



RESEARCH SPOTLIGHT

Real-Time Automated Batch Release Nirvana or Reality for Life Sciences?



www.lnsresearch.com

Introduction

Many Life Sciences companies are exploring what it might take to move closer to implementing an automated real-time batch release approach. Real-time release (RTR) has been envisioned for around 20 years. The FDA put out its guidance on Process Analytical Technology approaches, which includes RTR, in September of 2004. Real-time batch release is based on monitoring Critical Parameters defined in the Quality by Design (QbD) control plan, using principles outlined for Process Analytical Technology (PAT). RTR is triggered if everything goes to plan and the batch record doesn't need manual reviewing to release it.

Automated real-time release is another beast entirely. Automated RTR utilizes advanced digital tools, such as Advanced Industrial Analytics, AI/ML, and Robotic Process Automation (RPA), to achieve a "Review by Exception" approach to batch review and release activities.

Several significant benefits make automated RTR worth pursuing, such as:

- **Dramatically reduced finished product inventory levels.** RTR moves manufacturing closer to the demand from customers/patients, taking potentially weeks of inventory out of the picture by shortening the time from completion to approval.
- **Reduced manual labor across labs, quality, and supply chain.** Pulling together everything required for a batch review is a daunting task that consumes a large amount of people resources. Automating and streamlining the approval process based on process conditions can save weeks of effort.
- **Improved quality of products.** The more batch reviews are an accumulation and review of manually aggregated records, the more likely mistakes will be made, resulting in recalls or, worse, a consent decree.

RTR requires an interoperable software system, including ERP, APM, MES, Analytics, and EQMS software. In a scenario where multiple different ERP or MES systems are deployed, it can be challenging for RTR to function, given the two-way communication of vital information and data across disparate systems. Some pharmaceutical companies have achieved RTR, but the lift to get there has been significant. Moreover, the maintenance of older, legacy systems supporting RTR is not trivial.

Some pharmaceutical companies have achieved Real-time Release (RTR), but the lift to get there has been significant. Moreover, the maintenance of older, legacy systems supporting RTR is not trivial.



Challenges to the Real-Time Release

There are several challenges to the realization of real-time release. We'll cover a few of them here.

Challenge #1: Technology transfer from development is manual

Achieving real-time release is highly dependent on the technology transfer activity from the development organization to manufacturing. Today's definitions of Critical Quality Parameter and Process Parameter are primarily manual, paper-based activities between R&D and manufacturing. Our Quality 4.0 research shows that while Design for Quality (DFQ) processes are top of mind to be automated, still less than 50% of respondents are looking at this automation (Figure 1).

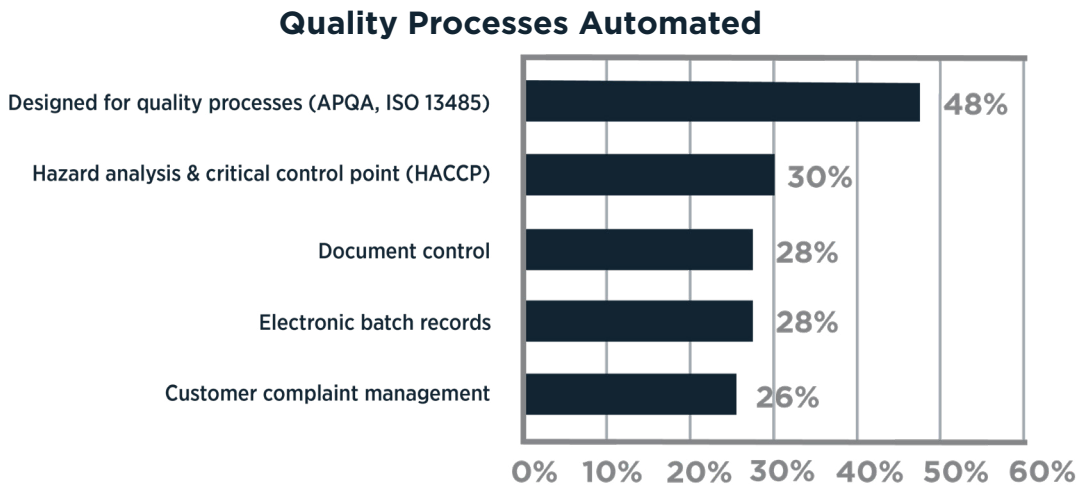


FIGURE 1 - Focus on automation is low

The COVID-19 pandemic illustrated the need for urgency. Our research shows that Life Sciences companies are missing several key drivers of efficiency and reduced labor burden associated with creating the digital thread for new product development to flow seamlessly into high-volume manufacturing. An example is that Quality 4.0 Leaders in Life Sciences are 37% less likely to have adopted a standard definition of development across the enterprise, and adopting a digitized technology transfer process across the enterprise is one of their lowest priorities. In fact, most Life Sciences Quality 4.0 Leaders in our research showed a remarkable lack of appreciation for process automation (Figure 2).

Automating key processes, including risk and compliance, core quality, supply chain, and product development, with software is just not a high priority. This lack of automation is surprising given the high regulatory burden in Life Sciences that demands much time and resources to manage and compile data and information for submittals and various other requirements.

