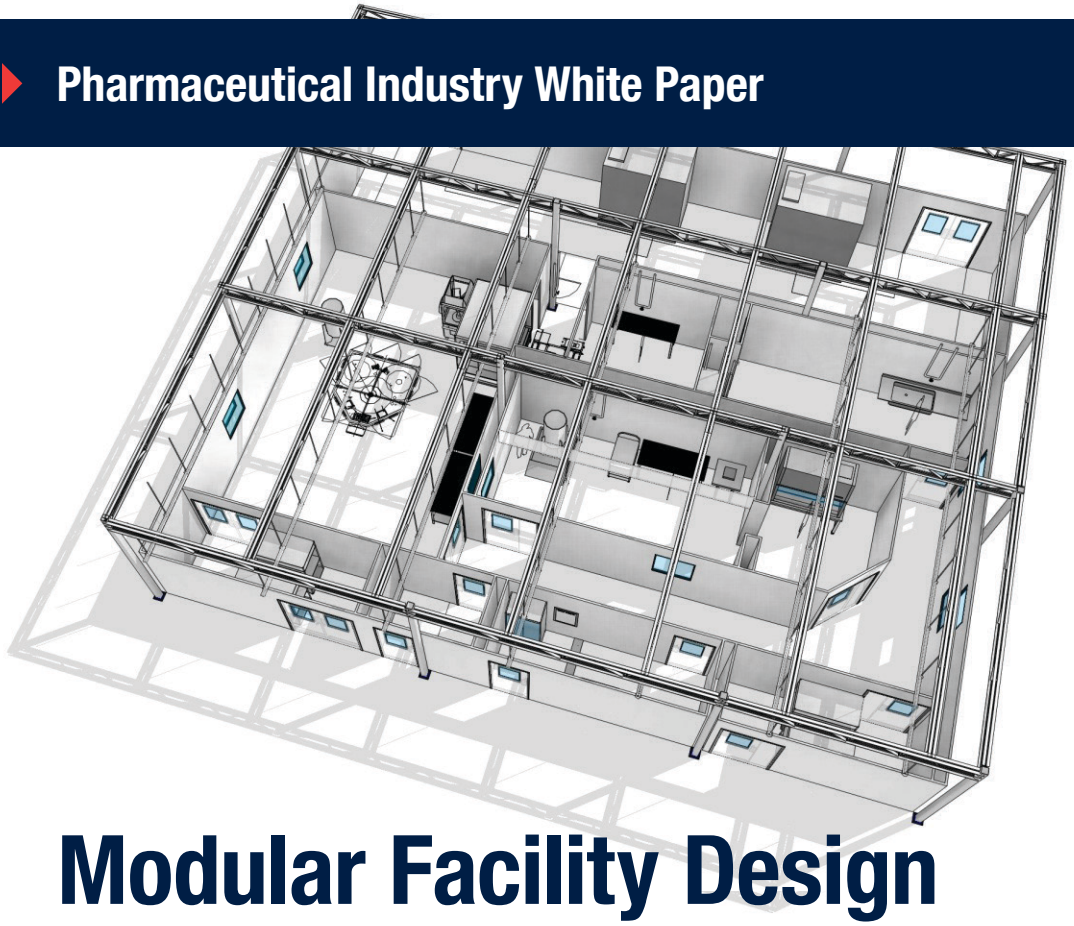

Presented by:

M+W GROUP

Modular Facility Design

A Cost-Effective Option in the Post-Blockbuster Drug Era

The pharmaceutical industry has undergone a sea of change in recent years as manufacturers have adapted to the end of the era of large-volume production of mass-market blockbuster drugs. With firms now focusing in on subpopulations of patients, there is a need for lean, adaptable facilities that can switch quickly between multiple products in multiple formats. Modular facilities can meet this need. While not a panacea, for the right project characteristics, **'Modularity in Design'** can deliver significant and quantifiable long-term value.

Modular facilities were initially introduced to an industry that still made most of its money by producing huge numbers of tablets and capsules for large patient populations, the prime example of which was the market for statins to lower cholesterol. As these blockbuster drugs began to lose patent protection around 2008, the massive, single-product manufacturing lines built to service the years of peak demand began to look like anachronisms. A series of industry-wide changes have made Modularity in Design appear more attractive to drug manufacturers today than in the past.

