

Project Delivery Methods for Pharmaceutical Water Systems: Case Studies on Delivering Affordable Innovation

The method of design-build-validate is being used successfully to deliver pharmaceutical water systems as sub-sets of larger projects, for critical utility upgrades, and for system retrofits or enhancements. Within this model, opportunities exist to provide affordable innovation (AI) within an expeditious time-frame. By limiting overall responsibility to a single entity, highly-skilled within a particular field, design and engineering costs are minimized; liberating capital for innovative technology and processes. This paper will examine the traditional delivery methods for pharmaceutical water systems, investigate current trends within the industry, and discuss methods of delivering AI. Additional design techniques using risk assessment tools to minimize project expenditures, streamline validation, and forgo unnecessary processes or mechanical design options will also be discussed.

There are numerous tools that can be used to streamline projects, reduce project resource requirements, and minimize overall costs. The delivery of a water purification, storage, and distribution systems into a biotechnology, pharmaceutical or other government-regulated facility is no exception. When part of an overall project, such as a new facility or an expansion of an existing building or manufacturing operation, the water purification system is generally categorized as part of the critical utilities or process support systems. For this type of project, an engineering or design firm may provide the design and engineering for the water purification system as well as the associated equipment and apparatus. The cost of this classical engineering effort for this type of process equipment generally ranges from 12-15% of the equipment cost but can be significantly higher for smaller capacity water systems. Sound project management, establishing target costs, and other computer-aided design tools can all further reduction in work and schedule. Suppose, however, that the design and engineering of these systems could be reduced even further, freeing additional capital dollars for an upgrade in technology or superior quality and easier to maintain system components. This would be a welcome alternative to an industry that is constantly pressured to reduce costs associated with research, scale-up, and manufacturing. The subsequent discussion will focus on methods and techniques that have been used to minimize the delivery schedules for pharmaceutical water systems and other means, such as process risk assessments, that serve to qualify the use of certain system and component attributes that affect cost and performance.

A traditional project delivery method for custom systems or process equipment for the pharmaceutical or biotechnology industries would involve an owner that solicits services from a consulting and engineering firm (C&E firm). This entity may employ scores of disciplines specialized in various processes or techniques. The C&E firm is generally responsible for overall specification of the project and soliciting and reviewing sub-vendor bids. The owner may also retain a general contractor (GC) or series of contractors for execution or construction of

the design developed by the C&E firm. Additional resources such as topical experts, consultants, third party-reviewers, inspectors, and others may be used by the owner to minimize risk. No one party assumes overall risk and responsibility for the water system. This method of design-bid-build has been modified over the past 20 years as contractors have increased the engineering and design competence and A/E firms have become more proficient in project and construction management. Thus, differences between the two traditional entities have narrowed such that many single corporations are able to execute projects as design-build or design-construct. This has led to a decrease in project timeframes, project costs, and shifted the overall project responsibility from the owner to the design-builder.

Reliance upon a single-source responsible contractor is an attractive delivery method which has been adopted by industries worldwide including the pharmaceutical and biotechnology industries in the United States. By 2005, some 40% of industrial projects in the U.S. are executed with this single responsibility method according to the Design/Build Institute of America.¹ Although a design/build project delivery method cultivates an opportunity for engineers and project managers to be creative and flexible, it does little to inherently spawn the inclusion of innovative products. Design-builders can save reduce equipment costs by relying more on vendors' standard products and specifying fewer customized components. For traditional design-bid-build projects, where the specification of components and systems were not systematically linked to their procurement, the specifying engineer is inherently more unfamiliar with the actual costs of these systems. The argument can be made that a traditional design-bid-build delivery method for pharmaceutical equipment actually creates more of an opportunity for vendors to introduce novel technologies and applications into the marketplace by working with the specifying engineers who may hold innovation more valuable than cost. This is apparent based on the frequency of value engineering that occurs when the contractors issue specifications that they did not generate. What methods can be used to reduce project costs so that affordable innovation (AI) can be introduced for pharmaceutical water systems into the marketplace?

