Guide to Maintaining Validation of Older Facilities:

Why, When and How

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There is no definitive guidance for the lifespans of specific equipment, utilities, and systems that make up manufacturing facilities — and aside from cleaning/sterilization equipment, very little guidance regarding how often each needs to be validated and maintained to comply with changing industry standards and production trends.

This guide explains some of the most common challenges found in aging facilities, tips for identifying when a facility requires revalidation, and how to assess aging facilities, utilities, systems, and equipment for revalidation or maintenance needs.

WHY Aging Facilities Pose a Problem

Pharmaceutical manufacturing facilities that are left to age without proper maintenance and upgrades can present serious implications, both in the quality of the drug produced and the overall market supply.

Consider these examples of risks associated with older facilities.

1. Potential Drug Shortages

As of December 2020, the FDA reported a total of 118 drugs in short supply.[1] The number of new shortages identified in a calendar year in the first two decades of this millennium peaked at 267 in 2011.[2]

2007 marked the beginning of a sharp increase in drug shortages with 129 — the same number identified in 2020 — with the total number fluctuating annually.[2]

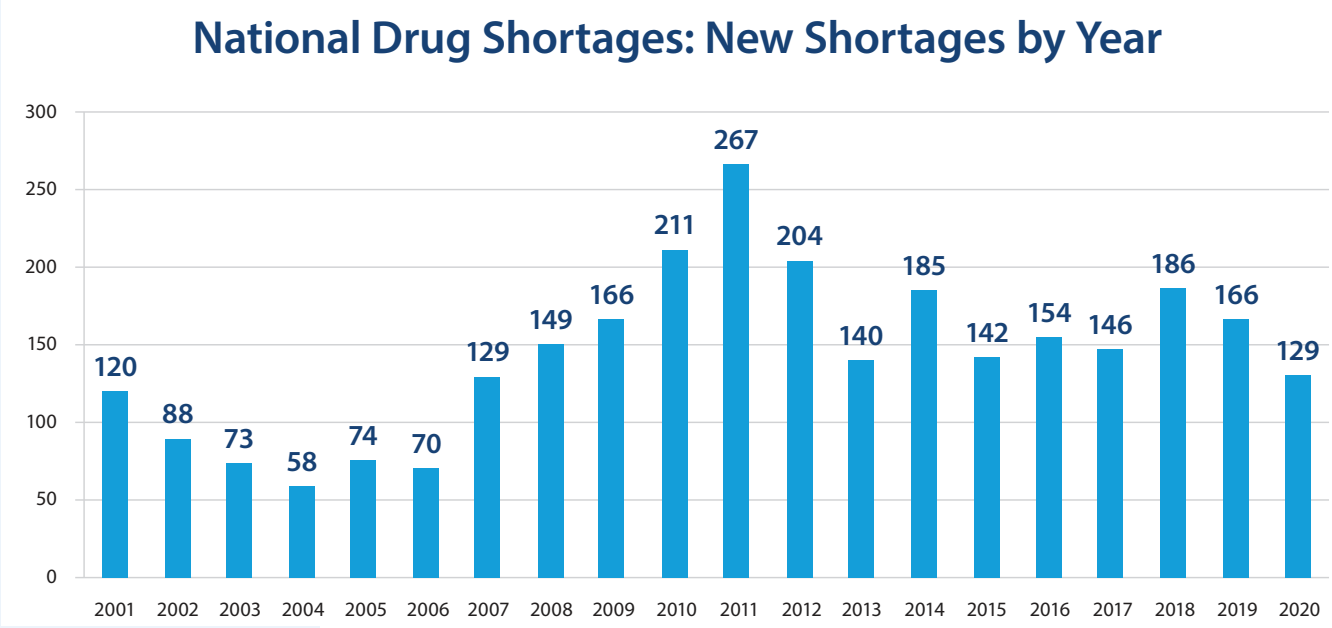

Figure 1. New drug shortages identified by year. Data from University of Utah Drug Information Service, sourced from American Society of Health-System Pharmacists (ASHP).[2]

The third-most cited known reason for drug shortages in 2020 was related to manufacturing, according to an investigation by the University of Utah Drug Information Service, preceded only by business decisions and supply/demand.[2]

What makes manufacturing such a critical bottleneck for maintaining appropriate drug supply? Limited access to raw materials, insufficient number of plants, production line availability, and quality issues — all of which require long-term planning and remediation.

2. Risk of Contamination

As manufacturing facilities age, potential contamination sources can steadily creep in, including equipment degradation, structural integrity issues, and declining air quality, which should be monitored by quality systems.

Facilities that are not regularly and holistically assessed for quality gaps run an enhanced risk of exposing products to environmental contaminants that can compromise product quality and human health.

3. Regulatory Citations and Costly Downtime

When an FDA audit reveals noncompliance with regulatory standards, the associated penalties and remediation work are far more costly than it would have been to appropriately maintain a validated state throughout production.

Many consent decrees are notoriously lengthy and costly, with some spanning over two decades and penalties eclipsing half a billion dollars for GMP violations and subsequent fines for missed deadlines.

