ENABLING QUALITY BY DESIGN

Through Continuous Process Verification, Manufacturing Anomaly Capture, and Proactive Quality Response

Honeywell

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MANAGEMENT SUMMARY

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The increasing complexity in the life sciences industry continues to drive digital transformation.

Life sciences manufacturers are faced with quality anomalies that can delay product release for hundreds of hours. Often, quality management systems rely on manual processes for data transfer. This proves to be inefficient, hinders visibility, creates data integrity concerns and causes lengthy delays. Additionally, despite the growing application of continuous process verification, many such programs don't use real-time automation data for verification which limits quality by design (QbD) value, increases compliance risk and threatens supply chain continuity.

- The key benefits of enabling QbD with AI-driven quality operations include:
- Connecting AI-enabled quality management and batch automation to provide real-time visibility
- Using real-time critical process parameter alerts to provide early detection
- Enabling proactive response to quality events through manufacturing anomaly capture
- Improving cost of poor quality without increasing the cost of good quality

QbD is enormously valuable and generates a lot of data and knowledge. Unfortunately, it tends to be underutilized, siloed and not operationalized. It is too often an exercise, executed at the early stages of product development but was always intended to be dynamic, increasing its value across the lifecycle of a product. Honeywell functionality is changing that.

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THE ULTIMATE FIVE IMPERATIVES OF ALL QUALITY LEADERS

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Regardless of industry or company size, quality leaders have five key imperatives in common.

They care about ensuring product quality and efficacy and—most importantly—patient safety. They also care about the continuity of supply in both existing product and new product pipeline. This has perhaps never been more important than it is now, in today's climate. Compliance is the final imperative. We've saved this for last because while a company can have a good compliance record, that doesn't guarantee good product quality, safety or supply. In fact, we find the converse to be true. A company with good product quality, patient safety and a robust supply chain tends to also have strong compliance performance.

While these five imperatives are top of mind for quality leaders, they are increasingly faced with a bi-modal challenge. Mode 1 is defined by operational stability, predictability, efficiency and incremental continuous improvement. It is driven by the need to lower the total cost of quality (TCoQ).

There is now a growing and competing tension with Mode 2. Mode 2 is defined by digital transformation and Industry 4.0 and involves innovative, out-of-the-box solutions that enable speed and big-step changes. These forward-thinking trends enable organizations to leverage technology and use data to innovate faster.

Industry doesn't operate in only Mode 1 or Mode 2. Rather, it has to operate in both modes at all times.

MODE 2 PRESSURES CAN BEST BE DESCRIBED BY SEVEN MACRO TRENDS:

PROCESS COMPLEXITY AND VARIABILITY: Quality process complexity and variability is a systemic issue of great burden across the industry. It arises from adding complexity onto processes because of external influences like regulatory inspections. This impacts product quality, threatens compliance and increases risk and associated costs.

PACE OF INNOVATION: The pace of innovation, to develop novel products such as biologics, gene/cell therapies and the like, in support of the growing trend of patient centricity demands equally novel and innovative approaches to quality management.

INDUSTRY 4.0: The disruptions introduced by Industry 4.0 have transformed the life sciences into the "Factory of the Future." The Industry 4.0 framework digitizes and integrates vertical and horizontal value chains, further digitizing product and service offerings, business models and customer access.

PATIENT CENTRICITY: The patient is now at the center of the life sciences value chain—a patient-centric view recognizes the patient at the core along with their increasing power.

NOVEL PRODUCT: Patient centricity can be attributed to the creation of many novel medical products resulting from the fourth industrial revolution.

SUPPLY CHAIN COMPLEXITY: Supply chain complexity is large and growing; upwards of 60 percent of the supply chain being external and coincidentally, about 60 percent of the growth in the industry is inorganic coming from mergers and acquisitions.

RISING TCOQ: Achieving optimal Total Cost of Quality (TCoQ) is only possible if an organization can first measure it. The TCoQ across the business can barely be measured let alone controlled and reduced but we know it is a significant portion of total operating costs.

