations are emerging alongside traditional formulations

significantly (exponentially with concentration) to 20–60 centipoise (cP) (**6**).

It is not as easy to sterile-filter a highly concentrated MAb feed as a low-concentration feed. High aggregate contents have been reported with increased MAb concentrations (**7**), compromising filter capacity, and the high viscosities affect filter flux (**4**). Both factors often can be compensated for by using oversized filters for what traditionally would be considered "small" batch volumes: e.g., a 254-mm (10-in.) filter for a batch of 10–20 L.

The assumption that a relatively large filter is needed for those batch volumes can lead to questions of filter compatibility, including adsorption of critical formulation components or addition of leachables. So testing membrane compatibility with both product and excipients is critical and must be part of a filter-selection process (**3**).

Significantly, oversized sterilizing filters create excessive hold-up volumes of expensive fluid in a device's upstream volume, membrane, and downstream volume. In a closed filter system, that fluid is hard to recover, and a few hundred milliliters of held-up commercial product can cost thousands of dollars. Materials are scarce in process development, when held-up fluid can limit availability of material for preclinical testing and clinical trials.

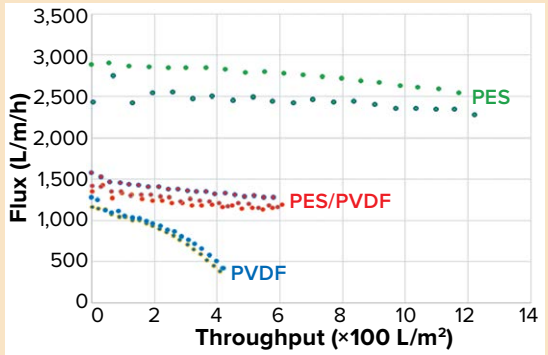
The volume of nonrecoverable fluid can be minimized through good system and process design, a key part of which is the sterilizing-grade filter specification. Implementation of a compact filter with a small area (enabled by high-capacity/high-flux membranes) will improve yield and can alleviate compatibility concerns that might otherwise arise with an oversized filter.

Liposomes are the first nanoscale drug-delivery systems that have been used successfully in clinical applications, and they also are used as adjuvants in vaccines. Liposomes continue to be investigated for those purposes as well as for gene delivery.

Liposomal drug formulations tend to be more difficult to sterile-filter than conventional formulations are. Because of their size (100–200 nm), liposomes can cause premature filter blocking of sterilizing-grade filters. The potential effect on filter sizing should be considered early in development of a liposome filtration process to prevent the drawbacks of selecting an oversized final filtration system, as reported above for high-concentration MAb formulations.

A sterilizing-grade filter with a high-capacity asymmetric membrane that has a high filtration area in standard 254-mm (10-in.) format is recommended for liposomal fluids. This can help contribute to a more compact filter system at production scale.

Figure 2: Differences in capacity among three 0.2-µm sterilizing-grade filter membranes using a 100-g/L IgG as a model high-concentration monoclonal antibody; filtration at 10 psi, constant pressure



PES = polyethersulfone **PVDF** = polyvinylidene fluoride

Good control of liposome particle sizes and distribution also is critical to ensuring good filterability (**10**). Decreasing droplet size, distribution, and polydispersity — for example, by using multiple passes through a homogenizer — all have been shown to increase filtration capacities.

In addition, filtration capacities can be increased by processing liposomal formulations at a relatively high differential pressure of 2.07 bar (30 psi) across the filter, which helps to minimize adsorption and maximizes use of the membrane surface area (**10**).

Bacterial challenge studies of sterilizing-grade filters with low–surface-tension fluids (<62 dynes/cm^2) have shown that reduced bacterial retention can occur under such conditions (**8, 9**). Along with emulsions, lipids, and lipid-like solutions, liposomes fall into the category of low–surface-tension fluids. Although reduced bacterial retention is rare, if it is overlooked and later found to occur, that can force work-arounds that affect process development timelines. To ensure a successful bacterial challenge with liposome formulations, Pall recommends selecting filters that are known to perform most reliably with liposomal fluids. Filter candidates should be subject to bacterial challenge as part of designing liposomal formulation and filtration processes.

Lentiviral Vectors: Significant industry effort is under way to develop a high-yielding manufacturing platform for gene therapies. Many such product candidates use lentiviruses as their vector to deliver genetic material, with the sterilizing-grade filtration step providing a key process optimization opportunity.

