Engineering Design Considerations for Column Packing in Large-Scale Biotechnology Facilities

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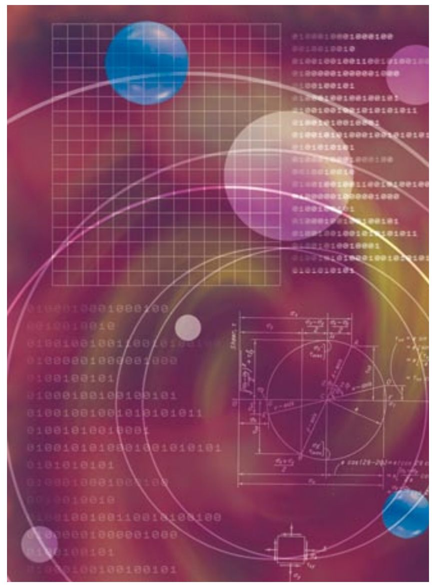
As the biotechnology industry grows, bioreactors are being designed and built to ever-increasing capacities, with cell culture batch volumes approaching 30,000 L and microbial fermentor volumes approaching 300,000 L. Larger production capacities have led to an increase in chromatography column sizes and often more demanding operating schedules. At the same time, regulatory and economic factors continue to require high reproducibility and efficiency. To support these higher capacity requirements, chromatography columns of 1–2 m ID are now typical in the industry. The use of such large columns presents unique challenges to design teams in column packing and facility design.

Column manufacturers have responded to the challenges by producing new columns and packing equipment, such as automated pack-in-place systems that allow for more consistent, more efficient packing with shorter turnaround times. Situations remain, however, in which operational requirements do not justify the added cost of automated systems, so more traditional packing approaches can be used.

Often the tendency during conceptual or preliminary design stages of a project is to focus on major unit operations of a process and defer critical decisions regarding support operations (such as column packing) to later on in the engineering design. Such an approach could be costly as the decisions made might be further reaching than they initially seem. Careful planning and consideration of the column packing approach in conceptual and preliminary engineering stages in the project life cycle can lead to considerable savings. Packing solutions must be integrated into an overall facility design. Space requirements, electrical classifications, HVAC classifications, building layout (both production and storage facilities), as well as environmental issues and waste handling can all be affected by a column packing method.

Column packing operations contain elements that introduce design challenges. Recognizing the potential impacts of column packing and maintenance on facility design — and the consequent importance of making decisions early in a project life cycle — design engineers must immediately consider a number of questions. The answers will directly affect the initial capital costs and determine how a facility will operate for years to come.



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- How often will columns be repacked, and what is the required turnaround time for column packing based on the desired operating schedule?
- Will columns be packed in the site of their use, or will they be moved and packed in a dedicated column packing room?
- Will column packing be a manual or automated procedure?
- What support equipment is required for column packing operations?
- Are chromatography resins shipped and stored in ethanol? How much resin will be stored on site, and where will it be stored?

PRODUCT FOCUS: ALL BIOTECH PRODUCTS

PROCESS FOCUS: FACILITY DESIGN AND PROCESS DEVELOPMENT (DOWNSTREAM)

WHO SHOULD READ: MANUFACTURING AND PROCESS DEVELOPMENT, PROJECT MANAGERS, AND DESIGN ENGINEERS

KEYWORDS: CHROMATOGRAPHY, FACILITIES, AUTOMATION, NONAQUEOUS SOLVENTS

LEVEL: BASIC

• Will resin handling and column packing introduce environmental or waste handling issues that must be addressed?

Deciding or changing direction on packing approaches too late in a design often leads to changes both difficult and costly to implement (Figure 1). Note that the potential for cost savings is greatest early in the design. In early stages, where information may be limited, making such decisions can be daunting. However, certain key factors can be used to guide such decisions for an efficient and sound design. Some include data and information often defined relatively early: e.g., the number and sizes of columns, the facility's operating schedule, the frequency in which columns must be repacked, the value and nature of chromatographic resins being used, and the value of the product being manufactured. Other factors that influence decisions relate less to the process: the type of facility, whether it will be dedicated to a single product or many campaigned projects, the overall "feel" of the facility (highly automated, highly manual, or somewhere in between), and the company's experience with column packing as well as with GMP concerns and considerations.

