Pharma Quality: Time to Transition from Fixing to Prevention

Abstract

In the pharma and biopharma industries, product quality is inspected during and after manufacture. Quality is mostly tested through inspection and fixed in case of a failure. However, without real-time monitoring, such failures sometimes go unnoticed, increasing appraisal cost and, in turn, Cost of Bad Quality (CoBQ). Breakthrough technologies, such as the tools and techniques of Business 4.0 and new age quality benchmarks, can fix these issues and reduce failures.

This paper focuses on predicting and preventing such quality failures using contemporary technologies that were not available in the past. We have tried to highlight the significant problems in biopharma upstream, tablet manufacturing, and other related industries. Additionally, the paper offers a view into solutions for these issues using the current breakthrough technologies.

Introduction

A batch failure in the pharma manufacturing industry can cost about USD 1-2 billion[1] depending on the type of drug. The cost of QA investigation (additional appraisal cost), additional cleaning, and miscellaneous costs can push the amount even higher. Moreover, a batch failure will delay the next batch. The CoBQ will include the cost of fixing internal failures and implementing CAPA.

The CoBQ will also increase the Cost of Quality, which amounts to 15-25%[2] of the operation cost (see Figure 1). Per Juran[2], we need breakthrough improvements to shift the needle from CoBQ to Cost of Good Quality (CoGQ). Such breakthroughs can be in the form of new tools and technologies like advancements in manufacturing technology and analytical capabilities. Nevertheless, can IT advancements help shift this needle?

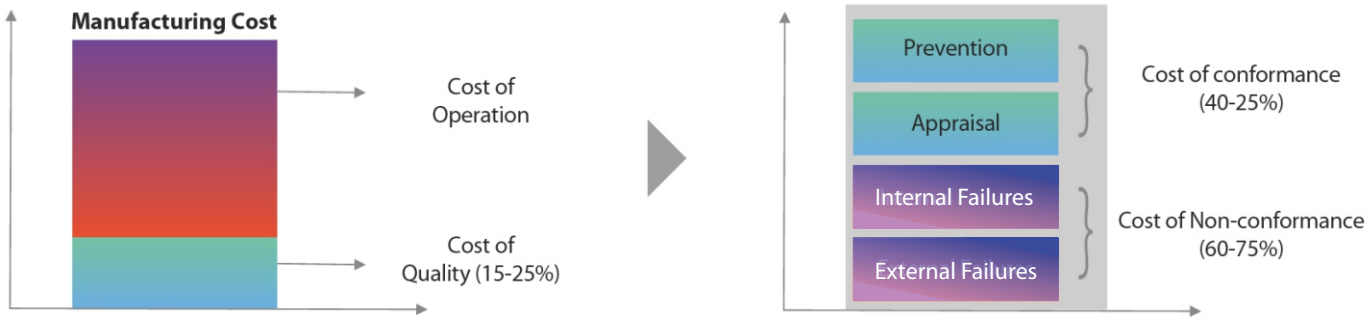

Figure 1: Cost of Quality

The answer is yes. It is possible to transform CoBQ to CoGQ today — the digitalization of quality management and its impact on people, processes and products[3]. New age quality benchmarks leverage connection, intelligence, and automation for better quality. Additionally, breakthrough technologies will connect and automate the process, people and systems, something that wasn't possible five years ago. A combination of Business 4.0 and new age quality technologies can enable prediction and prevention of failures, reducing additional appraisal cost post-failure.

Monitoring Failure

Upstream manufacturing processes in the biopharma industry include several parameters, physical (temperature, pH, DO) and chemical (c-source, anti-foaming agent), that are monitored periodically depending on the types of proteins and cells (bacteria/fungi/mammalian) involved (see Figure 2). Changes in the parameters can impact protein yield and product quality. Post-transcriptional modifications particularly may affect product efficacy and safety, leading to catastrophic failures. Despite monitoring, failures occur due to legacy, disconnected, semi-automated systems. Offline analysis, which delays results, is a significant cause of failure in drug manufacturing.