Lentiviral vectors are about 0.12-µm in size, which complicates passing them through 0.2-µm filters. The viruses must travel through a tortuous flow path, with filter pores that are not much bigger than the viral particles. This can lower the yield of such high-value products, which (as with high-

Table 1: Summary of challenges when sterile-filtering complex formulations; MAbs = monoclonal antibodies

Liposome Drugs	High-Concentration MAbs	Lentiviral Vectors
Filter blockage with 80-nm to 120-nm particles	Filter capacity for viscous feeds (≤250 g/L, 30 cP)	Reliable transmission of lentivirus
Reliable bacterial retention with liposomes	Adsorption of active and excipients (e.g., polysorbates)	Loss of high-value product (hold-up volume in filter device/system)
	Loss of high-value product (hold-up volume in filter device/system)	

concentration MAbs) can limit availability of material for testing and clinical trials.

Purification of lentiviral vectors also is complicated by a highly shear-sensitive bilipid envelope and low virus half-life of 8–12 hours (**11**). Special considerations must be given to process timing (including for sterile filtration). Continuous downstream processing in a cold-room environment can help maintain viral stability all the way through to final sterilizing filtration.

Specialists at Pall Biotech are working closely with cell and gene therapy process developers to understand those challenges and find the best ways to sterilize gene-therapy products through filtration.

Solving the Challenges of Complex Formulations

Pall Biotech has a comprehensive sterilizing-grade filter product range and expertise to support the manufacture of traditional drug products and to meet the needs of the teams working on next-generation life-changing drugs, therapies, and vaccines. We realize that it can be challenging to specify a sterilizing-grade filter for complex parenteral formulations and that combining the right filter and support for qualification and validation will help you meet your development timelines and ensure high commercial production yields and operational efficiencies.

Whether you are looking to run filterability trials to find the right filter membrane for your drug, optimize your process conditions to get maximum yield, or validate your process — or you want us to develop your complete process — our scientific and laboratory service (SLS), biotechnology specialists, and Accelerator process development and validation services can help. Request a consultation with a specialist at https://go.pall.com/sterile-filter-consultation.html.

References

1 CDER/CBER/ORA. *Guidance for Industry: Sterile Drug Products Produced By Aseptic Processing — Current Good Manufacturing Practices.* US Food and Drug Administration: Rockville, MD, 2004; https://www.fda.gov/media/71026/download.

2 Allmendinger A, et al. Sterile Filtration of Highly Concentrated Protein Formulations: Impact of Protein Concentration, Formulation Composition, and Filter Material. *J. Pharm. Sci.* 104(10) 2015: 3319-3329; https://doi.org/10.1002/jps.24561.

3 Zhou JX, et al. Non-Specific Binding and Saturation of Polysorbate-20 with Aseptic Filter Membranes for Drug Substance and Drug Product During mAb Production. *J. Memb. Sci.* 325, 2008: 735–741; https://doi.org/10.1016/J.MEMSCI.2008.08.046.

4 Garidel P, et al. High-Concentration Protein Formulations: How High Is High? *Eur. J. Pharm. Biopharm.* 119, October 2017: 353–360; https://doi.org/10.1016/j.ejpb.2017.06.029.

5 Zhang Z, Liu Y. Recent Progresses of Understanding the Viscosity of Concentrated Protein Solutions. *Curr. Opin. Chem. Eng.* 16, 2017: 48–55; https://tsapps.nist.gov/publication/get_pdf.cfm?pub_id=922423.

6 Yadav S, Shire SJ, Kalonia DS. Factors Affecting the Viscosity in High Concentration Solutions of Different Monoclonal Antibodies. *J. Pharm Sci.* 99(12) 2010: 4812–4829; https://doi.org/10.1002/jps.22190.

7 Wang W, Nema S, Teagarden D. Protein Aggregation: Pathways and Influencing Factors. *Int. J. Pharm.* 390(2) 2010: 89–99; https://doi.org/10.1016/j.ijpharm.2010.02.025.

8 Folmsbee M, Moussourakis M. Sterilizing Filtration of Liposome and Related Lipid-Containing Solutions: Enhancing Successful Filter Qualification. *PDA J. Pharm. Sci. Technol.* 66(2) 2012: 161–167; https://doi.org/10.5731/pdajpst.2012.00771.

9 Folmsbee M. Evaluation of the Effect of the Volume Throughput and Maximum Flux of Low Surface-Tension Fluids on Bacterial Penetration of 0.2 Micron Rated Filters During Process-Specific Filter Validation Testing. *PDA J. Pharm. Sci. Technol.* 69, 2015: 307–316; https://doi.org/10.5731/pdajpst.2015.01026.

10 Iwaniec A, et al. Poster: *Understanding the Sterile Filtration of Complex Fluids Using a Liposomal Model Fluid.* Pall Biotech: Port Washington, NY, April 2020; https://www.pall.com/en/biotech/posters-presentations/understanding-sterile-filtration-nanosuspensions0.html.

11 Dautzenberg I, et al. The Stability of Envelope-Pseudotyped Lentiviral Vectors. *Gene Ther.* 24 September 2020; https://doi.org/10.1038/s41434-020-00193-y.

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