# Rethinking the Economics of Chromatography

## New Technologies and Hidden Costs

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**If the hidden expenses associated with laboratory purchases — labor, cleaning, buffers, validation, time delays — are identified, reduced processing costs, higher throughput, and accelerated time-to-market are possible. This comparison between resin and membrane chromatography helps shed light on some hidden costs.**

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In making technology choices, it is crucial to consider cost. That point may seem trivially obvious, but in fact, it is often ignored. Even scientists, who understand the craft of detailed analysis, frequently fall into the trap of making purchase decisions without considering the hidden costs they are also taking on. Sometimes costs that might be thought of as incidental — labor, cleaning time, supplies, and so forth — can make the difference between a decision that makes economic sense and one that merely looks like it does.

To illustrate the point, we'll use as an example a new technology the authors are intimately familiar with: membrane-based chromatography. Membrane chromatography can offer advantages over traditional resin-based chromatography, particularly in operations that require high dynamic capacity. The technology, however, is often regarded as prohibitively expensive: A membrane suitable for processing a batch of several thousand liters can cost several thousand dollars and is used once, then discarded. Over the course of a thousand cycles, membranes alone cost several million dollars — many times the cost of a traditional column setup. A description of membrane science can be found in "The Technology of Membrane Chromatography" sidebar, which describes and compares the flow rates and dynamic capacity of membrane-based and resin chromatography.

But equipment and media are not the only costs of chromatography. As we look closer at expenses, we find some surprises.

### Comparing Costs

To compare membrane and resin-bead chromatography, let's look at a familiar example: removal of DNA using either a membrane unit or a standard 90-L column. We will assume a starting concentration of about 10 μg DNA/mL. We used a 90-L Q anion-exchange column to achieve the desired flow rate of greater than 20 L per minute. The one-liter Q membrane chromatography capsule/cartridge was chosen because it possesses an adequate capacity. The flow rate for the capsule was about 50 L per minute.

**Equipment and medium.** A 90-L column and packing station costs about $200,000. If the column costs are amortized over 1,000 cycles, or about seven years, the equipment expense would run about $200 per cycle. In addition to the chromatography hardware, the medium required for a 90-L column costs approximately $70,000. If the media is used for 50 cycles, the cost per cycle is approximately $1,400, bringing the total per-cycle cost (equipment and media) to approximately $1,600.

The initial outlay for one large membrane chromatography equivalent costs about $3,500, and each membrane is used for one cycle. Therefore the per-cycle cost for equipment is $3,500 — more than double the cost of the column and medium. (For the sake of simplicity, we won't consider the costs of a backup column, which should be purchased as a safety net. The cost of a backup membrane capsule is small in comparison to the cost of a second column.)

**Labor** is a significant cost component in biopharmaceutical operations. The initial equilibration wash for a 90-L column takes about 30 minutes. Negative chromatography to remove DNA and endotoxins takes about 1.75 hours, and cleaning takes another 1.75 hours. Three hours are needed to test the resolution (the peak symmetry), the cleaning efficiency including DNA and *Limulus* amoebocyte lysate (LAL) quantitation, and the colony forming unit (cfu) and microbial growth measurements. An average column chromatography run, therefore, takes a total of about seven hours.