4. Inheriting Older Facilities and Processes

With mergers and acquisitions in the pharmaceutical industry at an all-time high before the COVID-19 pandemic ($414 billion in 2019)[3], companies are inheriting older facilities and the challenges that come with them, including disparate processes, dated records, and varying degrees of documentation of past qualification activities.

Without an overarching, cross-facility quality systems integration strategy, CQV policies and procedures are left to the individual facilities, which can lead to the aforementioned quality, compliance, and supply issues.

Industry thought leader, Maik Jornitz, suggests that companies can slow the aging process by reinvesting funds into technology improvements and maintenance programs.

> *"Ultimately, running assets until they break down will cost much more than continuous improvements. If (companies) can show that new technology improves patient safety and avoids drug shortages, I think regulators will listen."*
>
> **Maik Jornitz**
> President and CEO, G-Con Manufacturing
> Co-Chair, Parenteral Drug Association's former Aging Facilities Taskforce[4]

WHEN Is It Time to Revalidate a Facility?

Manufacturers should strive to maintain a validated state for all equipment in the facility, but with differing recommendations on revalidation timelines, it is generally not feasible or pragmatic to keep each piece of equipment on a predefined validation schedule.

Instead, your best course of action is to implement a reliable and robust engineering and quality change management program and ensure your quality system is structured to support a dependable validation maintenance program.

Beyond those proactive steps, consider revisiting your validation strategy if any of the following apply.

1. It's Been Over 10 Years Since You Initially Qualified Your Facility

In the past, experts have estimated that pharmaceutical facilities are designed to run well for 20–25 years[4], but rapid advancements in equipment, techniques, and science have made the turnover much shorter. Imagine if your facility was still operating as it did at the turn of the millennium?

If you initially qualified your facility more than 10 years ago, it's likely time for a revalidation. Ideally, you would have undertaken several risk assessments and performed general maintenance and upgrades during that timeframe to ensure good manufacturing practices.

2. You're Planning to Manufacture a New Product

Equipment and utility requirements can vary even for similar products. Long before the planned manufacture of a new drug product or component, be sure to assess your current facility's suitability by looking closely at your cleaning and sterilization processes, airflow and air quality, computer systems, and more.

3. Your Facility Does Not Meet the Latest Industry Regulations and Guidance

With industry recommendations and mandates constantly in flux from the FDA, EMA, ICH, WHO, ISPE, PDA, ISO, and many other global regulatory agencies, it's inevitable that equipment and processes fall out of compliance.

Try to stay informed of the latest proposed, drafted, and finalized standards that impact your facility. If new guidance calls for a deviation from your standard operating procedure, it's best to immediately assess your equipment and processes against the latest standards and make upgrades accordingly to ensure compliance.

4. You Have Not Followed a Regimented Facility Maintenance and Update Schedule

General maintenance is simple in nature, but paramount to quality, clean production. Check the building's structural integrity regularly to spot signs of water or air leakage, wall or foundation cracks, and general wear-and-tear of doors, windows, pipes, and more — ideally before the damage advances to a point where the product could be compromised.

When it comes to equipment, pay special attention to mission-critical components, but don't lose sight of the more understated pieces. Contact the equipment manufacturer to ensure your team has all the skills and instructions necessary to adequately maintain the machinery and secure any spare parts required to carry out repairs.

People are just as important as technology, so invest in robust and ongoing training programs to ensure maintenance professionals are equipped to handle any repairs or regularly scheduled maintenance as needed.

Lastly, establish and track KPIs to know if your maintenance program is making an impact on your facility's performance.