Today, generic copies of former billion-dollar blockbuster drugs for major indications are adequately treating various diseases and other medical indications. At the same time, a growing understanding of the genetic causes of cancer and other diseases has shifted the focus on developing lower dose yet highly potent biopharmaceutical compounds for targeted treatments. The shift has split large populations of patients into smaller subgroups. Pharmaceutical mergers and acquisition activity continues, resulting in excess capacity, plant consolidations and closures. The resultant unmet need has triggered fewer large projects, and total project investment size has contracted in some markets. Offshore CAPEX investments and global contracting is on the rise. Finally, a growing emphasis on speed in clinical development and speed to market has amplified the value of production facilities that can be delivered, scaled up, and redeployed quickly if necessary.

The upshot of these trends is manufacturers now need facilities that are flexible and can perform small-scale runs of multiple highly potent drugs in various formats including (but not limited to) solid, liquid, semi-solid, and parenteral dosage forms. They need facilities that can be assembled easily with manufacturing equipment arrangements that still offer distinct functional unit operations, yet are flexible enough to be repurposed for other dosage forms with minimal facility or business impact. Faced with this new set of requirements, manufacturers are starting to show more interest in modular facilities and using modularity in design approaches. With multi-product, multi-purpose, smaller batch sized facilities representing the new normal, this demand has also encouraged equipment manufacturers to revisit their product offerings.

Equipment manufacturers responded by introducing a wide range of technological improvements such as complete pre-assembled irradiated single-use kits that no longer require piecing together individual single-use components (filters, tubing, etc.), single-use bags, single-use mixers, and single-use product sampling kits. The demand for ready-to-use or ready-to-sterilize components, containers and delivery systems has increased. Reliance on robotics and improved levels of automation provide better sterility assurance. Manufacturing higher potency drugs, such as oncological biopharmaceuticals, requires increased levels of product containment and operator safety, and the industry now readily accepts isolation technology and restricted access barrier systems (RABS) over conventional barrier equipment enclosures, when warranted, to address those needs. Autonomous cleanrooms and modular downstream processing equipment are just some of the other readily available flexible technologies. The task now is figuring out which of these evolving technologies and facility design alternatives are most applicable, and then assembling the business case for modularity through a vigorous analysis.

Making the Business Case for Modular Facilities

There are many modular solutions offered in the marketplace. When one considers the spectrum of modularity, deciding on what makes the most business sense can be unnerving. At one end of the spectrum you have simple skidded process systems, and at the other end there are entire modular production facilities. In between these extremes, there are pre-engineered, modular cleanroom wall systems, 'house-in-house' modular cleanrooms and a variety of modular processing technology considerations (Figure 1).