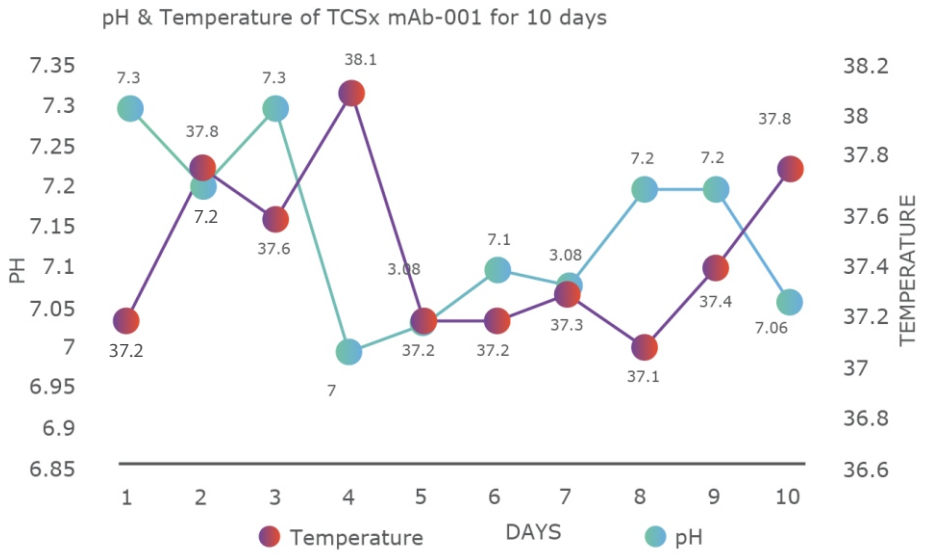

Figure 2: Data indicating mAb's pH & temperature variation over a period of 10 days

Online monitoring has been made possible by technology. Sensors and actuators monitoring production in real-time and ensuring quick intervention in case of errors have enhanced product quality. Online and at-line analyzers — in conjunction with Artificial Intelligence (AI), Machine Learning (ML), and automation — proactively and continuously scan upstream and downstream processes to detect the slightest variations in critical parameters and automatically make necessary corrections without human intervention.

However, complex upstream processes in a bioreactor can impact cell growth and productivity. Legacy systems do not allow the prediction of the effect of various components and parameters on cells. This affects the cell population and overall productivity, requiring experts to spend considerable time and effort to optimize the process. But despite such effort, process prediction overall remains a black box.

A Technological Leap

A bioreactor digital twin can overcome the challenges. A virtual representation of the process of a real bioreactor — a bioreactor digital twin of a cell-culture bioprocess helps predict cell physiology in a bioreactor environment. This can prevent complex issues and meet challenges in biopharmaceutical industries. A bioreactor digital twin can be used with AI/ ML to correlate current and historical data to draw conclusions that inform decisions about current batches.

We now have data monitoring technologies, sensors, and actuators that can predict changes per minute/second. Connected systems and automation allow the tracking of minute process variations. Abstract data model, graph, and DB can be leveraged for prediction-and-prevention, data crunching, and pattern finding. Just like Google's new AI algorithm can predict heart disease by scanning a person's eyes (see Figure 3), a new crop of breakthrough technologies can detect, and thus prevent, minute changes in processes.

Figure 3: Google's algorithm can predict heart disease by scanning a person's eyes

In the tablet manufacturing industry, spots and specks are common quality issues. Spots are imperfections residing on the tablet surface, while specks can be present anywhere in a tablet (see Figure 4). Specks can either be visible on the surface or hidden within. Spots and specks appear due to leaks, over-lubricated upper punches, and undetected high temperatures. These can be grey, black or almost any other color, including white.[4]

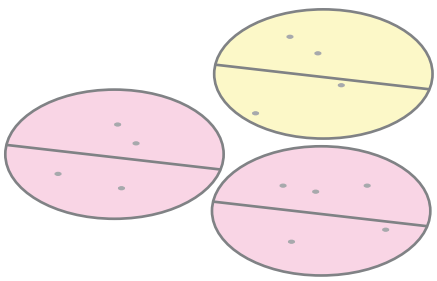

Figure 4: Tablets having spots and specks

A batch of more than 10,000 tablets can be compressed and readied for packing before spots and specks have been identified. Based on in-process checks, the Quality team would stop further processing of tablets, investigate the batch, and finally reject it. In such a scenario, what technology or tool can help best?