Quality Processes Automated

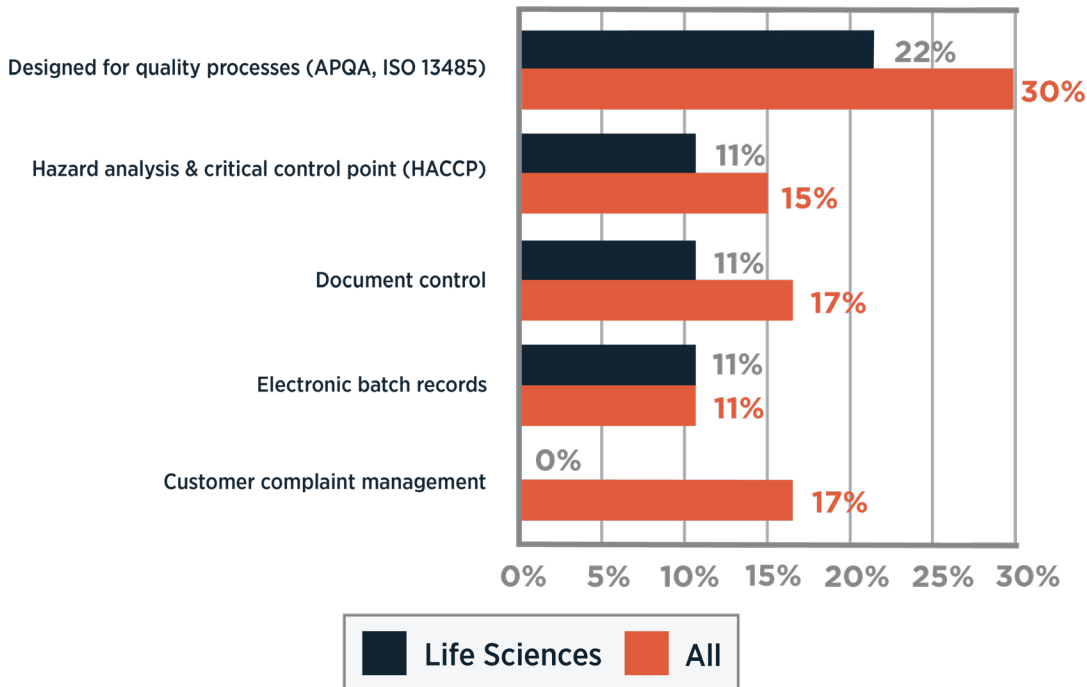


FIGURE 2 - Focus is not on automation in Life Sciences

Another data point that is interesting here is that Quality personnel are only the sixth most likely to be applying analytics to Quality data and to improving Quality management using analytics (Figure 3). Quality Leaders in Life Sciences are missing the boat here. Across multiple research areas, LNS Research finds Advanced Industrial Analytics growing in importance, becoming the top approach to delivering quick benefits in the face of potential economic uncertainty. Of course, EQMS, even if deployed enterprise-wide, is only part of the solution to move the needle on RTR.

Roles Engaged in Applying Analytics to Quality Data

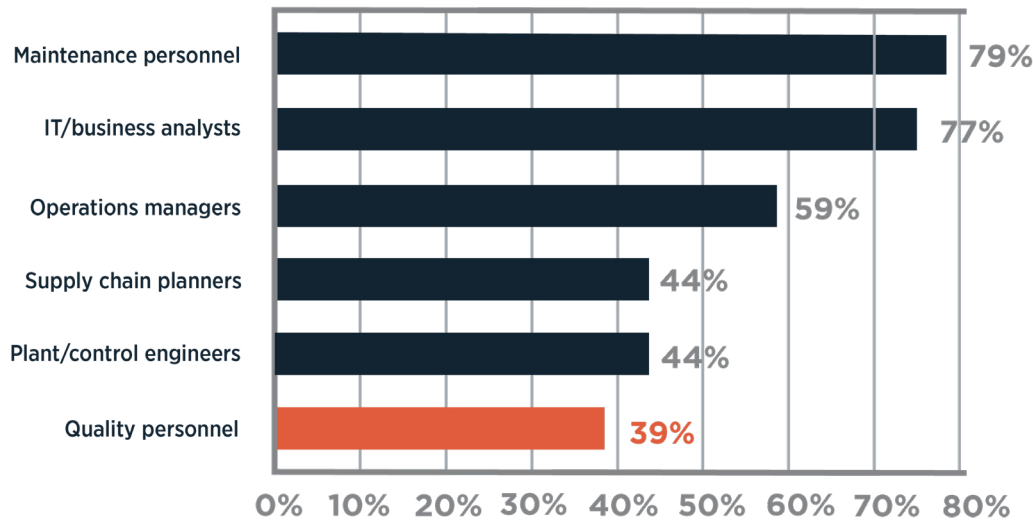


FIGURE 3 - Quality is missing the boat on analytics

Challenge #2: Conservation and cautions

The burden of gathering information and making a regulatory submission has created a deterrent effect on pharmaceutical manufacturers, contrary to the wishes of some at the FDA. Pharma manufacturers consider processes "frozen" after regulatory approval. This stifles innovation in manufacturing processes due to the uncertainty of regulatory approval of changes that result from innovative manufacturing improvements. The FDA's guidance on Process Analytical Technology (PAT) acknowledges this hesitancy and envisions a risk-based framework that could result in a lower regulatory burden, giving pharmaceuticals flexibility to innovate while maintaining or improving product quality.

