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COMMENTARY

A Review of the Aging Process and Facilities Topic

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ABSTRACT: Aging facilities have become a concern in the pharmaceutical and biopharmaceutical manufacturing industry, so much that task forces are formed by trade organizations to address the topic. Too often, examples of aging or obsolete equipment, unit operations, processes, or entire facilities have been encountered. Major contributors to this outcome are the failure to invest in new equipment, disregarding appropriate maintenance activities, and neglecting the implementation of modern technologies. In some cases, a production process is insufficiently modified to manufacture a new product in an existing process that was used to produce a phased-out product. In other instances, manufacturers expanded the facility or processes to fulfill increasing demand and the scaling occurred in a non-uniform manner, which led to non-optimal results. Regulatory hurdles of post-approval changes in the process may thwart companies' efforts to implement new technologies. As an example, some changes have required 4 years to gain global approval. This paper will address cases of aging processes and facilities aside from modernizing options.

KEYWORDS: Aging facility, Drug shortage, Single-use technology, Modular facilities, Post-approval changes.

The Problem Statement

Aging facilities are a reality and a rising concern, not only in the traditional drug manufacturing regions, but also in emerging markets. The problem is accelerated by the desire to reduce cost of goods sold to stay competitive or fulfill healthcare cost demands. Strict cost of goods sold control may mean the lack of investments either in manufacturing redundancies or improvement activities (1).

Many aging facilities can work capably without problems, but that may be the exception and not the rule. Aging processes and facilities most commonly run smoothly due to the experienced workforce running the same. Well-trained personnel with a process ownership mentality ensure that such facilities run, but it is only a question of time when such personnel will move, be promoted, or retire. Personnel following the initial process owners have to be well trained and adopt a similar mindset, or the facility or processes will experience issues including excursions.

Even when experienced personnel run the process and facility, ultimately equipment will age even with routine

maintenance. It is a question of time as to when the skilled production personnel can no longer compensate for the lack of equipment modernization. Facilities, processes, and analytical tools become obsolete, run out of spare parts, and lose the necessary performance properties. In some instances the facility, processes, and analytics receive the required attention, continuous servicing, and improvements, but these are the exception and not the rule especially when the focus is costs or the production capacity prohibits a slow-down.

The most common practice is an annual shutdown of the site and the running of the maintenance program within that timeframe. This approach may work over a period of time but not over the long run. Servicing and improvement within the shutdown period is under time scrutiny, and improvement robustness may vary from shutdown period to shutdown period. Given the time constraints, a "Band-aid" approach may prevail, which will result in predictable surprises (2). A major reason for the latter is the focus on cost reduction; the attitude that every possible cost needs to be squeezed out of the cost per dose. That can only happen when the equipment and facility is utilized to the fullest without improvements and the attendant costs. It is a question of time when this cost saving approach will be surpassed by the cost of poor quality, assumed savings may turn into major liabilities. When the process finally breaks down, multiples of those savings are

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spent to regain control of the process and facility. Many times, however, the process cannot be recovered in such an exercise. Examples of the described scenario should not be considered exceptional. Too many recent examples can be readily found in a review of the literature (3, 4).

Notably, companies that implemented continuous improvement and modernization activities actually realized more savings than the ones who focus on milking overstressed equipment and maximizing facility utilization without maintenance and proper upgrading (5). There are many examples where the facility and process may not be aged, but the production capacity has been extended or scaled-up over years to meet rising demand. Oftentimes this results in technology differences from the original area to the extended area, leading to difficulties in synchronizing the technology status or the flows of materials, people, and waste. Process technology improvements in existing facility infrastructures can also be difficult, if not impossible. For example, many companies have tried to implement modern single-use technology into their existing cleanroom infrastructure, but it quickly became apparent that fluid transfer and movement of equipment was hampered by the old infrastructure (6).

Another form of aging facility is one that still runs efficiently but the product, which was produced in a space dedicated entirely for it, loses patent protection or has been replaced. These processes, if not total facilities, are mothballed and become unutilized assets or, more aptly, liabilities. Facilities such as these must be secured, insured, heated, and cooled (at least minimally). They are taxed; usually at very high values given the prior use and value of the products produced. A planned demolition is expensive, time-consuming, and requires significant regulatory and governmental involvement.