Failures usually happen when they go undetected, or there is no predictive alarm in place. Right technology can save the tablet industry money, time, and resources gone to waste because of specks and spots. Ultra-fast moving cameras using visual analytics, can capture and detect a problem in tablet production, alert relevant stakeholders, or automatically rectify it. Ultra-high-speed cameras with fast data transfer and analysis capabilities can record the entire production process.

Industrial Internet of Things (IIoT) allows operators to observe and stop the process over the phone (see Figure 5). The low cost of data, now in the region of $0.021 per GB (source: AWS), makes this a feasible option. Current technology is flexible enough to ensure the storage of only useful data after a batch completion and the rejection of only 100 tablets in a batch instead of 10,000.

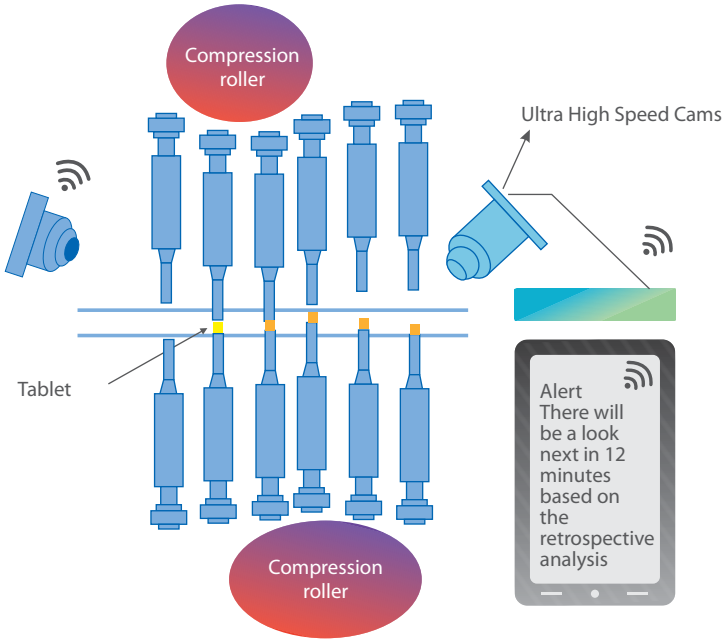

Figure 5: A high-speed camera in combination with visual analytics and AI/ML predicts failures in tablet compression

Humans typically do the repetitive work involved in granulation, drying, punching, validation, and final packing. This results in a lot of errors during manufacturing and data generation. Robotic process automation (RPA) — a software with a set of commands that communicates with the digital

system to perform error-free tasks — can better execute such work and help reduce QA review time. A combination of current technologies, such as cognitive ML and deep learning with bots, will advance industry capabilities, moving from a predictive to a prescriptive model.

Benefits of Robust Prevention

While used frequently, the term 'transformation' is often misunderstood. The technologies discussed above do not transform a company; they optimize quality and manufacturing. For example, a pharma company used the cloud[5] for supplier quality management (see Figure 6). All critical raw material suppliers were part of this, and Quality teams got to know of supplier changes as soon as it happened. This not only spread the quality culture for the manufacturer but also among all critical suppliers linked in the cloud.