However, recent experience with "Operation Warp Speed," the delivery of multiple versions of the COVID-19 vaccine in record time, has shown pharma manufacturers the potential for PAT in the real world. To accommodate this rapid environment, some pharma manufacturers are placing big bets on Agile methodologies for not only tech transfer but also Industrial Transformation (IX).

Challenge #3: Riding two horses at once is difficult

The FDA's PAT guidance envisions pharmaceutical companies migrating from batch-style manufacturing to something resembling a continuous process. There are two components to the FDA's guidance:

1. Strong Process Understanding
2. Application of Principles and Tools, including:
 - Multivariate understanding of critical process and product parameters
 - Process Analyzer application
 - Process Control tools
 - Continuous Improvement, learning, and Knowledge Management

Pharma manufacturers consider processes "frozen" after regulatory approval. This stifles innovation in manufacturing processes due to the uncertainty of regulatory approval of changes that result from innovative manufacturing improvements.



The application of Process Analyzers as proxies for actual sample measurement is a challenge to achieving real-time release. Process Analyzers typically don't measure product quality requirements directly but a set of process parameters that must be tied statistically to a product quality characteristic. This places a significant burden on developing a thorough and complete characterization of the product and the process, as well as for continuous learning as the process is operating. This high expectation for thorough process and product characterization is a challenge for realizing real-time release as a part of exploring a continuous style manufacturing process.

There is an additional issue for pharmaceutical manufacturers that provide drug products internationally; not all regulatory agencies are in lockstep on PAT and, even within the FDA, there is no single, unified voice on PAT. This situation leaves the manufacturer to maintain at least two different process schemes to support the FDA's PAT and traditional approaches required by other agencies. This adds to the hesitancy to jump into the deep end of the pool of PAT-supported RTR.

Challenge #4: New business models incorporating outsourced research and manufacturing add to inefficiency concerns

Contract Design & Manufacturing Organizations (CDMO) are on the rise in Life Sciences. As such, this creates challenges around efficiency and speed through design, trials, regulatory submissions, and validation milestones (Figure 4). RTR adds another set of challenges for data sharing or specifying requirements for the CDMO to adopt at a higher cost than standard batch and test processes that exist today – especially in the early stages when PAT might not be the norm across the CDMO footprint.

High expectations for thorough process and product characterization is a challenge for realizing real-time release as part of exploring a continuous style manufacturing process.



Inefficiency Challenges

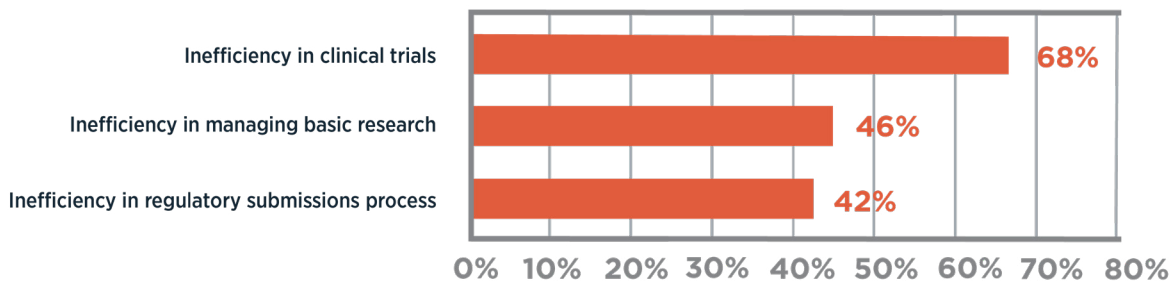


FIGURE 4 - Inefficiency is a top of mind concern

Our research shows that the Quality function is engaged very early in the product development cycle; over a third of survey respondents reported that Quality is engaged in concept development activities and requirements gathering (Figure 5). Early engagement is essential to identify the critical data that a CDMO needs to manage and report back to the parent.

The growing use of CDMOs creates logistical, infrastructure, and collaboration challenges to real-time release that essentially require the CDMO to act as an internal manufacturing unit of the parent. As a result, this allows the CDMO to achieve real-time data sharing that enables pharmaceutical manufacturers to develop trust that an RTR from a CDMO would represent them well and not cause a patient or regulatory issue.