Here we introduce some issues that should be considered in the decision-making process and attempt to provide a feel for the impact of those decisions on final facility design. Discussion of technical details is beyond our scope, as is a full description of the benefits and drawbacks to available automated pack-in-place systems. Other articles have addressed these issues (1–3), and the expertise in column packing resides with column vendors and resin manufactures. Additionally, whereas decisions regarding column maintenance also affect facility design and may be mentioned, it is not our primary focus here. We are most concerned with the impact of column packing decisions on facility design and operations.

Column Packing Options

Column packing details depend on the resin being packed. Many resins are shipped prehydrated, often in an antibacterial solution such as ethanol. Column packing usually involves creating a slurry of the resin in an agitated vessel or container. That slurry is then transferred from its container into the column, where it is conditioned by various buffers and cleaning agents before use.

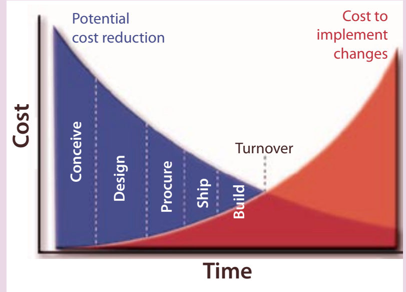
Two fundamental options of column packing are where the column will be packed and whether that process will be manual or use one of the automated systems that have been available since the mid 1990s (1) . Both manual and automated packing can occur with a column located in its site of use (*pack-in-place*) or at a dedicated packing location in the facility (*pack-out-of-place*).

Manual Packing: Traditional, manual column packing is done by removing the top head of a column and pumping (or for smaller columns, pouring) a predetermined amount of slurry into the now-open column through a flexible hose. Once chromatographic resin is introduced, the top head of the column is lowered and reattached. Often a buffer then flows through the resin-containing column, causing the resin to settle as a bed. The top distributor is further lowered until it rests on that packed bed. Because the resin has been open to the environment, a newly packed column and its associated skid are often cleaned at that point with a caustic solution (or otherwise sanitized) before being placed into service.

Manual unpacking is performed similarly, but in a reverse process with the column head being removed, a slurry of resin created in the column, and that slurry pumped out of the column into a container. Depending on the type of resin and impurities it may have trapped during operations, it may be discarded or cleaned and processed for reuse.

The traditional manual packing method is by nature an open process: Equipment and consumables are exposed to the room environment, and operators are exposed to the process. Local controls are often used with open processes to provide protection for the product and/or operators. In column packing, control often comes in the form of a higher air classification. Also, a hoist is generally required to remove a column head, and a lay-down area must be designated for column parts.

Figure 1: Chart showing the impact of design decisions on potential savings and costs as a function of the time of the decision



Automated Packing: A number of column manufacturers sell columns equipped for packing without top-head removal. It is typically done using valves located on the top and bottom of a column that can be positioned in any one of three configurations. With one valve setting, resin slurry can be passed into or out of the column through the valve. In a second, the valve allows high flows of buffer to enter the bottom and/or top head of the column to form a slurry of the packed bed for its removal. The third valve position allows a column to operate, with the chromatographic resin held as a bed within it and liquid flow distributed evenly across the bed through the column frits. Photo 1 is an example of a three-way valve separate from its column head to show the inlet piping typical for such valves (product, slurry, and buffer lines).

In addition to automated packing valves, some manufacturers now offer additional column enhancements such as a built-in hydraulic unit to lift a column head or allow for axial compression during column packing. All automated packing systems come with some form of packing skid. Although the complexity of skids can vary, key components are usually one or two diaphragm pump(s) and necessary valving to direct the flow of buffers or resin slurries to appropriate valves on the column or slurry vessels.

Column costs are about 15–35% higher when equipped with automated packing valves, the percent increase being smaller for larger columns. Packing skid costs range $25,000–

Photo 1: A three-way packing valve removed from its column-head location to show the connections for product, buffer, and slurry lines. The valve is adjusted during operation to allow the column to function in process, packing, or unpacking mode.
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60,000 depending on their features and options. Offsetting the added capital necessary are reduced labor costs and indirect savings gained by more consistent column packing. Although columns can be retrofitted for automated packing nozzles, it is rarely done. The decision regarding manual or automated packing is generally made before the purchasing columns.