All of this is underpinned by the fourth industrial revolution that we find ourselves in. This digital revolution brings amazing advances in digital technology but also contributing pressures of its own.

WHAT EXACTLY IS DIGITAL?

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It's first important to understand that digital is much more than the cloud.

While cloud has inherent value, a digital ecosystem is much more than that. Research from PWC1 shows that there are many more contributing digital technologies that encompass a true digital ecosystem:

- Mobility
- IoT or the Internet of Things utilizing smart sensors and connected devices and assets
- Advanced human/machine interfaces and even augmented reality and wearable devices— connecting the deskless worker
- Authentication and fraud detection—cybersecurity at the operational technology (OT) layer
- Big data analytics and advance algorithms (powered by AI) artificial intelligence

ARTIFICIAL INTELLIGENCE

The EU parliament defines AI as "the capability of a computer program to perform tasks or reasoning processes that we usually associate to intelligence in a human being. Often it has to do with the ability to make a good decision even when there is uncertainty or vagueness, or too much information to handle.

NATURAL LANGUAGE PROCESSING

According to McKinsey, NLP is a specialized branch of AI focused on the interpretation and manipulation of human-generated spoken or written data.

PREDICTIVE ANALYTICS

Gartner describes Predictive Analytics as "a form of advanced analytics which examines data or content to answer the question "What is going to happen?" or more precisely, "What is likely to happen?", and it is characterized by techniques such as regression analysis, forecasting, multivariate statistics, pattern matching, and predictive modeling.

MULTIVARIATE ANALYSIS

The National Center for Biotechnology Information defines Multivariate Analysis as being "based in observation and analysis of more than one statistical outcome variable at a time. In design and analysis, the technique is used to perform trade studies across multiple dimensions while taking into account the effects of all variables on the responses of interest.

MACHINE LEARNING

McKinsey describes Machine Learning (ML) as the algorithms that can learn from data without relying on rules-based programming.

THE FACTORY OF THE FUTURE IS HERE

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Not long ago, everyone was talking about the Factory of the Future.

Well, it's here. Only now it's the digital factory, the digital plant and the smart lab. It's still developing but the level of digitalization, automation and connectivity on the shop floor is growing rapidly.

To truly power the digital plant, laboratory and value network of the future we must start with Research and Development (R&D) where we not only design a product but the processes by which we build that product.

The ability to link data and information from the functional players across the life sciences value chain from R&D through post market surveillance, and back to product and process design, in a closed loop that the quality management system was always supposed to be, will provide tremendous business and competitive advantages to life sciences companies.

Proactive quality does not only track quality, but it also improves quality, manufacturing and new product introduction (NPI).

DIGITAL QUALITY DELIVERS IMPROVED BUSINESS OUTCOMES

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The life sciences industry is facing unprecedented levels of change.

For example, the growth in the number of patents, particularly in the area of precision medicines that are driven by complex manufacturing processes, highlights issues such as the cost of quality. Digital quality not only drives proactive quality, it also delivers real business benefits that addresses this and other challenges.

Recent data from LNS Research2 shows the value of quality data on business operations improvement. This includes providing quality staff with access to plant data in time to make timely and appropriate decisions and having the quality data included in a holistic data model.

Companies have seen significant business benefits in key metrics such as:

- On-time delivery
- Overall equipment effectiveness (OEE)
- Successful new product introductions
- Capacity utilization
- First pass yield
- Decrease in defects per million opportunities

Digital quality connected to transactional manufacturing data helps companies at any level of quality maturity, including the most mature. It also uniquely delivers improved cost of poor quality (CoPQ) without increasing the cost of good quality (CoGQ).

THE TRADITIONAL APPROACH TO QBD

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QbD is a methodology that's been applied across the life sciences for several years now.

It started as an advanced six sigma process but has since become popular in the medical device and pharmaceuticals industries. The concept was conceived by Dr. Joseph M. Juran, on the principle that quality should be designed into a product and that the majority of quality problems and crises are directly related to the way a product was designed.3

The FDA has encouraged QbD principles in manufacturing, drug development and regulation. The agency recognizes that increasing product testing does not correlate with great product quality, rather quality should be built into a product. 3

A lack of quality during design directly correlates to quality events and poor quality later, sometimes in the post-market.