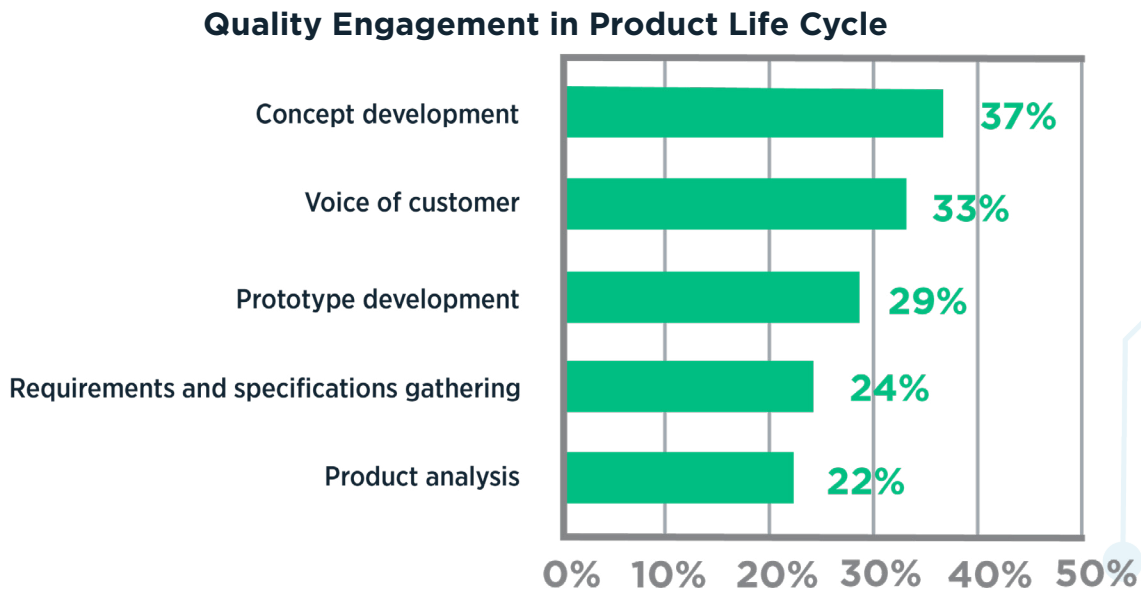


FIGURE 5 - Quality engaged early

Challenge #5: Digital data availability

RTR assumes ALL the data is available electronically. That would include maintenance data on equipment, process data, product quality data, raw material data, etc. The pace of digitization controls the pace of the adoption of automated RTR. This limitation could drive a partial adoption of automated RTR for a portion of a process where digital data is present.

LNS Research's Quality 4.0 data shows paper or flat-file data is a significant issue, with 72% of Life Sciences respondents indicating that their Quality data is in paper, spreadsheet, or email form (Figure 6).

How Quality Data is Managed

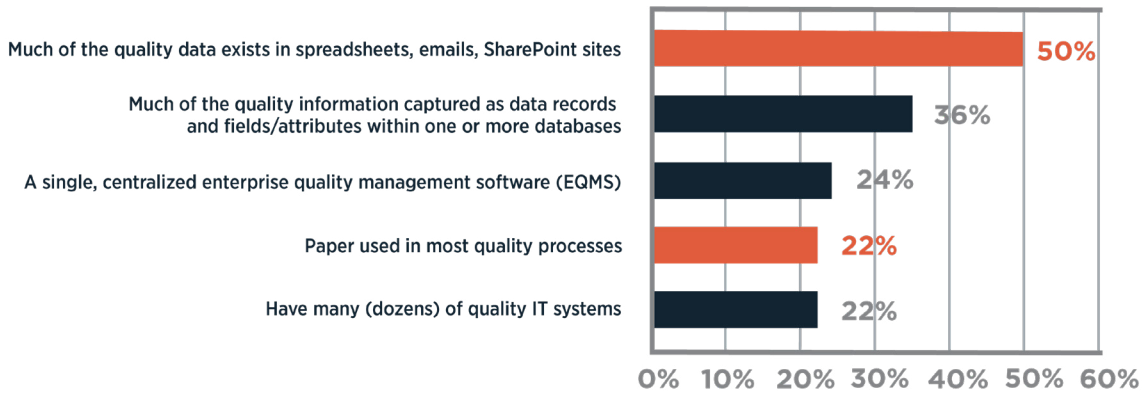


FIGURE 6 - Digital Data availability is an issue

Solutions to Make Real-Time Release a Reality

What is required to achieve automated real-time release? Four categories of action need focus to move the needle toward real-time release. They include:

1. **Real-Time Release depends on the interoperability of MES or Batch Control System capabilities.**

The FDA's guidance on Process Analytical Technology (PAT) creates a framework but not a prescription for real-time batch release. The reality is that Process Analyzer technology is not there yet to cover the entire line for all the essential data needed to achieve real-time release. As new Analyzer technology is developed and proven, early adopters for real-time release will need a hybrid approach of Analyzer coverage and prioritized lab testing to achieve near-real-time release (NRTR).

Of course, all of this depends on an interoperable MES or batch control system to collect all the analyzer inputs and analyze the results to determine if the batch is a candidate for release.

These software systems must have onboard analytical capabilities to analyze data inputs as near real-time as possible and feed the results to a supervisory system. Such a system must include Robotic Process Automation-enabled workflow capabilities to evaluate results against criteria to make the data-based decision on a release or some other process.

