

Advanced Filtration Optimizes High-Viscosity BFS

To resolve bottlenecks, Spanish CMO Unolab switches to Pall's polyethersulfone membrane filters to great effect

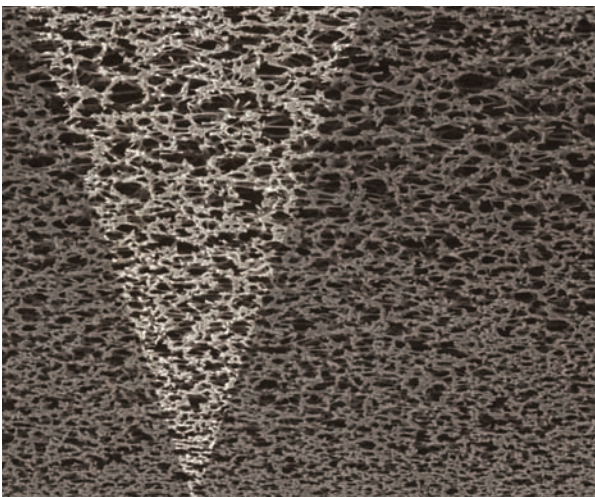
BY TOM WATSON, PALL LIFE SCIENCES

UNOLAB MANUFACTURING S.L., a Spanish CMO dedicated to the manufacture of sterile monodose par-parental products, offers its customers access to advanced blow-fill-seal (BFS) technology to accomplish sterile filling of these products into their final dosage containers. Specializing in liquid ophthalmics, Unolab processes a variety of formulations including highly viscous, high-density, large molecule formulations with viscosities as high as 80 centipoise.

Liquid handling in BFS systems is now sufficiently well developed to enable the filling of a broad range of formulations, including those which may be more difficult to process and prepare for filling. One particularly challenging process step for viscous formulations is sterile filtration.

Parenteral products which are heat-labile are filter sterilized to maintain efficacy and to render them safe for injection in humans. Filters designed to achieve sterility are usually rated at 0.2µm and will have been validated to produce a sterile effluent under the end-user's operation conditions, having already been qualified by the filter vendor as retentive for *Brevundimonas diminuta* at a challenge level of 10^7 cfu/cm² membrane area in challenge tests correlated to ASTM Standard Test Method F838-05 (ASTM F838-05).

At the fill stage of a given pharmaceutical



Cross-section of highly asymmetric filter membrane used to facilitate high flow/high throughput filter performance.

manufacturing process, low-viscosity aqueous fluids are commonplace and considered easy to filter. These fluids do not tend to incur a rapid deterioration in filter throughput or flow rate performance at a given differential pressure. As a result, they present a low likelihood of filter blockage and consequently any undesirable filter change-outs and associated costs.

There are also plenty of liquid formulations that require viscous properties or contain suspended particles to ensure

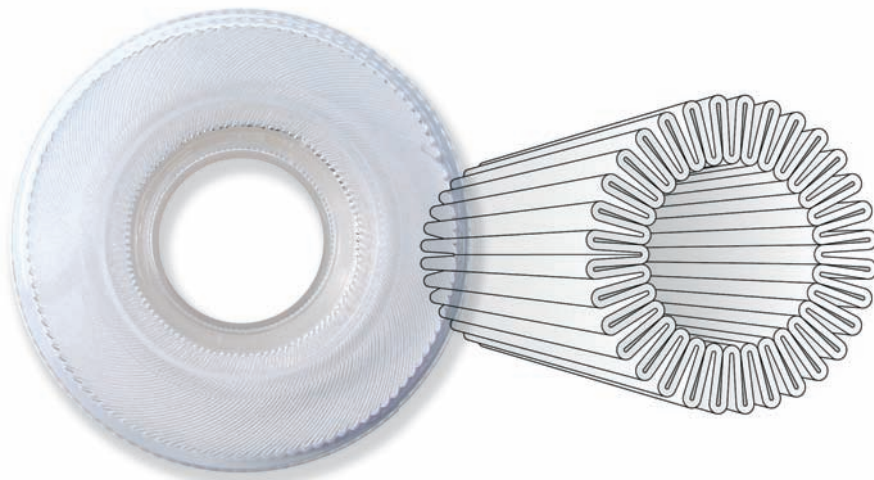
IT WAS TIME TO SPECIFY A HIGHER-PERFORMING FILTER DESIGNED FOR VISCOUS PARTICULATE-LADEN FORMULATIONS.

the right environment for stability and the correct delivery of the active pharmaceutical ingredient. The composition of such fluids may feature a higher particulate load, or be of a viscosity which may not be easily accommodated by a sub-micron rated membrane filter. Examples of hard-to-filter final formulations containing active ingredients of a more particulate nature would be those incorporating liposomes or nanoparticles. Those of a more viscous nature may use active ingredients such as hyaluronic acid or carboxymethyl cellulose (CMC).