QbD traditionally comprises three key elements:

QUALITY TARGET PRODUCT PROFILE

The first element is to define the quality target product profile. This is a summary of the product's quality characteristics that are critical for ensuring the finished product meets the required standard of quality.

CRITICAL QUALITY ATTRIBUTES

The next element is to define critical quality attributes (CQA). These are the physical, chemical, biological or microbiological characteristics that need to be within a limit/range in order to ensure product quality. If we're more mature in our approach, we execute our studies of critical to quality (CTQ) flow-down, understanding how each CQA effects the next.

CRITICAL PROCESS PARAMETERS

Finally, it's important to identify the critical process parameters (CPP). CPPs are variables that can impact CQAs. These could be equipment type, batch size and mixing order and time. Raw material attributes must be kept within limits in order to ensure product quality. Examples of CPPs include temperature, pressure, pH, dissolved oxygen, agitation and many, many more.

They must be monitored in order to ensure early and accurate detection of deviations that fall outside of acceptable limits. Real-time CPP alerts provide organizations with early detection and corrective action guidance of quality issues. This improves batch quality, yield, and reduces the risk of rejected product.

Let's take for example, the review of the performance of a CPP, in this case dissolved oxygen. When reviewing the performance of a CPP, this tends to be a reactive, rear-view-mirror look at process performance, one parameter at a time. Traditional statistical process control (SPC) chart analysis tends to be retrospective, looking at data that was generated in the past.

As a result, failure investigation is time consuming and costly and results in a product disposition process that can take up to 60 days or more, even if the process goes well.

Historical QbD identifies which parameters are critical, and we monitor them, and sometimes we can gain insight from failures that have occurred, which can inform us of our understanding of the CQAs and CPPs. But it tends to generally be reactive, responsive and after the fact.

MAXIMIZE THE POWER OF QBD

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The key to maximizing the opportunities lies in unlocking the potential of QbD and making it a dynamic methodology that we can apply throughout the lifecycle of a product.

Industry rightfully spends millions of dollars on QbD. It's an investment of many cross functional dollars and resources across R&D, design quality, and manufacturing. The intent is that we design quality into the products and the processes by which we make that product—throughout its life.

However, the value returned from investment in QbD is suboptimal. This is because continuous process verification (CPV) programs can't use real-time, transactional manufacturing data optimally, both during production and, importantly, post-market for triage and investigation of issues that escaped the factory. Dealing with quality anomalies in manufacturing can delay product release for hundreds of hours. Quality management systems aren't integrated with batch automation, instead using manual processes for data transfer, which is inefficient—it limits visibility, creates data integrity concerns, and causes lengthy delays.

The solution lies in directly connecting quality management and manufacturing automation systems. This results in:

- **Integrated Quality and Batch Operations** that give organizations real-time, end-to-end visibility, enable faster and better decision making and proactive response to quality events.
- **Real-Time CPP Alerts and Corrective Action Guidance** to provide early detection of manufacturing anomalies, prevent quality violations and ensure higher product quality.
- **Process Context for Quality Investigations** to reduce the time needed to investigate quality issues, increase operational efficiencies and provide AI-enabled auto-categorization and correlation.
- **QbD through Continuous Process Verification** which provides real-time automation data for verification, closes the loop on process verification and increases compliance.
- **Integrated Product Release** provides faster batch reporting, review by exception, and real-time release for improved time to market.

AI-ENABLED QUALITY BY DESIGN

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A paradigm shift

While industry has made great strides in terms of the traditional approach to QbD (Quality target product profile, CQA and CPP), the enabler is the ability to deliver continuous process verification of those CPPs and real-time monitoring of those process parameters against established standards.

Real-time and continuous monitoring of that data is streaming off a connected asset such as a bioreactor or near-real-time of that data is sitting in a data lake.

The Honeywell Experion solution delivers that capability and is integrated with TrackWise Digital to detect manufacturing anomalies. These include process anomalies, trends, diversions in performance before they even become breaches of a warning limit of failures of a specification. It's a paradigm shift.