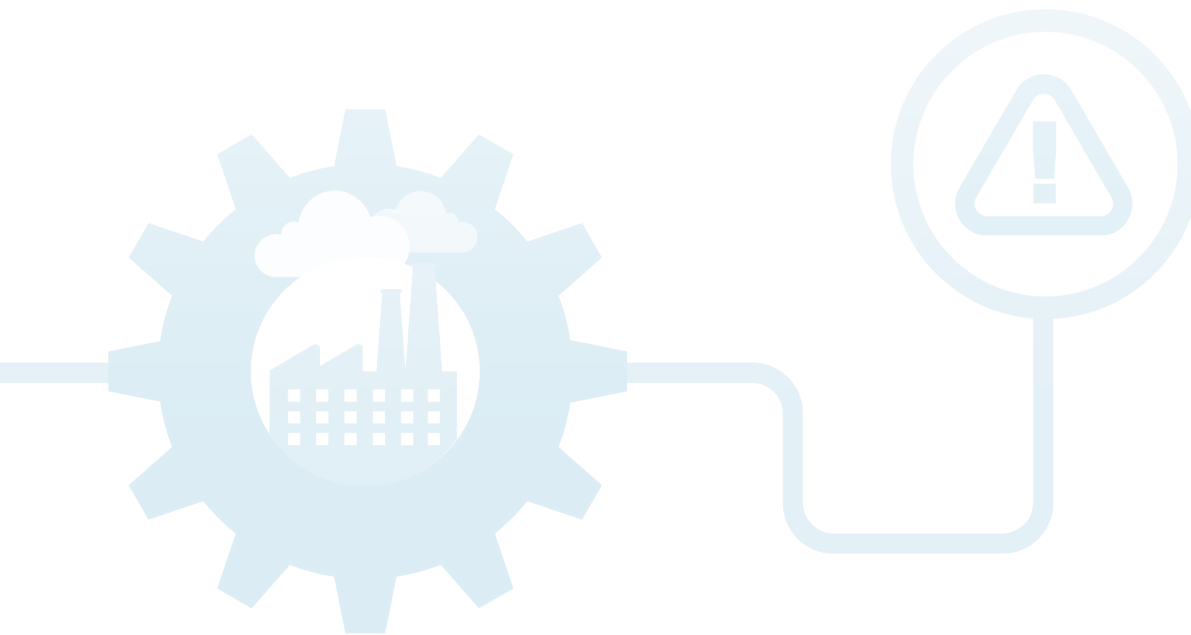


2. Explore the new "risk-based" approach while at the same time managing various regulatory requirements.

The FDA has long claimed to be open to the advancement of new manufacturing innovations in pharmaceutical manufacturing. The guidance on PAT is 20 years old next year. The FDA encourages a "risk-based approach" and even envisioned a roll-back of the perceived regulatory burden by adopting the suggested risk-based approach. However, the FDA does not speak with one voice on this issue. Often, auditors do not align on the PAT approach.

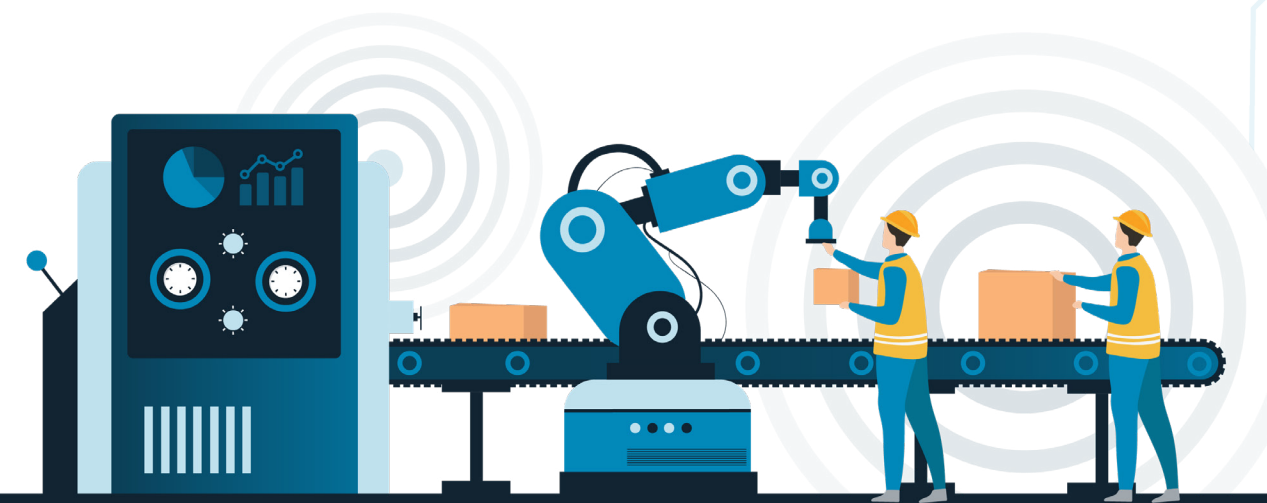
The behavior of regulated pharma and device manufacturers has been to "freeze" manufacturing processes once regulatory approval has been granted.

For pharma manufacturers interested in exploring the risk-based approach and working out the regulatory approval threshold for this method, it is best to start small by identifying a small portion of a redundant process of record; it should be well-supported by existing and proven Process Analyzer technology and a robust statistical management approach implemented through an advanced MES and or Batch Control System.