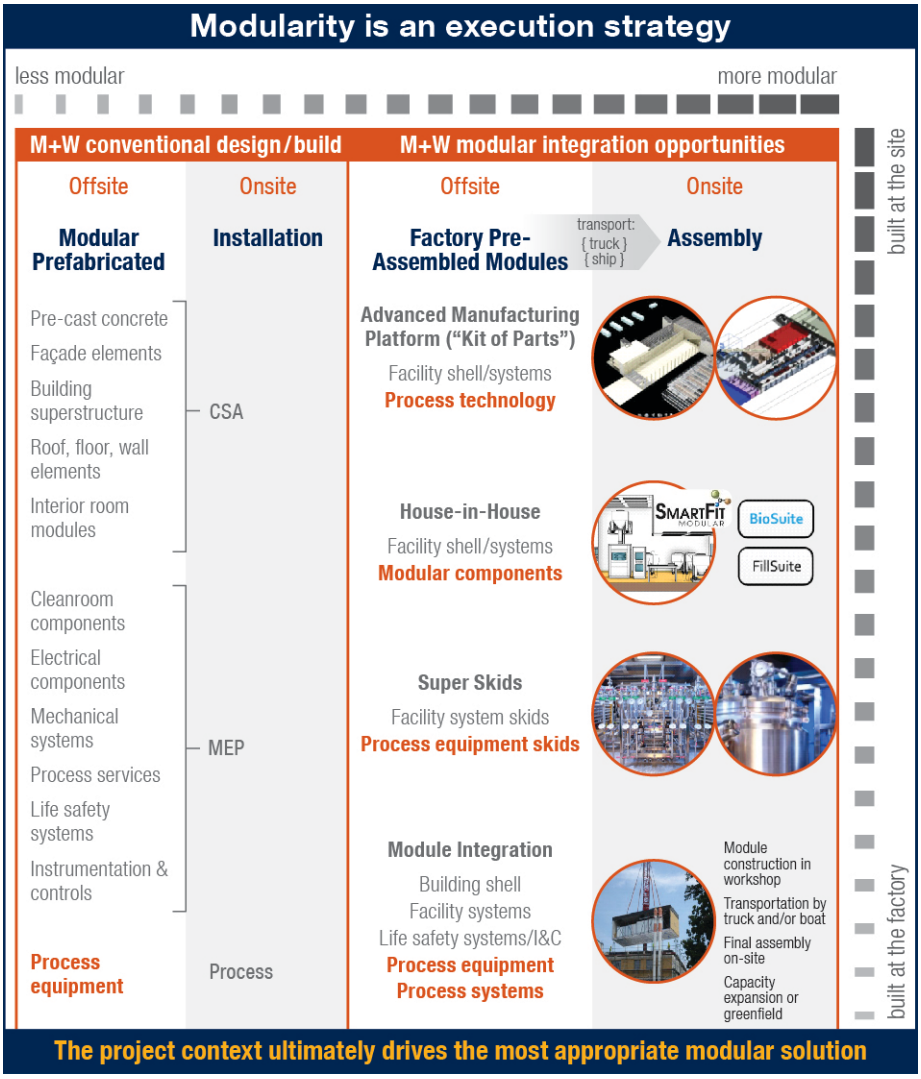

Figure 1: The Spectrum of Modularity

The smaller batch sizes, elimination of washing, depryogenation, and sterilization operations through adoption of ready-to-use containers (vials, cartridges, and syringes) and components (plungers and stoppers) coupled with flexible aseptic filling lines that can process multiple product, multi-container formats can significantly reduce capital investment, increase equipment utilization, reduce space, and support facility requirements. A modular facility that fully leverages barrier technology-enabled relaxation of area classifications also reduces heating, ventilation, and air conditioning (HVAC) requirements. These and other technological advancements have the potential of shrinking the overall building footprint by 30%–40%, which significantly drives down facility operating expenses.

Modularity and standardization also deliver value over the longer term. Modular, standardized facilities can reduce design and engineering costs since there are fewer field-related construction challenges. Setting up a fully-integrated modular facility can take considerably less time to realize than a more traditionally designed and constructed facility. Other less obvious efficiency gains from modularity include the higher predictability of a successful outcome in commissioning and qualification that comes from buying a complete pre-engineered system — which lowers management costs and increases quality — plus the ability to 'bolt on' incremental capacity in certain circumstances at a later date. If the time saving results in a product coming to market sooner, the long-term financial benefits of modularity could be significant.

The usual view, however, is that modularity is something that costs more, especially in regards to the higher upfront facility and equipment cost. In a straightforward comparison of the cost per square foot of stick-built walls vs. modular cleanroom wall systems, for example, the modular wall system components on an isolated unit base price usually cost more. However, this