This, in turn, allows for a proactive quality response with the immediate identification, capture and documentation of this quality event.

This is predictive—it's pre-failure.

And as the whole system is one of continuous improvement, industry's understanding of the CQAs improves and we can better characterize and tighten our CPPs.

Let's consider our dissolved oxygen control example in this new paradigm.

Not only can we now detect warning limit breaches, specification failures and trends, but we can also detect manufacturing anomalies; within tighter limits established dynamically from QbD and historical data.

An AI-enabled CPV and QMS monitors and responds to that data real-time—proactively.

The result is a response to emerging trends in real-time and enabling correction prior to it becoming a failure, bringing it back into appropriate control limits.

So, while historical QbD identifies which parameters are critical, the combination of AI-enabled CPV and quality helps narrow down what those ranges should be, dynamically

This means we can now detect anomalies sooner, detect anomalies not previously defined or characterized and increase the level of analytical sensitivity.

In short, we can enable proactive, even preventive quality.

An AI-enabled CPV and QMS monitors and responds to that data real-time— proactively.

In our dissolved oxygen example, monitoring individual CPPs is good but a complete set of bioreactor CPPs, for example, can include over 200 variables. The resulting combinations of interactions translates into almost 2,000 feature sets. The average human can only interpret 2-4 parameters interacting at a time.

Take, for example, if we're also monitoring pH, pressure, agitation speed, weight and temperature. Each individual CPP could be within their respective limits...but what if two are low and two are high and their interactions at these points creates an issue, not previously characterized?

This is where AI and multivariate analysis come in to allow control to what is called "golden batch conditions" and detection of unexpected anomalies. With AI enabled quality management, we can now predict what might happen and prevent problems before they occur.

KEY CAPABILITIES

Proactive Quality Response: Immediate identification, documentation and investigation of quality events, ensuring proper identification of root cause.

Manufacturing Anomaly Capture: Automatic detection of process anomaly or diversion that leads to deviations from the quality standard.

Continuous Process Verification: Real-time monitoring of process data against CPP standards and CQAs.

Quality Target Product Profile: A summary of a product's quality characteristics that are essential to ensure the finished product meets the required standard of quality.

Critical Quality Attributes: Any physical, chemical, biological, or microbiological characteristic that must be within a limit/range to ensure product quality.

Critical Process Parameters: Variables that can impact CQAs and must be monitored to enable early & accurate detection of deviations outside acceptable limits.

AI UNLEASHES THE POWER OF CPV

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Artificial intelligence (AI) is the key that unleashes the power of CPV

We defined a few major elements earlier: NLP, Machine Learning, Predictive Analytics, Multivariate Analysis and IIoT.

Honeywell uses these technologies to build the growing portfolio of innovations detailed below.

QUALITYWISE.AI | AUTOCATEGORIZATION

QualityWise.ai Auto-categorization points the AI engine at a single record or data; a single complaint or quality event or, like in the dissolved oxygen scenario, a single manufacturing anomaly.

It then consumes all the structured and unstructured data in that record or anomaly. Then, based on historical data—AI, ML and multivariate analysis—suggests to the user the most likely categories of critical data elements with statistical probability, such as anomaly type, severity and more.

The remaining fields and requirements of the process and the associated records then auto-populate on the users' acceptance of that suggestion. The result is augmented human decision making, increased timeliness of these critical actions and providing consistent categorization, improved efficiency and prioritization.

QUALITYWISE.AI | INSIGHTS

QualityWise.ai Insights aims those AI algorithms across your entire quality data set, including manufacturing anomalies, corrective and preventive action (CAPA), investigations, deviations and change controls. It then rapidly identifies patterns, trends and occurrences of quality events across that entire historical and current quality data set.

Auto-correlation of related, same and similar records and data sets clearly identified with statistical relationship Now we can detect relevance, correlation and sensitivities to better determine what the ranges should be for our CPPs

QUALITYWISE.AI | ROOT CAUSE ADVISOR

Ineffective root cause analysis is a significant challenge for the industry. The QualityWise.ai Root Cause Advisor uses AI that assists quality teams efficiently and effectively identify root cause using historical data along with future learnings, to train the algorithms.