Through the years, end-users, vendors, and system integrators have adopted different methods and programs in an attempt to decrease project timelines and costs for critical utility systems. Several have adopted standard pharmaceutical water systems, design scenarios or processes, often developed by a corporate engineering group, for implementation on a plant-level worldwide. These standards, developed in the same spirit as corporate specifications, are intended to drive consistency or a baseline standard throughout an organization and also help minimize capital and operational costs. However, standards for pharmaceutical water systems are more difficult to implement when compared to other packaged equipment and components. The operation of pharmaceutical water systems

are unique; with no two feed waters identical, product water requirements varying with process and product, and operation and maintenance inherently different from plant to plant. It is inevitable that the first of these three variables leads to the greatest concern as the feed water quality, temperature, microbial content, cost, and availability are always distinct for any given feed water source. In addition, the availability of local service, groups specialized in preventive maintenance, consumables, and spare parts as well as the preferences of the ultimate owner of the system, may also influence system design or components.

The benefits of using corporation-wide standard water systems and designs can be debated. The ability for a corporate entity to dictate finite details regarding system design and operation to a plant level can result in disagreement among the parties, over-designed systems, and poor system operation. Unfortunately, because of the variability of source waters, a universal design is difficult to implement. This practice can actually lead to an increase in engineering and design and possibly re-work including expensive field modifications. For example, one may not often require the same high-class system for pilot scale applications vis-à-vis product manufacturing. However, the use of standard procedures regarding operation, cGMPs, or product water quality can be a vital tool towards adopting a sound global policy regarding any critical utility system.

The implementation of these companywide standards can extend to the structure or procedures for validation of pharmaceutical water systems. To complement company-wide water standards, templates for validation protocols and acceptance test and criteria can be developed based on the system or process. While project-specific customization is inevitable, developing templates from scratch is avoided. The familiarity with validation, commissioning, quality assurance, and facilities personnel with similar equipment and systems qualified at a specific site can also lead to cost savings.

Fully pre-engineered pharmaceutical water systems may eliminate the requirement for engineering or design firms in total for certain projects; the equipment can be procured by the end-user and installed by a contractor. It is likely that the end-user, along with the equipment supplier, must take ownership of the process warranty in this case. Having designed or been intimately involved in the details of the process, the owner has the benefit of understanding the value of all of the features of the system. When the water purification system is a subset of a larger project, the delivery method for company standardized equipment can be more complex. Although engineering and design time is minimized, an owner may not be able to have a design-build firm agree to take responsibility for a design or process that they did not engineer. The concept of "black-boxing" the water system as a stand-alone process, when part of a large overall process, can led to confusion regarding scope, responsibility, warranty, and intra-system inconsistency with instrumentation and controls.

Regardless of the potential perils discussed above regarding company-wide standard water systems, by minimizing engineering and design

project costs, additional capital can directed toward innovative products. By investing resources upfront, working with select vendors to leverage the procurement of multiple systems of identical design, and adopting a company-wide edict to enforce adoption of the standards (this being a critical element), expenditures and time are curbed. It is doubtful this program could succeed without a strong dedication from management, procurement, and a centralized corporate engineering group familiar with pharmaceutical water system design, installation, commissioning, and validation.

A second method to reduce the time and overall installed cost of pharmaceutical water systems has been driven by the equipment suppliers. Pharmaceutical water generation systems consist of several unit operations provided as part of a process purification trains. For systems associated with water for manufacturing purposes, the operations can be quite large. Although all of these components are generally purchased from a single supplier, they would require field piping and wiring among the various skids or process components. Recently, "modular", or more appropriately termed single skid systems, have been introduced by the original equipment manufacturers (OEMs). This concept has been used for reduced capacity laboratory water systems for years. For smaller systems (often up to 20-30 gallons per minute of product) all of the unit operations associated with each treatment step can be mounted on a single skid. This facilitates system installation and allows for execution of a more integrated factory acceptance test (FAT). These pre-designed and pre-engineered systems have mostly been implemented to Produce USP Purified Water for R&D, laboratory, clinical, and pilot-scale production facilities. Caveats associated with their implementation include maintenance and accessibility issues dictated by a limited skid footprint as well as the ability to handle variable feed water conditions. Also, as with any pre-engineered process component, the flexibility to forgo certain preferences must be tolerable. These may include preferences such as valve or instrument types and manufacturers, automation, controls, and possibly certain codes and standards.