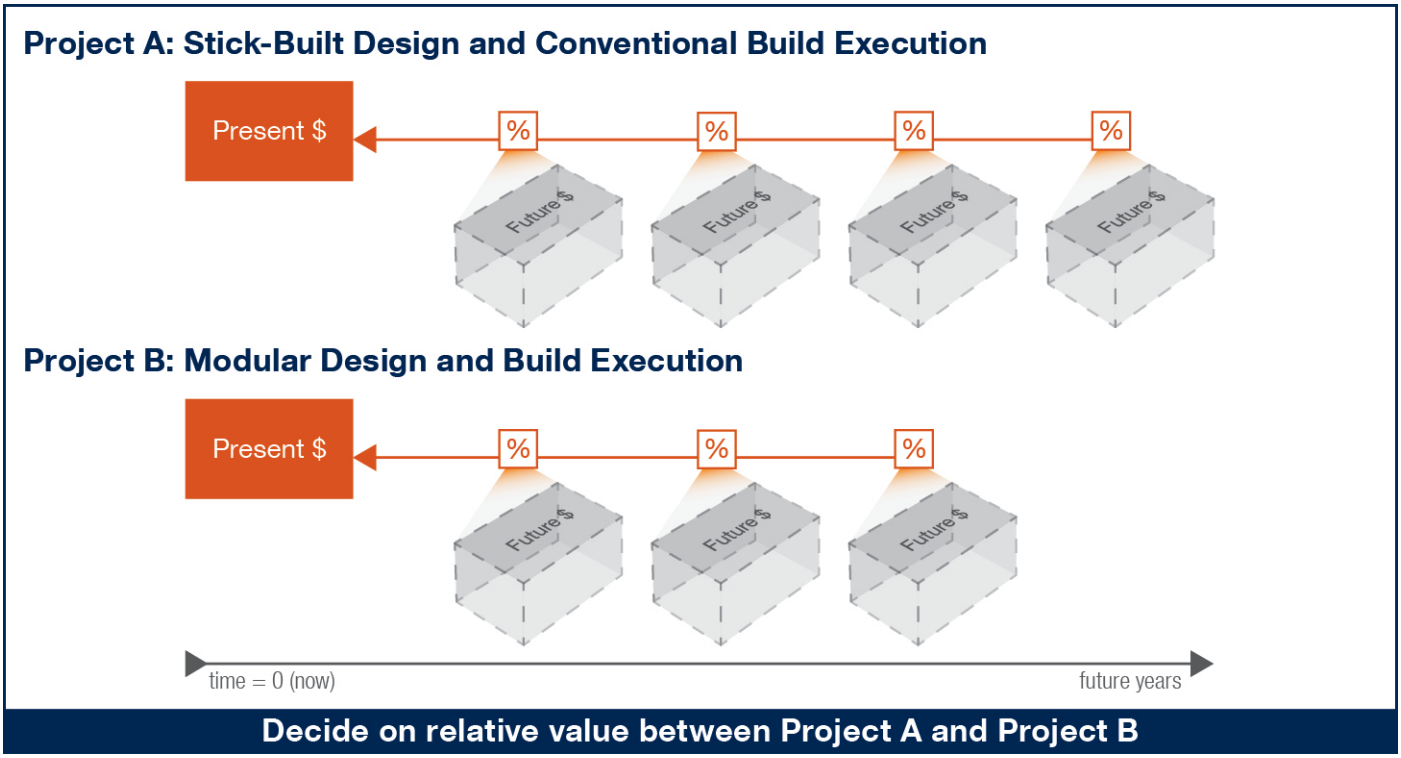

Figure 2: Comparative Net Present Value (NPV) Approach

economic evaluation is short-sighted. Given some of the hard costs for modularity are more expensive, you should not be considering isolated unit prices as the basis of your decision. There are many other considerations that factor into the equation. For example: how do modularity in design and the associated construction affect the sequencing of activities? How does modularity affect quality? Rework? What impact will it have on project direct and indirect costs? Associated contingencies? Risks?

The distinctive needs of each manufacturer and a multitude of other factors make it seem as if there simply are no shortcuts in determining the value of modularity. However, there is a well-defined process for making the evaluations — a comparative net present value (NPV) analysis. This discounted cash flow technique takes a holistic view of the costs and benefits to estimate the relative worth of investment propositions. As such, NPV considers all of the upfront costs and future cash flows to determine which alternative represents the best value for a project.

NPV is a holistic assessment used to determine whether a prospective investment will be profitable. This technique measures the discounted cash inflow to the present value cash outflow on a project. In other words, it provides the present value of the anticipated future cash flows less the initial cost outlay. If the discounted cash inflow over the project timeline is greater than or equal to the initial investment, say at time T=0, then the investment will probably be profitable. When running a NPV analysis against two or more alternative design approaches, this technique can provide greater transparency on relative costs and benefits (Figure 2).For example, a comparative NPV analysis can be run against a conventional stick-built approach versus a modular facility design, or a design that incorporates varying degrees of modularity in design and execution. Start by estimating the future cash flows expended in the conventional design-bid-build approach, and then compare them against the modular project by discounting both cash flows into lump-sum present value amounts. This approach can help predict the profitability of differing investment strategies. It is a useful tool that can assist project teams in determining if modularity actually provides the best overall value prior to presenting their capital-deployment cases to management.

As stated earlier, modularity is not a silver bullet. The project content ultimately drives the most appropriate modular solution, if applicable. Addressing both the near- and longer-term savings and comparatively weighing alternative approaches against the other is recommended to make a sound business case.

How 'Modularity In Design' Is Enabling New Production Networks

Large batch processing has long been the predominant model in pharmaceutical and biopharmaceutical manufacturing. The smaller batch size requirements of personalized medicines and other trends, like continuous manufacturing as a disruptive technology, are well served — and even made possible — by modular design. Today, a growing number of companies are moving away from having one or two big production plants that manufacture their global supply of a particular product to running a network of smaller sites, each serving their local market. Such an approach simplifies logistics and is essential in certain circumstances, especially in countries that mandate 'for country, in country' production.