## The Technology of Membrane Chromatography

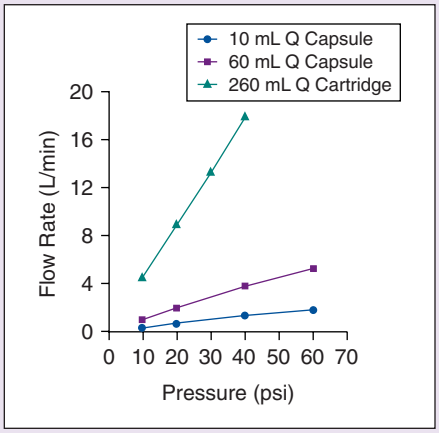


**Figure 1.** The linear relationship of flow rate and pressure drop for three sizes of Q membranes

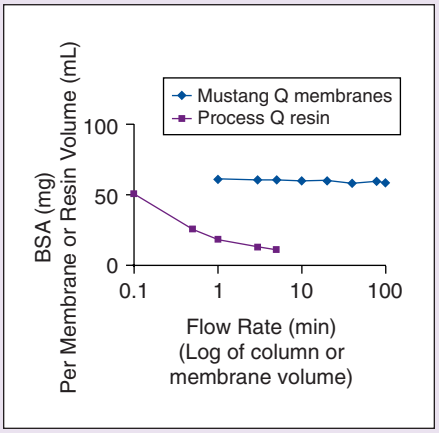


**Figure 2.** Flow rate and dynamic capacity compared for a process Q resin and a Q membrane

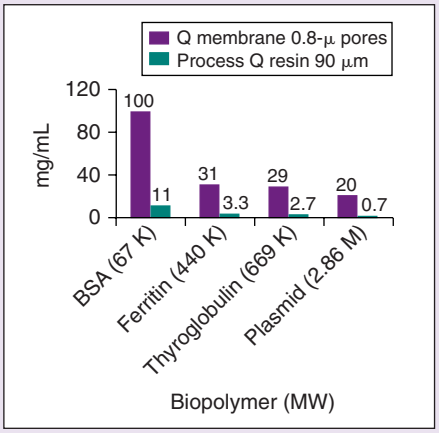


**Figure 3.** The inverse relationship between dynamic capacity and molecular size at three column volumes per minute

Membrane-based chromatography offers some advantages that help close the gap between drug processing and drug delivery.

**Flow rates.** Membranes are capable of high flow rates. The flow characteristics of membrane chromatography units are similar to typical microporous filters — a linear relationship between pressure and flow rate (Figure 1). Most process chromatography resins have a linear flow versus pressure relationship until the rate reaches 0.3 column volumes (CV) per minute.

**Dynamic capacity.** Chromatography using membranes has a high dynamic capacity; that is, membranes have a larger capacity at higher flow rates. Although the static capacity of traditional chromatography resins and membrane chromatography columns are similar, the dynamic capacity of the two can be quite different. Figure 2 shows that resin capacity is good at low flow rates, but membranes maintain high capacity at the higher flow rates of 100 CV per minute. The performance of adsorptive membranes and gel matrices have been compared and theoretical models have been developed in the literature (2–8). Other researchers have examined the capture efficiency, throughput, and suitability of membrane chromatography for large-scale downstream processing of biopharmaceutical products (9–14).

This increase in dynamic capacity is the result of a membrane's convective flow, which minimizes diffusion distances. Unlike resin-based columns, DNA and protein binding is not limited by long diffusion times when membranes are used. Diffusive bead pores have an inherently limited capacity for capturing plasmids or viruses because of the physical constraints of the pores. Figure 3 shows the inverse relationship between dynamic capacity and molecular size. Although both chromatography beads and membranes lose capacity as the molecular weight increases, that loss is most prominent in process chromatography beads. For plasmids (shown in Figure 3), the dynamic capacity is 28–fold greater for a membrane chromatography unit than for a process chromatography resin. In essence, the pathway in which biomolecules bind to a charged membrane is shorter than it is for resin beads.

Because a membrane unit can capture biomolecules in a short time, this technology is useful for genetic therapies, during which large volumes of fluid must be processed to capture a relatively limited number of plasmids or viruses. For example, a chromatography unit with 16 membrane layers can bind $10^{13}$ adeno-associated viruses per milliliter of packed bed.

A membrane capsule is certified to be endotoxin-free (as measured by LAL) and can be made sterile before use. After completion of a run, the cartridge is discarded, so no resources are spent on cleaning. As a result, the process of testing and washing the capsule and processing the batch requires approximately one hour, using a 2,100-L batch with a membrane that has a 50-L per minute flow rate, the process of testing and washing the capsule and processing the batch requires about one hour — about six hours of labor are saved by using a membrane chromatography unit.