Procurement of OEM standard equipment may also lead to additional time or resource savings during commissioning and qualification of the system. A recent trend for direct impact sys-

Table 1: Design-Build-Validate Project Delivery for Pharmaceutical Water Systems Using Specialized Firms

Advantages	Concerns
<ul style="list-style-type: none"> • Capital savings leading to AI • Single point of accountability • Process/Performance guarantee for entire system performance through points-of-use • Integration of validation into project lifecycle • No repetition of testing activities • Project timeframe reduction • Expertise of DBV firm within specific field • Creates environment for imaginative methods for cost reduction 	<ul style="list-style-type: none"> • Experience of DBV firm with all areas (engineering, design, procurement commissioning, validation, preventive maintenance, and on-going operation) • Forgoing certain design review steps, preferences, or sub-contractors may be required for fast-track projects • Level of trust must exist between DBV firm and client/owner • Detailed User Requirements Specification (URS) required to guarantee establish expectations • Expertise with auxiliary systems

tems includes pre-qualification of systems and processes as extensively as possible in an attempt to minimize the commissioning and qualification work in the field. Extensive FAT testing for pharmaceutical water systems is now a frequent occurrence. This includes factory testing the performance of individual unit operations such as reverse osmosis (RO) and continuous electrodeionization (EDI) systems. Many companies are now employing FAT documentation and test results to be considered an integral part of system validation, forgoing repetition of testing and assessment during the commissioning and qualification phase. As example, Installation Qualification (IQ) activities are not repeated in the field if they have already been executed during the FAT. While this practice may be more onerous on the OEMs, IQ and OQ site activities are most definitely streamlined.

Several OEMs for pharmaceutical water generation equipment have developed these modular systems based on state-of-the-art equipment. Full-fit pharmaceutical-grade RO membranes, EDI technology, hot water sanitizable components, and all stainless steel tubing systems are often included. This standardization has made innovative products more affordable and attractive to a broader range of projects and companies.

The use of company or vendor standards can be integrated into a project regardless of the overall delivery method provided that there is motivation on the part of the owner. Both of these methods can also be used to drive the qualification process upstream into the design, engineering, and factory testing to minimize downstream, costs. This becomes more difficult in a traditional design-bid build project which involves a separate CM and AE, and may also involve a third party validation group. The use of a design-build-validate project delivery technique can be used to integrate and augment all of these prospective savings. Expanding the concept of design-build to include validation, and using a responsible group highly skilled in the design, engineering, installation, and commissioning, to deliver a validated pharmaceutical water system can result in significant savings that can be used to deliver AI all within an attractive budget and timeline.

The use of a design-bid-validation organization specializing in pharmaceutical water can lead to significant cost savings systemically throughout a project lifetime. These may include the use of standard systems as discussed above, but will also include reduced engineering and design fee due to the high-level of experience held by the specialized firm. Specification development and review, design hold points, and owner involvement can all be minimized to reduce schedule. Procurement costs can be reduced by sole-sourcing or forgoing extensive purchasing specifications. Procurement of identical systems to other sites for a certain company can also minimize engineering costs.

Undoubtedly the biggest cost savings available within this method is the time saved on logistics from not having multiple groups involved. When a new group becomes involved in a project, be it for engineering, design, procurement, project management, commissioning, validation or other activities, it inevitable takes a certain time for this individuals assigned to the project to become familiar with the project details. Having the same group or individuals start-up and commission the system that was responsible for the design leads to not only a detailed familiarity with all components and functions of the system, but a strong sense of ownership and accountability. This intangible benefit is invaluable. Table 1 lists some of the advantages and possible concerns related to the design-build-validate method of project delivery for pharmaceutical water systems.

Case Study #1

A manufacture of medical diagnostics required a new USP Purified Water Generation, Storage, and Distribution system as a result of concerns regarding the operation, maintenance, and performance of an existing system. Based on commitment to replace a temporary system within an exist-

ing timeframe it became apparent that a traditional approach of proceeding with a conceptual design, proceeding to a detailed design, bidding execution of the project, and then contracting services for validation would not be possible within a mandated six month time period.