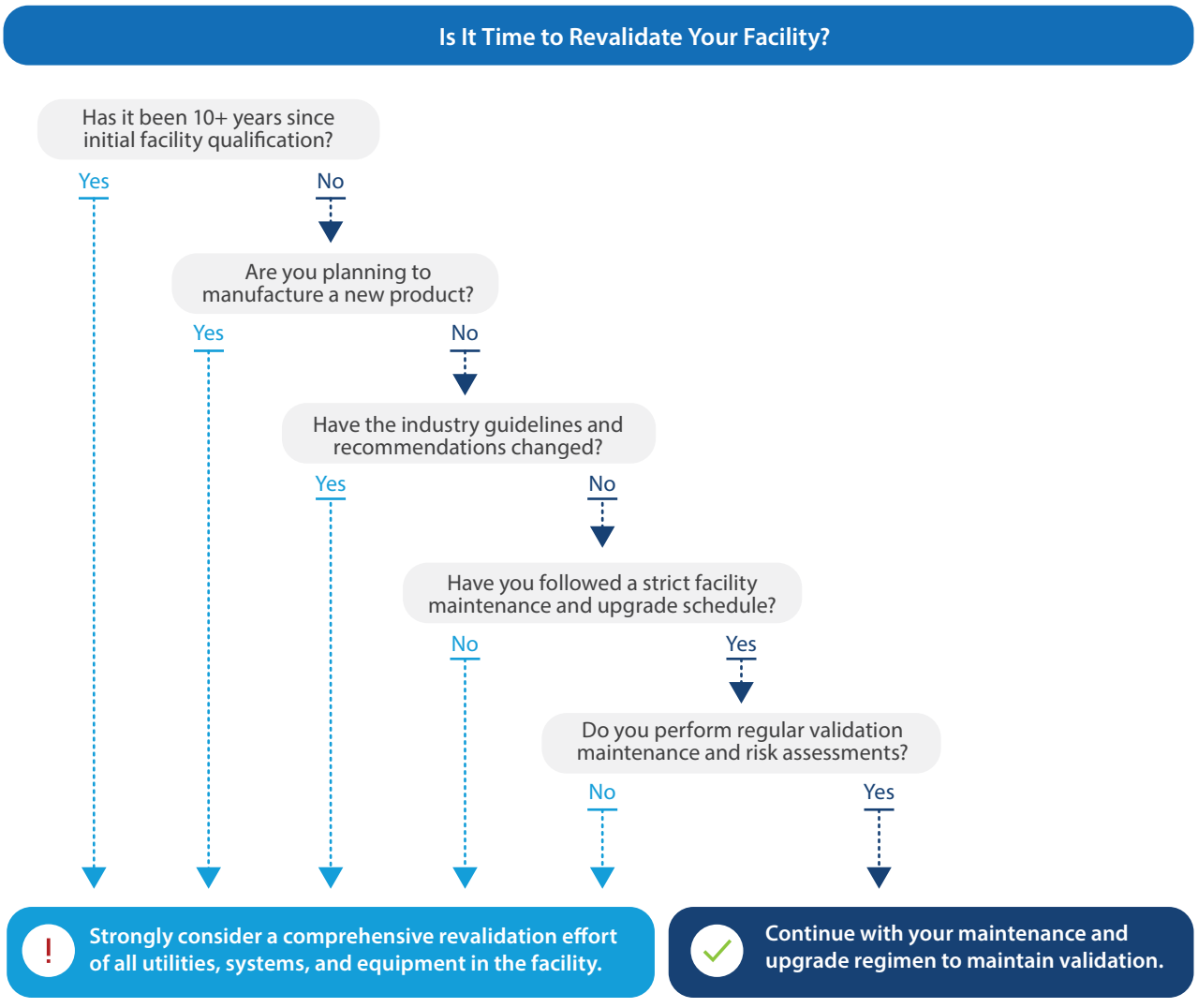

Figure 2. A simple decision tree to evaluate if your facility should be revalidated.

HOW to Assess and/or Revalidate Aging Facilities

Knowing when and how to perform a revalidation are both critical to keeping older pharmaceutical manufacturing facilities in safe, compliant working order. Use the following list when assessing your facilities, utilities, systems, and equipment and planning for the proper course of action.

1. Start with a Strategic Gap Assessment

A strategic gap assessment takes a comprehensive look at each of your assets, compares all components to current regulations and industry guidance, then prioritizes upgrades and replacements as needed.

If this has not been done at your facility in the past 12 months, make it a top priority. Continue with a strategic gap assessment every 6–12 months or as needed based on changing industry regulations or new production plans. Integrate these periodic gap assessments into your validation maintenance program for best results.

2. Review and Update Validation Programs

Validation maintenance programs, revalidation procedures, and general CQV programs can become outdated over time if not consistently updated to keep pace with new equipment, techniques, and regulations.

Revisit these programs at least periodically to keep them up to date. Not only is this process much easier and more efficient when done regularly, but your facility quality will benefit as well.

3. Consider Where "Old Meets New"

Any time you are retrofitting a facility for a new purpose, it's important to consider where new equipment and systems will meet with existing infrastructure. These intersections are common areas for contamination and inefficiencies.

- Do existing utilities have the capacity to support new equipment and systems?
- Is the air quality in the existing building up to standard?
- Are temperature and humidity controls adequate?

4. Plan How You Will Meet Demand During Downtime

Proper planning can minimize manufacturing downtime during necessary facility upgrades. If downtime is unavoidable, be sure you have an adequate product supply to meet market demand during renovations until you can ramp back up to full production.

5. Train Employees in Advance

Train all employees on your facility's new equipment and processes so they are capable of running an efficient and compliant operation as soon as the facility is ready.

Consider virtual training programs and instructional videos that employees can review before the facility is ready to use, followed by hands-on instruction once the equipment is in place.

6. Implement an Engineering Change Management Program

An engineering change management program can lead to many efficiencies not afforded by a quality change management system alone. Primary among these efficiencies are the time and resource savings gained through a more streamlined review process.

As long as no critical components are impacted by a change, an engineering change management program can bypass many of the checks required by a traditional quality management program.

A Revalidation Case Study: Genzyme

When a viral contaminant discovered at Genzyme's Allston Landing plant resulted in a complete shutdown and costly consent decree, the production of two life-saving drugs was significantly compromised.

A comprehensive commissioning and qualification program was built into the Allston Landing plant's overhauled operating procedures, and at the same time, was applied to a sister biomanufacturing facility in nearby Framingham.

As a result, Genzyme:

- **Maintained 100% right-first-time metrics at the Framingham plant, ending the consent decree requirements one month ahead of schedule**
- **Achieved FDA and EMA approval of the new Framingham facility ahead of schedule**

References

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