It correlates similar anomalies and narrows the scope to other similar events. It also extracts contributing factors and identifies factors that are common, ranks factor relevance based on overall contextual relevance.

Finally, it provides the investigator with a curated list of the most likely factors to investigate

It ultimately helps find true root cause, faster.

QUALITYWISE.AI | MANUFACTURING ANOMALY CAPTURE

Let's consider AI and IIoT enabled manufacturing anomaly capture with our dissolved oxygen scenario. Honeywell Experion provides real-time monitoring of the dissolved oxygen level in the production of a glycoprotein in our bioreactor.

If our manufacturing anomaly lower limit is set to 40 percent, as performance drops to 38 percent, that anomaly is detected—before it becomes a failure—and an alert is immediately sent to the TrackWise Digital quality management system (QMS) with all the relevant contextual data and information the quality engineer needs.

A manufacturing anomaly record is automatically generated and then auto-categorized and auto-correlated. Immediate corrective actions are automatically returned to the production cell but only within known, allowable tolerances defined by QbD.

The production unit makes the recommended agitation and aeration adjustments, and our dissolved oxygen level rises back into control, avoiding loss of the product.

Furthermore, as a subsequent investigation is completed, and CAPA implemented to change the design of some critical machine parts of our bioreactor, we can use this technology to continuously, proactively monitor dissolved oxygen performance over the three or five batches, or defined time period in a continuous manufacturing process. This is to verify that the implemented CAPA was effective and demonstrate that effectiveness in real-time.

QUALITYWISE.AI | REVIEW BY EXCEPTION

Finally, what this does for us is enable review by exception, and eventually, real-time release, which is vital for the optimization of continuous manufacturing.

QualityWise.ai Review by Exception provides recommendations based on analytics from all that transactional manufacturing data and production reports provided by Experion, which highlights the single anomaly we encountered (in our example, the low dissolved oxygen), along with any other processes outside of control limits, thereby optimizing that batch record review.

This means we don't need to spend up to 60 days trawling through reems of paper to review every detailed element of the master batch record (MBR). We only need to review those process steps for which any issue was identified.

THE HONEYWELL ORCHESTRATION LAYER

A common concern voiced by the industry is "islands of automation" and silos of data. Many manufacturing sites have these islands of automation where standalone units have been brought into a facility over time with limited interconnection between them. Issues of data silos, data integrity, paper-based processes and lack of broader operational visibility are common in this scenario.

This is where the Honeywell orchestration layer can be added to existing unintegrated lines or new equipment to achieve centralized, real-time visibility across the entire process.

Honeywell can add the orchestration layer for an overall visualization of the system so organizations can achieve visibility across operations.

This value can be delivered regardless of a company's existing automation and supply chain architecture, by leveraging existing process equipment and its built-in controllers.

Due to the orchestration layer solution leveraging and building upon existing system validation, the implementation time and effort required are often reduced compared to more complex solutions.

MOVE INTO THE FUTURE OF DIGITAL QUALITY MANAGEMENT

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Traditional QbD brings enormous value but at significant cost...and the ROI is limited.

QbD should be dynamic, and it should live throughout the lifecycle of a product. With the combination of Honeywell's Experion and TrackWise Digital, CPV and AI-enabled continuous improvement of CPPs is a reality. AI helps detect relevance, correlation and sensitivities and monitors that data in real-time. We can now detect anomalies sooner and detect anomalies that were not previously well defined.

AI-enabled continuous process verification, manufacturing anomaly capture, and the resulting proactive quality response truly optimizes the power of QbD for the business. The result is a proactive, preventive approach to managing quality events that speeds up innovation, reduces the total cost of quality and ultimately, Improves the health and wellness of the global population.

While quality imperatives remain the same, industry is changing as innovation accelerates. Digital transformation provides the opportunity to positively disrupt the discipline of quality.

For more information
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Enabling Quality by Design | Rev 1 | 11/23

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