Location of Packing Procedures: Another question to be addressed with column packing is where columns will be packed. Options are to bring packing equipment to the column at its point of use or to move the column itself to another location set aside for packing. Each approach has its advantages and disadvantages.

Pack-out-of-Place: Packing columns in a location remote from their point of use offers some advantages: chiefly in the consolidation of equipment, piping, and any special room requirements into a single area. Consider manually packed columns. One approach to dealing with the open nature of column packing is to pack them in a room of higher HVAC classification than is used in the processing area. The common use of ethanol in resin storage has been previously mentioned, and reversed-phase column packing may involve the use of other solvents as well. Those factors often necessitate solvent-rated electrical classification of rooms.

As room requirements for a particular operation within a facility become more stringent, the cost of constructing the space increases. That makes the concept of having a small, dedicated space for column packing apart from the main purification suite attractive. In rough terms, an ISO Class 7 (Class 10,000) room is about three times more expensive than similar space conditioned to ISO Class 8 (Class 100,000). Additionally, if an area must be electrically classified as explosion-proof because solvents are present, it costs about three times more than a similarly equipped room that is not explosion proof.

In addition to the potential building cost savings, keeping packing operations remote from processing may be appealing from an operations standpoint. Depending on the method of packing, the process can be messy and could interfere with adjacent production operations. If the same column packing equipment is used for a number of steps in a downstream process, as is often possible for columns of similar size using similar resins, a dedicated packing room provides a convenient place to locate that equipment. And piping used to support the packing operations can be routed to a single location.

The chief disadvantage to this approach is, of course, that the columns must be transferred from one room to another and back. Moving larger columns requires the use of mechanical assistance such as a fork truck or some form of pallet jack. So the size of the column plays a key role in considering the pack-out-of-place option.

Pack-in-Place: Sometimes, because of column size or frequency of packing, movement of the column is impractical — and may be impossible. In such cases, the column will be packed where it is used for processing. Either the packing equipment is located in a fixed location relatively near the column(s) to be packed, or portable packing equipment is brought in and then taken away when not in use. As column sizes increase, so do resin volumes, so the slurry tank required for packing operations might be too large for portability. That could create additional design challenges.

The advantages and disadvantages of manually packing a column in place are largely the opposite of packing it out of place. With automated packing systems, however, some of the reasons for moving columns are lessened. Because column heads do not need to be removed, open processing is not an issue. And because automated packing occurs by manipulating valves at the top and bottom of columns, the operation is less messy than manual packing.

PROCESSING CONSIDERATIONS

A primary factor influencing column packing decisions is the size of columns to be packed. Columns are specified according to their diameter, and their weight and bed volume increase exponentially as diameters increase. Table 1 illustrates the impact of column size on such factors as column weight, resin volume, and the typical slurry volume associated with packing. The weight and physical space of large columns alone can drive the pack-in-place or pack-out-of-place decision. Column weight estimates in Table 1 were obtained by curve fitting data from acrylic columns in a number of different projects. Stainless steel, often used for larger columns, is heavier.

Moving columns over a meter in ID generally requires some mechanical lifting device such as a fork truck. If one is used, space must be allocated for its storage and provisions made for charging its batteries. Care must also be taken during the equipment layout portion of the facility design to allow space for columns to be maneuvered to a packing room and back. Safety issues also need to be considered. In our experience, 1.4-m columns are the largest that have been packed out of place — and doing so required the purchase of a specifically designed electric lifting device. However, the decision to move large columns should be made with full knowledge of its impact on an overall facility design.

Because the heads of large columns are both heavy and bulky, provision must be made for head removal and lifting for packing and/or maintenance

— regardless of the packing method chosen. There remains an advantage in not having to remove the column head for packing, an event that often occurs much more frequently than maintenance requiring head removal. Several column manufacturers offer hydraulic head-lifting capabilities as part of their columns. Where such systems are used, routine column maintenance may be possible without having to completely remove the column head.