The regulatory hurdle of post-approval changes (7) also leads to an aging facilities problem. Two issues face manufacturers in a post-approval process change decision are (1) how the change is classified? and 2) how much investment is required to gain global approval of the change? There is no clear path in classifying a change, which creates questions for the filing party and regulator alike. This disjunction can escalate the cost and time associated with the proposed change. Furthermore, if the manufacturer is a global supplier, multiple regulators will have to be satisfied, which makes the cost and timeline even more unpredictable.

This not only means that a global post-approval change can take up to 4 years to be accomplished, but production processes, lots, and inventories may vary in the interim due to the delay in approval status. This creates a tremendous stress and uncertainty on the manufacturing process, supply chain, and working capital of the medicinal drug supplier.

Technology advances are happening in every industry to enhance quality, efficiency, and capacity. One of the slowest industries in terms of implementation of advances is the pharmaceutical industry, with an average implementation time of 10–15 years for new processes (which often coincides with innovator drug product life-cycles). This extended timeframe shows that new technologies are most commonly implemented through the drug product development cycle and not as a post-approval change activity. Classic examples of new technologies that created tremendous advances but were adopted very slowly into the industry's processes are isolators, blow-fill-seal filling systems, single-use technologies, and more recently membrane chromatography. In most cases it took more than a decade to get the new technologies accepted and implemented. Although industry and regulators alike postulate that new technology implementation and modernization is required to advance production platforms and potentially reduce the cost per dose, the consensus of how to do so on a fast-track basis has not been reached.

Efforts To Date and Possibilities

In the mid-1990s, the PDA initiatives on post-approval changes, like SUPAC and PAC-SAS discussions, showed promise, though they fizzled out. The outcome was minimal and far from what is required to make a real impact on post-approval change speed and methodology. The initiatives taken would have supported modernization and innovation efforts within the industry, if post-approval change classification or methodologies were established. A Product Quality Research Institute (PQRI) initiative took the activity a step further and came up with a very helpful document, which utilizes risk assessment tools to determine the impact of the change (8). It probably was/is the most comprehensive and practical assessment of post-approval changes and may be a good basis for additional work and progress to be made. The excellent work by the authors of the document should not be forgotten, but rather picked up to further the effort and potentially use the risk assessment tool presented as a base method for post-approval changes, though the method

requires the risk assessment tool to be recognized by all regulatory parties.

Ultimately, swift process and facility modernization starts with the modernization of the global regulatory system. The current length and fragmented nature of the change process does not present any incentives to the industry. Rather, it prevents rapid deployment of technologies, which may enhance safety, efficiency, security, and quality. Regulatory harmonization of the post-approval change process and requirements would be a first encouraging step forward.

In the absence of a global regulatory approach, or perhaps even with the same, the industry must change its mindset. Too often, processes are built on legacy models or involve suboptimal steps. Time pressures with development cycles do not allow appropriate technology scouting and testing. Therefore, the same process or approach is utilized, even when the past has shown that process steps were suboptimal or required improvement, e.g., stick-build cleanrooms. The success and efficiency of a manufacturing process lies in its design and early verification testing. If a process consists of a patchwork of unsynchronized steps, the end result is predictable and disappointing. The weakness of the process puts significant emphasis on the human factor, which means that training and experience of the personnel is essential to keep the process stable. If the process is designed using new processing technologies, including automation and state-of-the-art sensors, the human factor impact is minimized and the process runs in a more robust fashion consistently. Peers within our industry who presented on their new technology implementations have shown not only consistent quality success using new technologies, but also the financial benefits of such initiatives (5, 9, 10).

The industry also needs to be willing to learn from successful implementations and reproduce the same. There is a vast amount of experience within the industry, but when one reviews all processes and the surrounding infrastructure it is noteworthy that there is rarely, if ever, an example of a cloned facility or process. This is true despite that fact that it would be cheaper and faster to build and to validate such duplicated manufacturing system, as one can build on the cloned project.

