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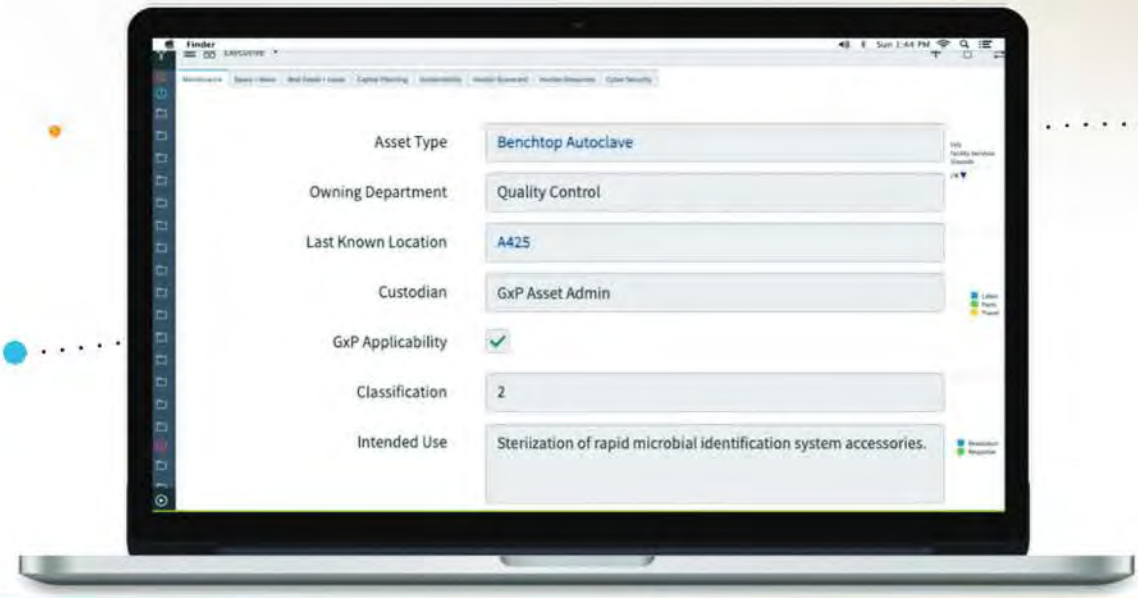

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Getting quality right the first time

CAPA remains an integral element of cost-effective quality management in pharma

By Steven Lynn, Executive Vice President; Susan Schniepp, Fellow;
Justin Anahory, Operations Specialist, Regulatory Compliance Associates

A well-functioning Corrective and Preventive Action (CAPA) program can make the difference between a deviation being corrected and prevented the first time, or reoccurring deviations that require reopened investigations — wasting limited resources and potentially causing product quality issues.

It's important to remember that a well-functioning CAPA program starts with a well-functioning investigations program. After you recognize you have a problem, the first step is investigating the deviation and determining the root cause. The root cause(s) will direct how, what and where the company will take corrective and preventive action.

Ultimately, as regulators note in ICH Q10, "CAPA methodology should result in product and process improvements and enhanced product and process understanding."

In his seminal book, quality guru Phillip Crosby succinctly states, "Quality is free.

One of the most useful strategies for investigations is to ask questions and avoid assumptions.

It's not a gift, but it's free. What costs money are the 'unquality' things — all the actions that involve not doing jobs right the first time."

To that end, setting up a CAPA quality system surrounded by adequate procedures, monitors and metrics to ensure that nonconformances do not occur now or in the future is the best and least costly way for a company to deal with any issues or defects.

REMOVING BLINDERS

While the two terms in the CAPA acronym may sound similar, there are crucial differences between 'corrective actions' and 'preventive actions' and when they're appropriate.

Once investigations and corresponding CAPAs address the root cause, impact on material or product and the direct correction to the issue (i.e., immediate correction), then the corrective and preventive actions must be addressed. Corrective actions are taken to prevent reoccurrence for a specific product or operation, while preventive actions prevent any occurrence for all products or operations.

One of the most useful strategies for investigations is to ask questions and avoid assumptions. Alongside inquisitiveness, fishbone diagrams (Ishikawa Diagrams), fault-tree analysis and the '5 Whys Method' are great tools that can be used to widen a company's ability to determine adequate root cause, which leads to robust CAPAS.

When conducting the investigation, companies must review multiple systems including manufacturing processes, machinery, equipment, environment, specifications, raw materials and people. Deviations are not limited to these systems and other systems should also be evaluated as necessary, but many deviations do reside within one of the listed systems.