In pursuit of continuous process improvement and operational excellence, as well as to avoid excessive downtime and costs related to filter change-outs when filtering highly viscous products, Unolab's process engineers identified an opportunity to update and improve filtration processes and remove a bottleneck that, among other things, diminished product yields. Unolab's operations director, José Ignacio Villarino Otero, characterized the issue this way: "We find that large molecule, high density formulations — essentially viscous products — can be challenging to sterile filter. These products typically present problems for us."

CHOKE HOLD

What was putting a choke-hold on sterile filtration throughput? It was the filters themselves; the use of a 30-year-old technology employing a polyvinylidene difluoride (PVDF) membrane. Though the filter technology Unolab traditionally specified functioned correctly in



A

(A) Laid-over pleat geometry, narrow internal core used in 10-inch Supor EX grade ECV filters

(1.04 m²) and (B) Traditional fan pleat geometry typically used in 10-inch filter elements with EFA of 0.5m²- 0.7 m².

B

the company's validated, compliant process, when used for the filtration of high viscosity, large-molecule formulations, Unolab found the use of these filters led to a significant compromise in performance and cost efficiency. This was thought to be due to the PVDF filter's symmetrical pore structure and comparatively lower clean water flow rate than that of other newer sterilizing-grade filters.

While Unolab's filtration operations are relatively straightforward, they have the potential to become labor and material intensive when viscous products are filled: They found that where one 30-inch PVDF filter would typically be required to prepare one batch of low viscosity product, for a highly viscous fluid using the same filter, seven filter change-outs were required to dispense 210 liters of product in final dosage format. Each change-out cycle required steam-in-place sterilization prior to resumption of filtration — a

total of 16 hours downtime per cycle — this generated 96 hours of lost manufacturing time per batch! Further, Unolab had to filter almost 350 liters of product to achieve the 210 liter per batch yield, due to inter-batch product loss.

Recognizing recent advances made in filtration technology, it became apparent to Unolab's process engineers that it was time to specify a higher-performing filter with a design that could offer improved flow rates and with a particulate capacity better suited to viscous particulate-laden formulations. The ultimate goal was a practical and economical filtration system for hard-to-filter fluids.

Filterability testing (assessment of filtration performance in terms of flow rate and throughput) with a bench-top filter test device indicated that Pall's 30-inch Supor EX grade ECV filter using the industry standard 3x10 inch filter element construction would offer dramatic advantages over their incumbent

(PVDF) filter of the same size.

The performance advantages of Pall's filter technology can be attributed to a highly asymmetric filter membrane, a structure which provides improved fluid permeability and more effective particle capture. The filter's performance is further augmented when deployed in 10-inch filter sub-units that support an effective filter area of slightly more than 1 m².

Ultimately, Unolab found it was able to use the Pall filter to process all the fluid required to fill a 210-liter batch of viscous product without a change-out, resulting in ease of use and cost advantages over the technology with which they had encountered considerable challenges.

According to Unolab's Otero, "Supor EX grade ECV filters have enabled us to optimize our manufacturing for a range of different product types. With these filters we can process up to five times more fluid. This means we can dispense more final dosage units per filter and optimize the manufacture of our bulk material. The result is not just reduced filtration consumable costs, but minimization of product losses and a lowering of time related costs: Supor EX grade ECV filters allow us to dose our ophthalmic products with BFS systems with fewer limitations."

Ultimately careful filter evaluation and successful implementation delivered significant process improvements to Unolab's highly critical process. In addition to benefiting from a reduction in consumables usage, minimized product losses and improved yields, Unolab is now able to enjoy savings in time-related costs including fewer start-ups, fewer sterilization cycles, reduced frequency of integrity testing and less information capture per lot. [®]

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