Modularity in Design can facilitate the

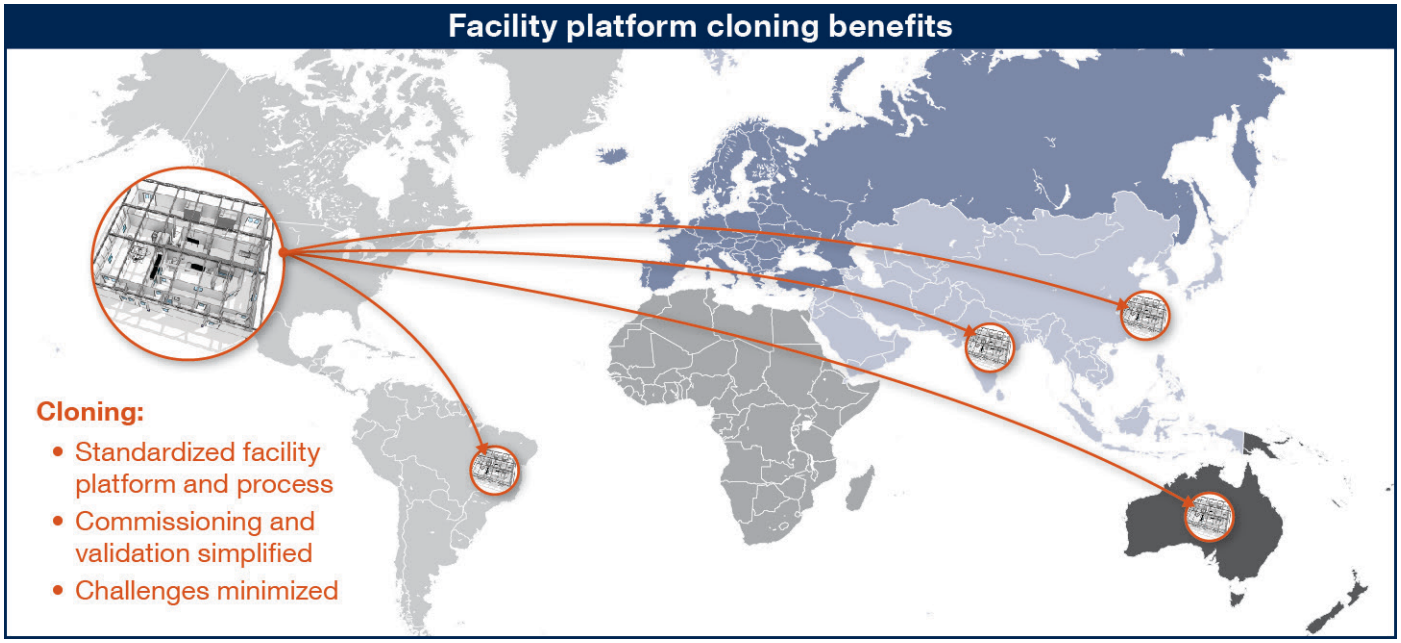

Figure 3: Global Cloning Potential

creation of such networks. Once a facility has been designed for use in one location, it can be 'cloned' and deployed around the world. While there are still certain levels of design activities specific to the country, including site adaptation, cloning greatly reduces design activities. Acting on lessons learned circumvents the risk of unforeseen delays and allows project delivery to become more efficient with each cloned facility platform (Figure 3).

Multi-product, multi-purpose facilities that incorporate Lean design attributes and enable faster facility deployments are the new normal. Designers, equipment manufacturers, and the market in general have responded by introducing a range of technologies that can support the new demands while significantly reducing the overall footprint of a facility. Combined properly with the right cleanroom/facility infrastructure and execution strategy, modular construction is made all the more appealing.

The array of options available to pharmaceutical manufacturers is greater than ever before and redefining what is possible for the construction of modular facilities with an eye on the efficient use of capital. The challenge now is to calculate which approach, conventional or modular, offers the best value for a particular project in light of the business drivers.

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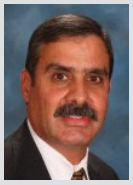

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Mike Salinas is the Director of Manufacturing Technology for M+W U.S., Inc., a company of the M+W Group (M+W). M+W is a global leader in the design, engineering, construction and fit-out of life sciences and chemicals facilities. Mike has over 25 years of experience in consulting, engineering design, and construction projects at a variety of technology-driven manufacturing companies, including Wyeth (now Pfizer), Johnson & Johnson, Amylin (now AstraZeneca), a world-leading consumer care products manufacturer, and a variety of others. Prior to joining M+W in 2011, Mike spent over 20 years in the life sciences market working for global A/E design firms, a large leading global drug company, and a mid-size generics drug manufacturer.

A pharmaceutical subject matter expert and contributing member of the International Society for Pharmaceutical Engineering (ISPE), Mike is a thought leader who specializes in the design of facilities and processes to safely make drugs in multiple dosage forms. He holds a Bachelor of Science degree from Columbia University, a Master of Science degree from Drexel University, and a Lean Six Sigma Black Belt Certification from Villanova University. Mike resides in the Delaware Valley region of Southeastern Pennsylvania.

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