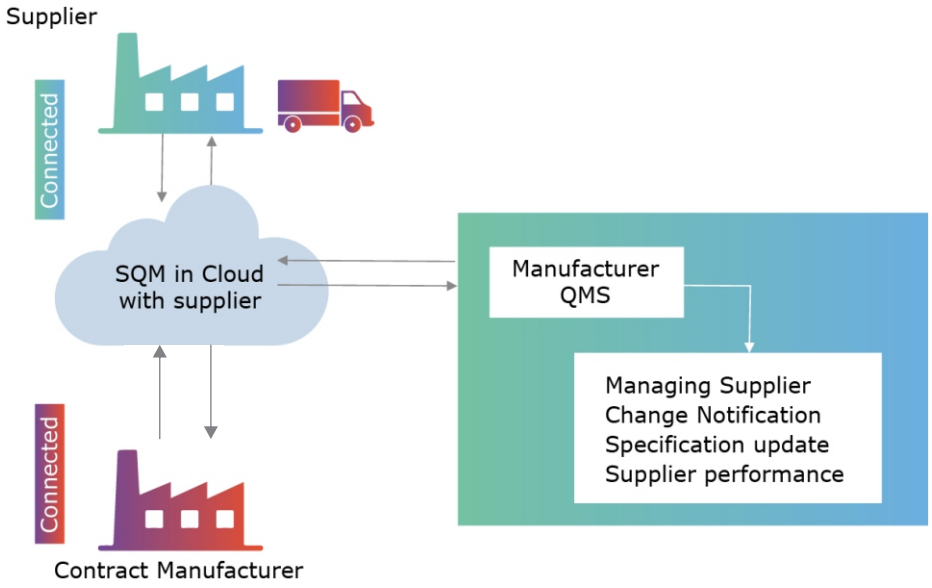

Figure 6: Cloud technology for supplier quality management

IIoT, a state-of-the-art technology, enables Quality and other stakeholders to obtain information online through mobile phones and computers (see Figure 7). A leading drug manufacturer has implemented IIoT for its Quality and production teams, enabling online process-status monitoring.

Most line clearance and eBMR approvals happen over QA mobiles and tablets, reducing hold time in production and allowing the QA to monitor processes in real-time.

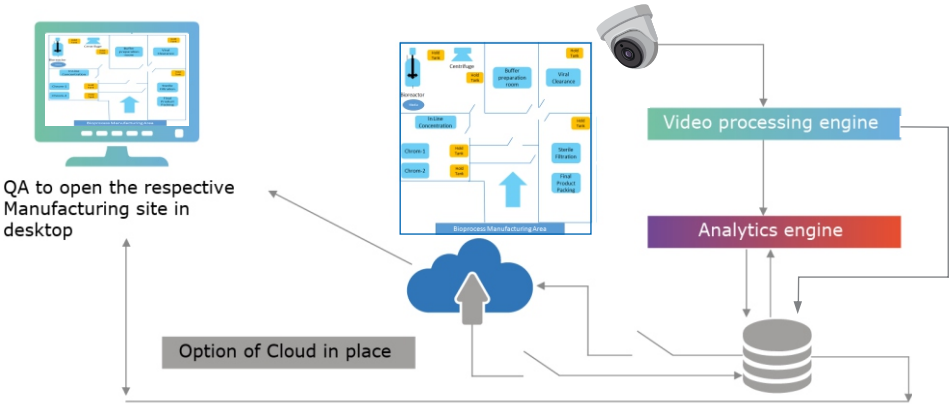

Figure 7: QA monitoring through video surveillance and analytics

Conclusion

Quality — equipped with robust preventive and appraisal tools and technology — can prevent 80% failures. Most failures happen because of a wrong chemical or procedure being used or the lack of tools for predicting failures. Using a combination of modern technologies, such as Edge Intelligence, Digital Twins, sensorization in conjunction with cognitive computing, automation (RPA, bots), video surveillance, analytics, IIoT, cloud, and breakthrough pipeline technologies, can help make the process more efficient. Predicting and preventing failures denote no defects in products, no holds, no investigations, no deviations, and no CAPA. In terms of business benefit, this means a 60-70% reduction in CoBQ.

References

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