Solvent Handling: The most obvious impact of resin bed volume is related to material handling challenges with larger volumes over smaller volumes. Less obvious, but usually having greater impact on facility design, are solvent issues associated with chromatographic resins. Because resins are often shipped and stored in 20% ethanol solutions, large column sizes will cause increased concerns about solvent handling. Additionally, packing reversed-phase resins may involve hazardous solvents. In fact, because of the necessary electrical and HVAC classifications, fire protection systems, and building codes, discussions of associated solvent issues often represent some of the more challenging aspects of a design. Solvent issues associated with resin handling come up in the course of nearly every biotech facility design project.

Whether packing is manual or automated, in-place or out-of place, solvent issues will likely need to be addressed. The presence of ethanol or other flammable solvents can necessitate classifying some areas of a facility for hazardous occupancy. Such classification is expensive and generally avoided where possible. In the conceptual phase of engineering, design engineers are encouraged to eliminate the use of hazardous materials in a facility, looking for viable alternatives wherever possible. Arrangements may be made with a resin manufacturer to ship resins in less-concentrated ethanol or even another antibacterial solution. For example, some chromatographic resins are shipped and the columns stored in 1% benzyl alcohol.

A number of strategies are available to avoid hazardous occupancy classifications: control areas and/or inside storage lockers, prefabricated outside storage lockers and buildings, outdoor tank farms, just-in-time delivery to prevent warehousing large quantities of hazardous materials, flashpoint reduction by dilution, and defining small areas within buildings for hazardous occupancy (4). Some approaches allow larger volumes to be stored within a facility, thus providing designers more flexibility in their design efforts. A complete treatment of this topic of solvent handling within facilities is beyond our scope here. Readers are referred to their local adopted building codes and fire codes for architectural discussion — they vary by location. Basically, it should be understood that the presence of solvents has a potentially large impact on the design of a biotech facility.

Waste Handling: If column packing and unpacking involves the use of solvents, then necessary disposal of solvent waste may create a requirement for a separate drain and treatment system — and a separate waste handling protocol. Column unpacking also can involve the removal of resins that have been exposed to hazardous chemicals. When considering packing options, removal of both liquid and solid waste must be part of your discussion.

Packing Frequency and Operating Schedules: The frequency in which columns are packed is also a key factor in determining what method of packing is used. Often the repacking schedule is determined by performance of a column in day-to-day operation. Those columns subject to high throughput are often exposed to "dirtier" process streams. If resins are exposed to some conditions that causes them to break down, they must be packed more frequently.

As columns are packed more frequently, the operational benefits of packing in place become more pronounced. It lowers the labor costs of column packing and prevents disturbances to surrounding processes. It is possible to manually pack a column as well as to do so with an automated pack-in-place skid, but the automated approach generally produces more consistently well-packed columns. Savings from subsequently increased yields are often cited by proponents of the automated systems.

Traditional packing of a large-scale column takes about eight hours to complete.Automated column packing is generally accomplished much more quickly because removal of column heads is unnecessary. Reported packing times are about two to three hours for the full operation, with the actual column being packed in 20–30 minutes. Shorter packing times are always more appealing in terms of labor and plant operations, but their real importance is often evident in the overall operating schedule of a plant.

Manufacturing facilities are designed to produce an amount of product in a given period. Step yields, success rates, and facility uptime determine the equipment set needed to meet a specified production schedule. Gantt charts are often used during the conceptual design of a facility to confirm that the appropriate equipment set has been chosen and that there are no overlaps. If a column is packed, for example, more frequently than once a month, then time for packing and maintenance must be taken into account.

Table 1: Impact of column diameter on column weight, bed volume, and slurry tank size

Column Diameter	Cross-Sectional Area	Approximate Weight of Empty Column[1]	Bed Volume[2]	Slurry Tank Volume[3]
30 cm	707 cm^2	96 kg	21 L	50 L
80 cm	5,027 cm^2	890 kg	151 L	335 L
120 cm	11,310 cm^2	2234 kg	339 L	798 L
160 cm	20,106 cm^2	4294 kg	603 L	1419 L
200 cm	31,416 cm^2	7127 kg	942 L	2218 L

[1] Based on a curve fit of data from 35 cm to 2 m (acrylic columns) with an approximate height of 220 cm

[2] Assumes 30-cm bed height

[3] Assumes 30-cm bed height and 50% slurry (typical for ion-exchange resins; slurry volumes vary with resin type) with vessel sized to be 85% full to top tangent line

Figure 2: A Gantt chart illustrates the impact of column-packing times on tight operating schedules.