Approaches around segmenting the production process to achieve real-time release for that portion of the process-of-record, that is covered by robust in, on, or at-line Process Analyzer technology, would make the most sense. A key element of the choice is that the process portion chosen should have a redundant pair that is not undergoing the transformation to PAT-supported RTR. That redundancy allows manufacturers experimenting with this approach to continue to support traditional regulatory requirements while exploring and proving the new risk-based approach.

Additionally, pharma manufacturers are not experts in continuous manufacturing processes. Pharmaceuticals are typically done in batch style. Maybe it is a lack of experience and expertise in a continuous manufacturing process. Pharmas that are interested in exploring continuous process for a small trial on PAT would do well to leverage experience from technology vendors that are experts in the space, such as Honeywell or Emerson, Siemens or Rockwell, and potentially look to hire in expertise from adjacent industries that are familiar with continuous processes, such as specialty chemicals or continuous extrusion plastics.



3. Digitizing and improving the technology transfer process from R&D to manufacturing starts with digitizing discovery.

A critical element of PAT is extensive product and process knowledge. R&D plays a crucial role in developing this product and process knowledge during their discovery process. Typically, discovery is documented in lab notebooks or other paper-based methods, making the technology transfer process labor-intensive and manual. Several digital tools can be brought to bear on tech transfer once the discovery process and information are digitized. Digital Twins is just such a high-powered tool. Digital Twins of product and process are becoming more prominent. Digital Twins can help with process understanding and product consistency before the first unit is produced, significantly reducing the discovery and development cycle time. For new pharmaceuticals, this advanced knowledge can contribute to a more robust technology transfer to manufacturing. Increasing adoption of this technology will push the envelope for speed to market (Figure 7).

Utilization of Digital Twin to Speed Development

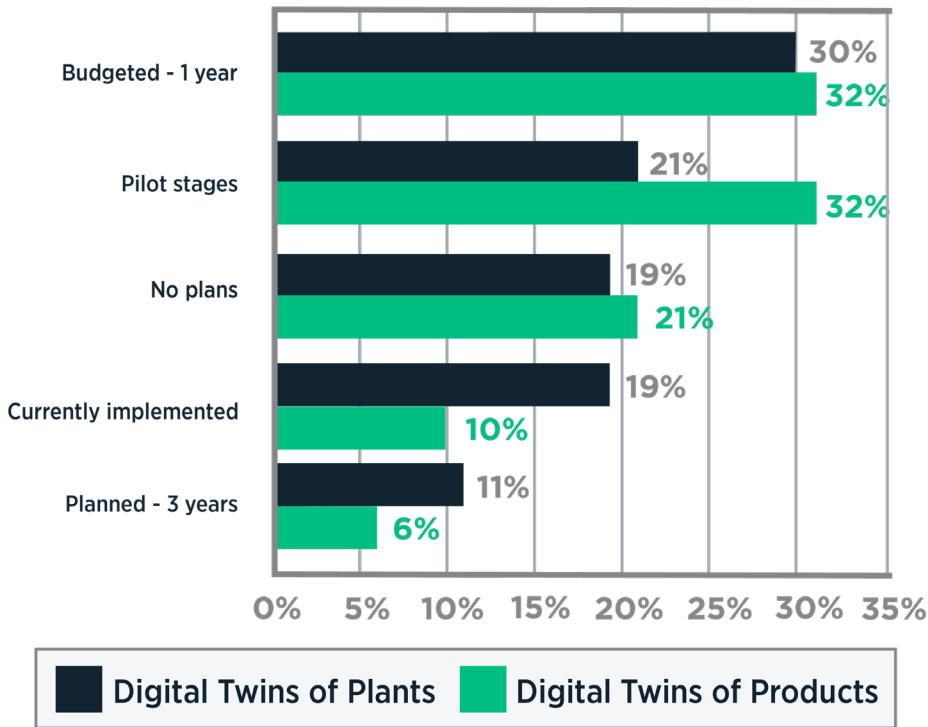


FIGURE 7 - Digital Twins can speed tech transfer

4. Getting the batch record together and approved is a gap in current technology.

The FDA envisions extensive use of Process Analyzers to achieve PAT and RTR. The problem is that Process Analyzers are not yet developed for some areas of a process-of-record. Data from those Process Analyzers would flow into a next-gen MES where the analytical work to check the boxes for RTR would occur. Where there are gaps in coverage by the current state of Process Analyzer technology today, the fallback plan is offline testing in an analytical lab to fill the gaps.

Unfortunately, this fallback plan reveals a weakness in the vision for PAT. Most analytical lab activities are asynchronous to the manufacturing activity, creating a challenge for RTR. The gap could be lessened significantly by robust, near-real-time automatic data collection. This can be done via a Laboratory Information Management System (LIMS) connected to lab metrology devices that collect the data from the device at the instant the test is completed. However, at best, this gets the release near-real-time (NRTR), not actually in real-time.