Another way to look at this concept is the metaphorical horse with blinders, where the blinders are used to keep the horse focused and moving forward. This same metaphor can be used to think about the investigation and CAPA process. If you go in with blinders on, just looking at the issue right in front

CAPA Guidance

The U.S. FDA's Quality System Approach to Pharmaceutical CGMP Regulations guidance states, "CAPA is a well-known CGMP regulatory concept that focuses on investigating, understanding and correcting discrepancies while attempting to prevent their recurrence."

The agency further defines CAPA as a "systematic approach that includes actions needed to correct ('correction'), prevent recurrence ('corrective action'), and eliminate the cause of potential nonconforming product and other quality behaviors."

The Q10 Pharmaceutical Quality Systems guidance from the International Conference on Harmonization (ICH) further details what is expected in a CAPA program: "The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring."

of you without reviewing other interconnected systems for issues, important details can be missed and more costly problems may result.

Once all the elements of the deviation have been investigated, the narrative of the investigation and its linked CAPAs should explain when and what happened, and who was involved. The narrative should also document the solution that was implemented to correct and prevent reoccurrence of the issue. This includes a rationale for the root cause identified during the investigation. All these items should be well-documented within your quality system.

ELEMENTS OF AN EFFECTIVE CAPA SYSTEM

A robust CAPA program should include a well-documented system that identifies the true root causes of a deviation, including nonconformances, system failures or process problems. In addition, the CAPAs must address the root causes and identify the corrective action for remediating the deviation. Then, the appropriate correction must prevent the deviation from happening again.

Qualified staff (with proper training, education and experience) should run the CAPA program and incorporate meaningful metrics to track the

performance of overall systems and provide early warnings for deviations/nonconformances. An appropriate Subject Matter Expert (SME) should be included in the process. Management should review potentially adverse information, oversee the overall adequacy of the CAPA program, and remediate identified deficient areas, including those that may need capital investment.

Once the appropriate solution has been implemented, evaluating its effectiveness should be ongoing. There should be a process for monitoring the recurrence of the deviation and closing out of the CAPA once the solution has been confirmed effective. All these items must be documented within the quality system.

The same level of depth and rigor of a CAPA for one issue may not be required for every deviation. For example, a small documentation error will likely only require a simple correction, while more serious deviations, like a confirmed 'Out of Specification,' will demand a much more robust investigation and CAPA. This follows the logic of Psychologist Abraham Maslow, who is quoted as saying, "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail."

The complexity of the deviation and its concomitant CAPAs not only determine the approach taken for the investigation, but also inform the timeline. For example, while some standard operating procedures may call for a 30-day timeline for investigations and CAPAs, that timeline may need to be extended. In this case, you'd need to document the rationale for the extension and get the quality department's approval. A critical caveat here is everything in the investigation leading to a CAPA does not need a time extension. If your company is extending a lot of investigations, then it may indicate another entirely different problem.

WELL-STRUCTURED INVESTIGATIONS

The key to establishing a successful CAPA is a complete and thorough investigation focused on finding the reason the deviation occurred. Failure to identify the correct root cause will result in possible failed effectiveness checks and the dreaded reopening of the CAPA. Everything plays a part in the investigation: people, machines, materials, processes, etc.

Management of these players is key to identifying the deviation's root cause. The process behind the investigations is crucial in addressing the issue at hand. The aim shouldn't be to find a single root cause that management believes to be the reason for the failure but to analyze all possible root causes across all systems. If an identified root cause isn't the true reason for the failure, then the root cause can be eliminated. Each root cause eliminated narrows down the investigation. Any potential root cause

that cannot be eliminated must be remediated, even if that root cause is not THE root cause of the failure.

A mistake companies make is identifying a root cause that needs remediation and stopping there. Companies should always identify all possible root causes and address them accordingly.

CAPA COSTS

When executed correctly, CAPAs help organizations remediate deviations/issues before they cause more technical problems and escalated costs. A practical example of an investigation and CAPA process is as follows: Company X had an investigation related to the detection of nonconforming vials, which were discovered prior to packaging. The inspectors on the line found the nonconforming vials, informed the quality team, and an initial investigation ensued.*

A robust CAPA program should follow the format:

1. Identification (clearly define the problem)
2. Evaluation (appraise complexity and impact)
3. Investigation (plan to research the problem including identifying all possible root causes)
4. Analysis (a complete and thorough assessment)
5. Action plan (list required tasks that must be done to correct and prevent)
6. Execution (implement the action plan)
7. Follow up (evaluate effectiveness)

The quality assurance team correctly put the lot on hold while the investigation was being conducted. During the early phase of the investigation, the nonconforming vials were sent away to be analyzed by a third-party qualified laboratory. The results came back stating the discoloration was due to chemical contamination. The chemical in question was not part of the formulation or the container closure system and was not on any product contact surfaces within the equipment.