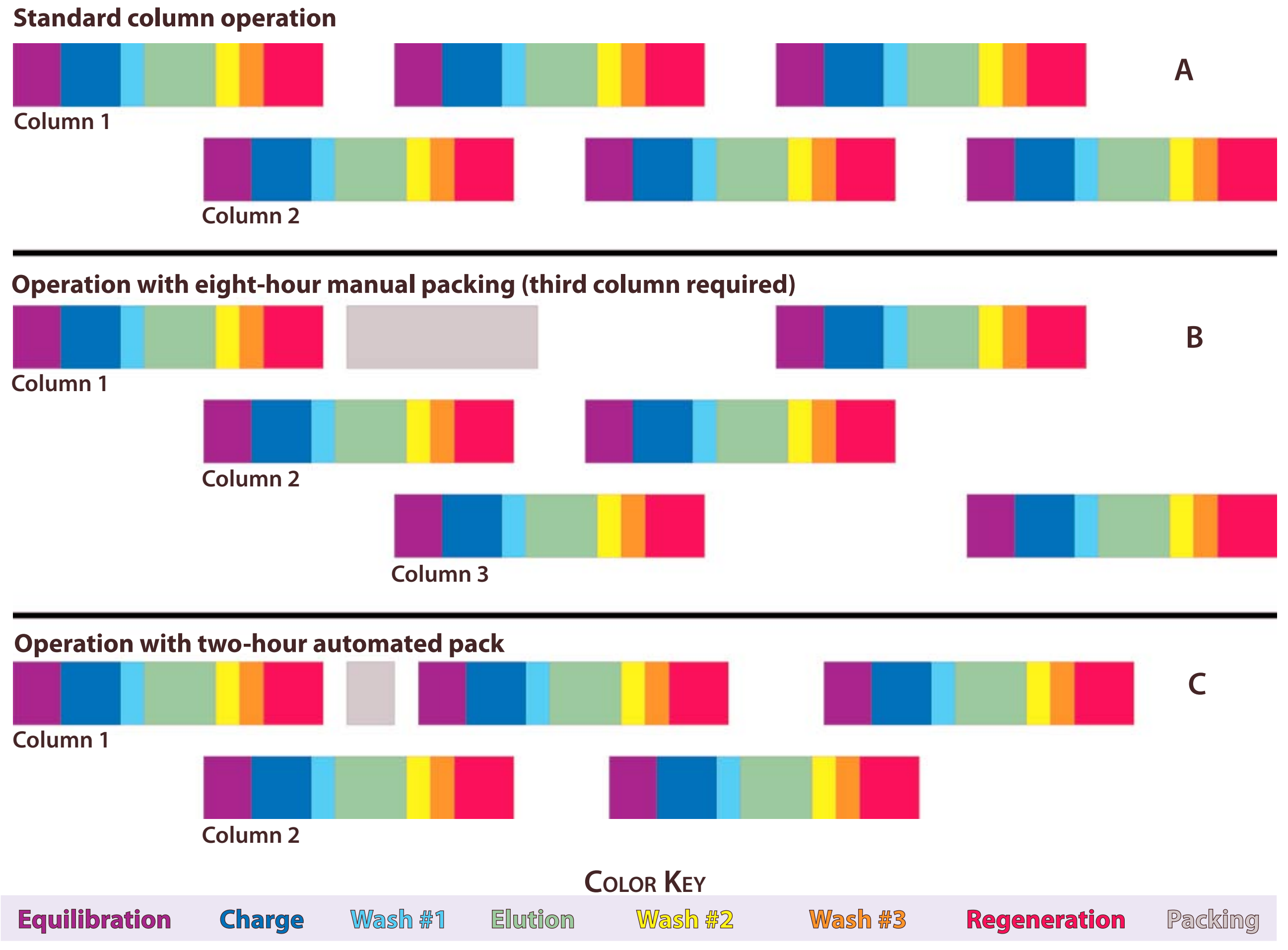

Figure 2 compares operating schedules for a two-column purification step. Figure 2A is a production schedule for one portion of a plant using two columns in a purification step during a normal, nonpacking portion of the production run. Under such conditions, the two-column arrangement is appropriate. Figure 2B shows the same arrangement when a manual packing step is involved. Because the packing step takes eight hours, Column A is not available for production quickly enough. Possible solutions might be to increase column size (and thus throughput) or add a third column train, but such options are not always practical or desirable. They are also expensive. A better solution might be to purchase columns with automated pack-in-place capability, thus reducing the packing turnaround time. Figure 2C shows the same operating scenario with a two-hour automated pack-in-place approach. Given the choice between buying new larger columns, purchasing the necessary equipment for a parallel column, or incurring the additional cost for an automated pack-in-place system, the latter is often an appealing economic solution.

Value of the Product: One advantage to purchasing automated pack-in-place systems is that the packing will be generally more consistent and of higher quality than with manual packing — thus providing better step yields. Whether an increase in yield is worth the added cost of a pack-in-place system depends chiefly on two things: the size of the yield increase and the value of the product. The size of the increase largely depends on a company's present expertise in column packing. High-quality, high-yield column packing can be achieved by trained, experienced workers. With such experts on staff, the improvement realized by automated systems may be small.

Higher yields take on greater importance to a facility as the value of its product increases. With lower-value products, the savings of small yield changes may not justify purchase of an automated pack-in-place system. Savings based on higher yields of higher-value products often cover the added cost of an automated system quickly. One approach to evaluation is to look at the range of yields from a manually packed chromatography column step. For comparison, assume the automated system will match the best manual pack and that such efficiency will be consistent. Knowing the value of your final product and examining the affect of a subsequent yield increase can prove useful in deciding the packing approach for your facility.

Value and Nature of the Resin: Chromatographic resins are generally quite expensive. Good packing design takes this into account and tries to minimize any resin losses to column packing. If a room is designed for pack-out-of-place, then slurry vessels and lines often can be designed to minimize places where resin might settle out of slurry. Similarly, if portable equipment is used to support a pack-in-place option, space and equipment configurations should minimize long lines through which slurry must pass. If that is not possible, then designers should not allow bends, low points, fittings, and other potential places for the slurry to settle.