It has been noted that the expectation for the future is that agile, innovative facilities will have to move to smaller footprints, with continuous manufacturing be-

coming a prevalent modus. Large capital budgets no longer exist, and the inventory of abandoned facilities is a constant reminder of the need to spend resources in a more careful fashion. Cloning such smaller sites or having a multitude of such processes in one site is even more efficient. The experience level of the operators and regulators becomes deeper and process modernization easier with smaller, less complex manufacturing systems. The more simplistic the process, the smaller the impact of a change.

We have seen the beginnings of miniaturization in bioreactor volumes within the biotech industry. Due to ever improving expression rates and process optimization, reactor volumes have moved from 20,000 L to 2000 L single-use systems and probably will shift to 200 L volumes in continuous bioprocessing in the future. What was a substantial investment, as well as a highly complex process, becomes a system with significantly lower complexity, faster deployment, easier scalability, and even possible redundancy. Such a shift aids in avoiding supply shortage and reacting to demand fluctuations.

The current discussions about flexible facilities, manufacturing on demand, and manufacturing of the future are very much based on such new technology implementation and the duplication of such successful executions. The trend to smaller, more flexible, multi-product or multi-purpose facilities and continuous processing is not just an idea, but it is quickly becoming a reality.

In considering aging facilities, equipment inside the facility should not be overlooked. Continuous improvement, process and equipment maintenance, and proactive prevention are all critical components to keeping a facility modern. With regard to process equipment, users should work closely with their equipment suppliers. The supplier's knowledge of the equipment lifecycle and maintenance needs are important pieces of the overall production process. Working with the supplier, a user can ensure that raw materials and spare parts are readily available thus preventing production stoppages or on-the-fly machine upgrades. For example, a circuit board, a component of a particular piece of machinery, is not any longer available, but a new design with new components and similar functionality is. This may mean the piece of equipment will experience substantial change with better functionality. Regardless of the improvement, the process has now changed and has to be handled as such. Such a change takes time to implement. Meanwhile,

the production has stopped during this process. A simple supply agreement could have prevented the same. The contractual agreement, which defined the timeframe for receipt of the component, material, or equipment such that the item could be implemented and validated in a timely fashion, could have prevented the stoppage. Similarly, requiring the supplier to provide an early warning system that notifies the end-user of upcoming changes could have prevented the stoppage. In addition, comparability protocols established by the supplier could support the end-user's activities. In each of these examples, the end-user and supplier are working closely together to proactively plan for, implement, and validate the changes.

Another component to keeping a facility modern is to establish and keep maintenance or improvement teams active within the end-user's organization. Such teams should continuously review the process, unit operation, and equipment functionality and robustness. If aging is witnessed, such teams can work together with the supplier base to identify and evaluate new solutions. These new solutions may not just replace old and obsolete equipment, but may increase the efficiency of the same. Such efficiency improvement, however, can have a ripple effect that should not be discounted. A more efficient process upstream could lead to a bottleneck downstream. Hence the phrase "proper planning prevents poor performance" should be heeded when process steps are evaluated for improvement or modernization.

Conclusion

Aging processes and facilities are not a rarity. Many examples, supported by regulatory citations, can be found. A major culprit for aging facilities and processes is the widespread belief that improvement activities will only increase costs without any incremental benefit. Woodcock and Wosinska elaborate on the fact that low-margin drug products make investments into aging processes unattractive. For this reason, older process equipment is utilized, even when it may mean manual interventions or breakdown. Examples of continuous improvement activities, however, show just the opposite. Proper improvement and modernization planning supports the efficiency and productivity of the processes and therefore financial gains (5). In addition to productivity, processes run at a higher quality and safety level without interruptions, regulatory scrutiny, and frequent human interventions.

Aging facilities and processes can be avoided with proactive planning, working together with suppliers, performing technology scouting and new technology implementations. The drug manufacturing industry to a large degree embraces all of these activities. Modernization of the post-approval change process, however, must occur before wholesale modernization efforts can happen.

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