The owner contracted a specialized firm to take sole responsibility of all activities from conceptual design through preparation and execution of the Operational Qualification (OQ) for the entire system. By waving certain engineering hold points and client review of specifications, the engineering and design time is minimal. Standard generation equipment was procured from a reputable supplier without issuing specifications for bid. This resulted in obtaining a complete hot water sanitizable RO/EDI systems at a fraction of the cost if the project was competitively bid. The USP Purified Water Storage and Distribution System were installed with minimal upfront engineering and no preliminary isometric drawings of the distribution loop, saving significant additional cost. This allowed for a completely orbitally welded Series 316L Stainless Steel tubing system, with complete boroscopic and video inspection and zero dead-leg use-point valves to be installed at a very reasonable cost. The USP Purified Water Storage System includes a state-of-the art, yet off-the-shelf, ozonation system that has eliminated any concern regarding microbial control issues at the site. By streamlining the validation activities and preparing protocols based on the design documents, by the same group, resulted in additional savings.

Case Study #2

A pharmaceutical manufacturer recognized that the USP WFI system used for several purposes in a multi-product facility had exceeded its useful lifetime and that a complete replacement of the system was required to minimize the poten-

tial risk of downtime. A system designed, engineered, installed and validated in accordance with cGMPs was required. Prior to gaining approval for the project, an initial conceptual study was performed which included estimates for the complete design, procurement, installation, and validation of a new WFI pre-treatment system and a new WFI Distillation Unit and Pure Steam Generator. Cost estimates were obtained from an AE firm, using a traditional design-bid-build deliver method and a specialized design-build-validate firm based on sole-source responsibility for the project. The cost estimates for the traditional design-bid build and the actual costs for the design-build validate with specialized contractor are shown in Table 2.

The universal cost savings for the design-build-validate delivery method can be attributed to many different factors. It is believed that the discrepancy in the equipment numbers can be attributed to the inexperience of the design firm with this type of equipment and mark-ups from a general contractor or sub-contractor procuring the equipment from an OEM. Cost savings were also realized by using existing client specifications, existing specifications from the selected firm, and using highly-skilled engineers with multi-disciplined experience to design, engineer, and commission the equipment. The client had a strong engineering staff and was able to assign an internal project manager and design review team for the Project. Working closely both the design-build-validate firm through regular project meetings and constant communication, expectations were always met. Two factors during the execution mode were extremely important. The design-build-validate firm established a field office at the facility, fully staffed and equipped. The day-to-day interface and exchange of material streamlined the design and engineering effort and resulted in a design that was highly responsive to the specific Site requirements. The second factor evolves from the field-execu-

Table 2 - Cost Comparison based on Quotations for Case Study #2 - All values in Millions of \$

	Design-Bid-Build with general A/E firm	Design-Build-Validate with specialized firm
Design / Engineering	\$2.0	\$0.2
Project Management	\$0.3	\$0.3
Equipment	\$6-\$8	\$2.7
Mechanical / Electrical Work	\$2.0	\$1.8 - \$2.0
Commissioning / Installation	\$0.5	\$0.2
Validation	\$1.5	\$0.3
Total Validated Cost (TVC)	\$15 - \$18	\$5.5 - \$6

tion method. The time to complete the project is reduced from years to months.

The discrepancy between the validation costs is more tangible. By relying on a firm to develop the validation documents and perform and assist with the execution of the system qualification, the validation costs were reduced from a conservative estimate of 10% of the project price to approximately 2%.

The system included a state-of-the-art dual train system with complete redundancy throughout. The highest quality of sanitary materials and components were used throughout, even in the process areas that are generally considered non-sanitary for pharmaceutical water systems. All components, including RO pretreatment unit operations have the ability to be automatically sanitized with hot water.