There is some good news here for Life Sciences firms. Quality 4.0 Leaders in Life Sciences are nearly 70% more likely to have invested in closed-loop processes between tech transfer, supplier, and Operations. This is an essential step toward RTR when measurement and analytics fill in the gaps. Of course, data digitization is a significant part of this, as mentioned in the challenges section earlier in this Spotlight. Digital enablement teams must tackle this problem, extending beyond Quality to manufacturing, suppliers, and maintenance activities.

Role of Analytics in RTR

Leader organizations are more than 40% more likely to apply prescriptive analytics to Quality data; oddly enough, it isn't Quality personnel that are doing it; IT/Business Analysts and maintenance are.

This finding, similar to findings across Quality 4.0, is perplexing because of the lack of engagement by Quality personnel in pushing analytics forward to what should be a common goal around RTR (Figure 8). This result suggests a lack of vision for the achievement of RTR on the part of Quality teams in Life Sciences. Until this is resolved or in-line analytical technology overcomes present gaps, RTR will not become a reality.

Roles Engaged in Applying Analytics to Quality Data

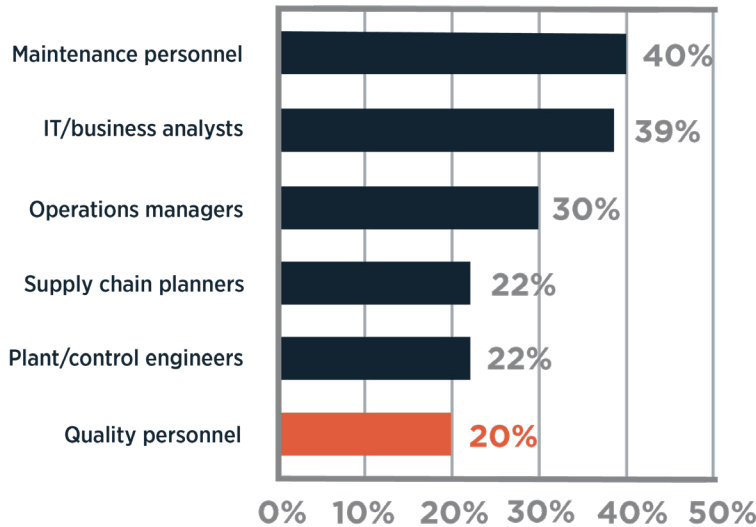


FIGURE 8 - Analytics are key to RTR

Further, our research shows a disconnect in the priority for Quality processes targeted for automation. Electronic Batch Records, a critical aspect of RTR, are not the top priority for either leaders or followers. Yet, four of the five top-of-mind challenges for Life Sciences companies were inefficiency or quality management issues.

Anything that can be done to automate or lessen the manual burden around data collection and batch record accumulation will greatly impact the effort to achieve RTR (Figure 9).