Assuming that two operators run a chromatography batch, the costs, including overhead, are roughly $150 per hour, per operator. Seven hours of labor at $300 per hour yields a per-batch cost of $2,100. The single-use membrane unit requires one hour for the process and costs about $300 in labor — a labor savings of $1,800 per batch.

The estimated cost per batch for equipment, media, and labor is, therefore, $3,800 for the membrane cartridge and $3,700 for the column — making the cost difference between membrane and column minimal. Many resin columns do not need to be tended throughout the length of a run. If, therefore, hours of labor are cut in half for some resin columns, membrane column savings are still about $950 per batch.

Of course, we've omitted some detail. Our analysis does not include column packing, for example, because it is possible to run several traditional chromatography cycles without the need to repack a column. Realistically, column packing can increase the labor costs

**Table 1.** Some of the costs associated with traditional resin columns and membrane chromatography per cycle for processing a 2,100-L batch

| Chromatography Process | Medium and Equipment Costs[a] | Buffer Costs[a] | Labor Costs[a] | Total Costs |
|---|---|---|---|---|
| Resin column chromatography | 1,600 | 10,000 | 2,100 | 13,700 |
| Membrane chromatography | 3,500 | 300 | 300 | 4,100 |

[a]Per cycle, in U.S. dollars

for traditional chromatography by 10–60 minutes for each cycle.

**Buffers** have been calculated to comprise approximately half of downstream processing costs (1). "Typical" buffer costs are difficult to determine because the cost of goods may or may not include variables such as water-for-injection (WFI) system maintenance, storage tanks, labor, and overhead charges. Some buffer and cleaning solutions can cost as much as $12 per liter; however for this comparison, we used an average cost of $5 per liter.

Traditional ion-exchange removal of DNA and endotoxins from a 2,100-L batch requires sufficient buffer to prepare and clean a 90-L column. The industry standard for each column wash is three to five column volumes (CVs). In our example, five CVs would be 450 liters. The batch requires about 2,000 liters of buffer, which includes an average equilibration, cleaning with various solutions, and storage buffers. The resulting buffer costs are, therefore, about $10,000 for each batch processed.

A single membrane chromatography unit used for that same batch consumes 60 liters of buffer — about $300. The dramatic reduction in the buffer consumption results from using disposable membranes — no buffers are needed for cleaning or storage. Because membrane chromatography has a higher dynamic capacity and shorter residence time, smaller units can accomplish the same task as larger chromatography columns. The total per-batch savings on buffers using membrane chromatography is, therefore, about $9,700, for a total savings of $9,600. The media, equipment, buffer, and labor costs are directly compared in Table 1.

**Other hidden costs.** Our example illustrates an important point. Cost savings don't always come where they are expected. For membrane-based chromatography, the benefit that many companies anticipate is speed. So they are likely to anticipate cost savings associated with the time saved. But in our example, the principal saving was from buffer costs. Another analysis, looking at different sets of variables, can reach different conclusions. Yet the underlying issue remains the same: The key to analyzing costs is identifying *all* the relevant costs, not just the obvious ones.

Our example has not yet identified all the relevant costs. Significant potential savings remain, but they are harder to quantify. For example, a traditional chromatography column is a large capital expenditure. It is often difficult to obtain budget approvals for large capital expenses. Delays can cost money, but how much money can be difficult to calculate.

**The most expensive hidden cost — validation.** Because membrane cartridges are discarded after each operation, they eliminate the need for cleaning and cleaning validation. Cleaning validation of traditional chromatography columns is a significant portion of process development, often requiring several months. If reproducibility problems arise in process development, that timeline can become even longer. Such problems can have a serious effect on time-to-market for biopharmaceuticals. Yet the value of rapid validation is difficult to factor into practical purchasing decisions for a new technology.

The adage "time is money" is particularly apt for biopharmaceutical processing — a single day of patent protection on a best-selling drug can be worth millions of dollars. As an industry, we need to find better tools — to become smarter — to deduce *how much time* is equivalent to *how much money*. Then we can take advantage of the immediate and long-term economic benefits from shining a light on hidden costs. ***BPI***

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