Other Issues

Certain factors that cannot be easily quantified also should be factored in to the choice of packing options. For example, the basic type of facility being designed can have a bearing on column-packing decisions. Generally, facilities dedicated to a single product or several products to be regularly campaigned lend themselves to a greater investment in packing solutions. Sizes of columns, chromatographic resins, packing frequencies, and any special packing support needs are generally known. The investment may be in a packing room and/or purchase of an automated pack-in-place system.

On the other hand, contract manufacturing facilities are designed and built with a goal of producing safe and effective products as inexpensively as possible. Because production lines must be shifted, and future products are often unknown, flexibility is also a key component of such designs. Manual operations generally allow more flexibility than automated operations.

Early in a facility design, decisions are made about the level of automation overall. In facilities where the decision is made to emphasize manual operations over automated ones, a manual approach to packing may be in keeping with that operational approach. Equally, the difference between a strictly utilitarian facility and one that is more of a showcase might determine the method of column packing. Special segregation of processing steps within a facility may also influence the decision.

Regulatory Compliance: In any biopharmaceutical facility design, compliance with good manufacturing practices (GMPs) is essential. Although adherence is vital, how it is done varies from company to company. It is shaped by each company's philosophy and history. Some areas of particular concern to packing operations include material handling issues, flow of materials and people if columns are packed out-of-place, open/closed processing, and the repeatability and monitoring of column packing procedures. In general, pack-in-place systems offer advantages in closed processing and in repeatability as well as in flow of materials and people. Pack-out-of-place operations can offer benefits in material handling because a dedicated packing area can be more easily designed to address specific issues.

Process engineers are confronted with a number of decisions to be made concerning column packing. Such decisions are best made early in facility design, when they can have the greatest positive affect on design costs and facility operations. Chromatography equipment vendors offer equipment suitable for all the various packing techniques. Of special note are the automated pack-in-place systems that allow packing to be done in a more closed and controlled manner than was previously possible. By carefully considering column packing within the context of an entire facility, design engineers can make decisions that will benefit that facility in both immediate costs and life-time operations.

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