All of the methods for delivering AI in the above examples are centered on ways to reduce other project costs to free investment dollars that can be allocated for technology. An additional technique for reducing unnecessary mechanical or equipment attributes while still maintaining a quality system should be investigated. It is all too common a practice in the pharmaceutical water industry

to concentrate on the materials and features of a process and discount the process itself or to spend an enormous amount of time and resources on qualification, but far less on process design and development. The former directive results in highly expensive systems, inevitably reaching far beyond project budgets, and requiring value engineering to contain costs. The ironic point is that value engineering requires additional engineering to perform.

To minimize unnecessary components, processes, and attributes for pharmaceutical water systems, one can review each item to

consider the actual impact that it may have on the system design or operation. In most pharmaceutical water systems, it is the ability to control microbial proliferation throughout the entire generation, storage, and distribution system that is most critical. Practical microbial control techniques should be investigated and more expensive techniques that deliver minimal return should be eliminated.² Current industry applicable documents such as the ISPE Baseline Guide for Water and Steam Systems² or Chapter 1231 of the United States Pharmacopoeia (USP28)³ are excellent references that discuss the considerations for Good Engineering Practices for Pharmaceutical Waters.

Once potential aspects have been identified, a simple risk assessment, such as a Failure Mode Effects Analysis can be used to determine their potential value. An example of how this assessment may be used as a process design technique has been cited.⁴ Consider a USP Purified Water Storage Tank that was either continuously ozonated or held at a temperature greater than 80°C. It would be common industry practice to require a surface finish on all contact materials in the tank to be less than

30 roughness average (Ra) or possibly as low as 15-20Ra. The smooth surface would be seen as a method to minimize adhesion of microbes to the surfaces of the tank and components and henceforth colonization and biofilm formation. The likelihood of gram-negative bacteria, those indigenous to pharmaceutical waters, to survive and multiply in the presence of continuous exposure to ozone or high temperature is minimal. The argument could be made that the surface finish of these components is a minimal factor in the microbial performance of the system under these conditions is also relatively low.

This same philosophy is consistent with the recent FDA philosophy⁵ identifying, controlling, and mitigating risks, but realizing that certain levels of risk are practical and acceptable can be used as a design tool for pharmaceutical water systems to minimize costs and eliminate frivolous componentry and attributes often a result of system over-design. The time and effort should be concentrated on the process and future operation. No amount of validation can overcome a process that is not fundamentally sound from the outset.

The same risk assessment tools can be used to determine what operations of a pharmaceutical water system may be classified as critical and non-critical. This same logic can lead to certain components that are commissioned and not extensively qualified. As an example, it may not be necessary to extensively qualify a water pretreatment process, such as coarse filtration, if its operation does not have a direct effect on the final product water quality. It could be classified as an indirect impact component even though it is a division of a direct impact system. This can not only lead to cost savings during system qualification, but during design development and ongoing maintenance activities such as calibration.

AI should not be considered an oxymoron when referring to pharmaceutical water purification and distribution systems. The key elements to delivering AI are to (1) realize what the true project costs are and minimize unnecessary engineering, design, and validation work, and (2) attempt to understand what are the crucial features and benefits for the equipment itself. The former can be achieved by selecting a delivery method such as design-build-validate which maximizes the potential for savings and the later tackled by using risk assessment models and tools to make process and equipment design decisions. A level of expertise with pharmaceutical water design, operation, validation and maintenance should transcend both approaches. The results are systems which deliver AI, low life-cycle cost, and years of reliable service.

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¹ www.dbia.org

² Collentro, Andrew W., "Practical Microbial Control Techniques for Pharmaceutical Water Purification Systems", *Ultrapure Water*, March 2002.

³ "ISPE Baseline Pharmaceutical Engineering Guide, Volume 4: Water and Steam Systems (Rev. C), International Society for Pharmaceutical and Medical Device professionals, (March 31, 1998).

⁴ 2005 USP-NF Supplement, August 1, 2005.

⁵ Collentro, Andrew W. "An Analysis of the Prime Factors in a Risk Based Strategy for Microbial Control in Pharmaceutical Waters", presented at the Barnett Utilities Qualification and Facility Validation Conference, May 10, 2005.

⁶ "Practical cGMPs for the 21st Century – A Risk-Based Approach – Final Report", Department of Health and Human Services, U.S. Food & Drug Administration, September 2004.