Life Sciences Quality Processes Automated

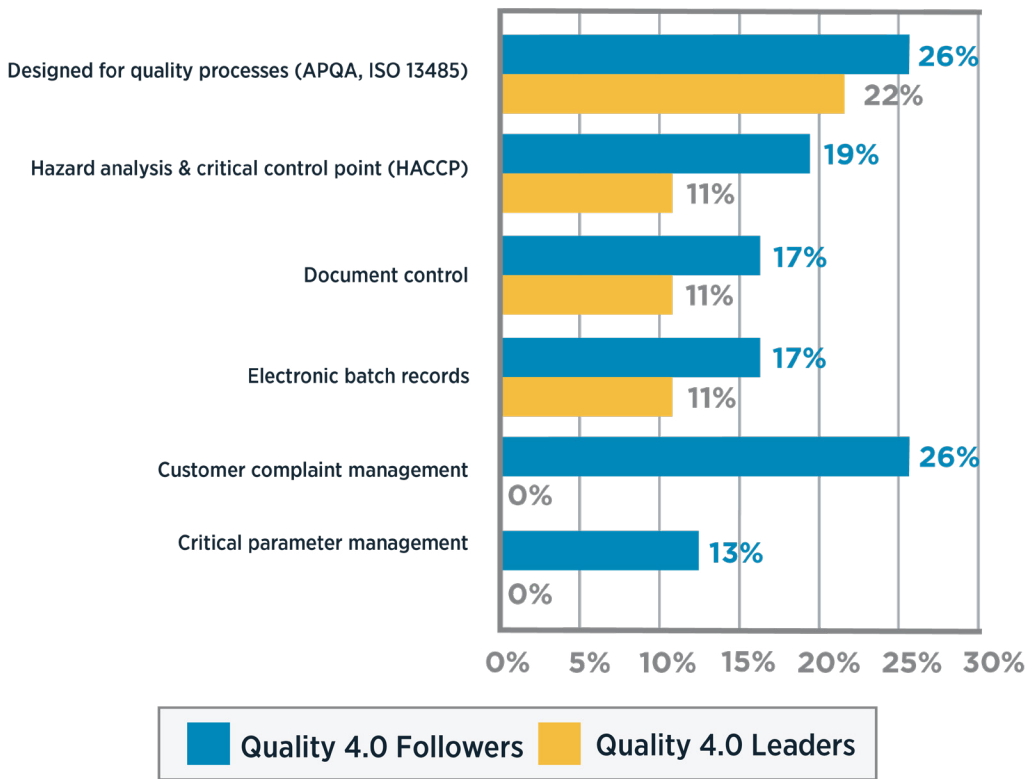


FIGURE 9 - Priorities for Automation not aligned with Challenges

Recommendations for Manufacturers

- **Start small with redundancy. The FDA's guidance on PAT is visionary.** There are several challenges for pharmaceutical companies to achieve the vision. To prove out the process and regulatory response while still managing last-gen requirements from other regulators, start with a portion or sub-process of your process-of-record, where other instances of the POR can still serve the traditional regulatory market while the PAT approach is being proven.
- **Digitize process and product knowledge.** PAT highly depends on product and process knowledge to deliver the critical process and product measurement needs to manufacturing. Most R&D teams in pharmaceuticals have paper-based record accumulation activities, making the technology transfer activity manual and paper-based to translate insights from lab notebooks to manufacturing. Many available EQMS solutions, such as Trackwise, ComplianceQuest, and Reliance, among others, have out-of-the-box (OOB) digital record-keeping functionality that can be leveraged to improve this process. Digitizing this record accumulation would enable the utilization of Digital Twins and other advanced digital tools to characterize product and process and speed up development and tech transfer.
- **Build out your Risk Framework.** The FDA recommends a risk-based approach that could serve as a springboard for reduced regulatory rigor, all predicated on process and product knowledge. The relationship envisioned by the FDA is the higher the process and product knowledge, the lower the risk of producing a poor-quality product. Frameworks for evaluating risk based on knowledge can be built, proved, and then digitized. This is a similar arch to our recent research on Digital Performance Excellence, showing that DPX Leaders are 82% more likely to monitor risk in real-time through connected data sources applied to established digitized risk frameworks.

Digital Performance
Excellence (DPX) Leaders are

82%

more likely to monitor risk in real-time through connected data sources applied to established digitized risk frameworks.

- **Adopt a near-real-time release stance.** RTR may not be achievable today for the sub-process chosen due to gaps in the technology for Process Analyzers and/or software to support RTR. Still, a near-real-time release (NRTR) might be achievable using a combination of in, on, or at-line process analysis, and coordinated, interoperable lab-testing to fill the gaps. NRTR is a step in the right direction, even though it is not the full achievement of RTR; NRTR can save significant time over today's offline batch approval processes. Align targets of opportunity for NRTR with business objectives, which helps build a solid business case for experimentation and gradual improvement.
- **Adopt an interoperable MES or Batch Control System.** These systems have onboard analytical capabilities to perform analysis as near-real-time to the data input as possible, gaining crucial time toward RTR. There are some vendors worth considering in this space. MasterControl, Fluxa, and Apprentice are among the vendors attempting to bridge the gap between tech transfer and manufacturing. These solutions have the potential to become the "knowledge repository" from tech transfer and into manufacturing, a vital component of the framework envisioned under the FDA's guidance on PAT.




RELATED RESEARCH ON INDUSTRIAL TRANSFORMATION (IX)

- RESEARCH** | [Pivot to Value for Industrial Transformation Success →](#)
- RESEARCH** | [Advanced Industrial Analytics: Four Proven Strategies to Scale Transformation During Uncertain Times →](#)
- RESEARCH** | [People in Industrial Transformation \(IX\): Leadership, Culture, and Organizational Best Practices →](#)
- RESEARCH** | [Taking Control of Quality Transformation: Strategic & Cultural Imperatives for the Quality Executive →](#)
- RESEARCH** | [Next-Generation Sustainability: Risk, Opportunity, and Competitive Advantage →](#)
- RESEARCH** | [Connected Workforce: Enable a Competent, Agile Industrial Workforce →](#)
- SPOTLIGHT** | [The Softer side of Quality 4.0 Transformation →](#)
- RESEARCH** | [Driving Continuous Improvement Through Digital Lean Tools →](#)
- RESEARCH** | [Digital Continuous Improvement in an IX World →](#)
- EBOOK** | [Enable Operational Agility with a Digitally Connected Workforce →](#)
- BLOG** | [Introducing the Industrial Transformation \(IX\) Reference Architecture →](#)
- BLOG** | [Understanding Industrial Transformation: Definition and Framework for Success →](#)
- RESEARCH** | [Industrial Transformation: Architecture and Analytics Just the Beginning →](#)
- RESEARCH** | [IX Architectural Paths 1 of 3: Three Paths & Understanding IX Infrastructure →](#)
- RESEARCH** | [IX Architectural Paths 2 of 3: Evaluating IX Platforms and IX Applications & Analytics →](#)
- RESEARCH** | [IX Architectural Paths 3 of 3: Looking at IX Strategic Partners →](#)
- RESEARCH** | [Industrial Transformation Success: How to Secure Operations' Buy in to Create Effective Leadership →](#)
- RESEARCH** | [IX Digital Readiness →](#)

AUTHORS:

James Wells

Research Analyst

james.wells@lns-global.com Follow James on LinkedIn**Matthew Littlefield**

President & Research Lead

matthew.littlefield@lns-global.com Follow Matt on LinkedInlnsresearch.com