Company X eventually decided the contamination happened at the vial manufacturer and closed the investigation. One week after the initial observation of the discolored vials was opened and closed, the same issue arose with another product and the original investigation was reopened.

* Example adapted from "Principles of Quality Costs" by Jack Campanella and Frank J. Cosgrove, American Society for Quality, 1982

When executed correctly, CAPAs help organizations remediate deviations/issues before they cause more technical problems and escalated costs.

The company subsequently audited the vial manufacturer, but the results were inconclusive, with no identified source of the chemical responsible for the nonconforming vials. The company continued manufacturing while the investigation was ongoing and began a 100% incoming material inspection. A week later, a line operator noticed a vial exiting the depyrogenation tunnel that had a discolored blob in it. Manufacturing was stopped and the vial was sent to the contract lab for analysis. Once again, the chemical in question was the culprit. The company sent a consultant to do a full audit of the vial manufacturer while they continued manufacturing the product. Similar to the initial for-cause audit, the external consultant could not find the source of the chemical leading to the nonconforming vials.

Finally, after opening the line for inspection, the company discovered that the contaminating chemical was associated with the HEPA filters. Manufacturing was finally halted on the line.

After completing a more thorough investigation, the root cause was determined to be faulty cooling valves in the depyrogenation tunnel. This was previously identified by the company as a potential root cause in the initial investigation, but was not pursued because it was classified as 'possible but highly unlikely' and ranked lowest on the list. There was no alarm associated with the cooling valve which explains why the issue was not caught under routine maintenance checks. Once the problem was correctly identified, the proper and effective corrective action could be taken, including the potential costly endeavor of evaluating all product made on the line and looking at other lines with the same depyrogenation oven.

COST OF POOR QUALITY

Hypothetically, let's say the cost of a critical deviation for Company X is a million dollars. When looking at the cost of poor quality (COPQ) of a defect, the cost is eliminated if and only if the pharma company's quality management system (QMS) is organized and designed to detect, investigate, correct and prevent issues/deviations. If the company can prevent defects with their robust QMS, they will save money because they allocated sufficient qualified resources toward an efficient QMS — which in turn meant they didn't have to address many

It takes diligence, thoroughness and a healthy number of questions to ensure you investigate, correct and prevent problems.

defects/deviations and CAPAs. Hence the quality system pays for itself.

If the issue is detected within the company before anything is shipped out, the cost rises tenfold to ten million dollars. This is due to the company needing to address the now-detected issue and implement corrections (corrective action) to rectify the issue, as well as put measures in place to ensure issues do not occur in the future (preventive action).

If the company detects an issue in a drug product after it has been released by quality and delivered to the customer, the cost raises tenfold again. The cost now includes recalls, as well as corrective and preventive actions. The cost of quality is important to understand — for Company X, they caused themselves a $100 million mistake.

Company X initially thought the issue seemed small and negligible, which led to an unfortunate quick closure of the investigation. Ultimately the deviation affected twenty-eight lots of manufactured products. These lots, produced over a two-month period for several clients, were rejected due to the nonconforming vials.

Company X should have utilized a more thorough investigation and root cause analysis strategy and taken more time to follow every possible root cause. Instead, the company chose what seemed like the easiest root cause and jumped to the wrong conclusion. Then the company quickly closed this initial investigation without a complete and thorough investigation, thereby creating a bigger issue and a compliance and business risk.

It takes diligence, thoroughness and a healthy number of questions to ensure you investigate, correct and prevent problems. But without this, the quality and efficacy of the drug product being manufactured could be jeopardized.

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What's your vision quotient?

Manage secondary packaging quality with 100% vision technology

By Lon Johnson, VP Sales & Marketing, Colbert Packaging

The Digital Age has presented pharma packaging manufacturers with a supreme challenge: to implement effective ways to manage and maintain the highest level of quality — as in 100%.

Replicating the pharmaceutical secondary packaging workflow system to protect the project from critical errors throughout each stage of the manufacturing workflow requires 100% vision inspection. The onus is on your secondary packaging supplier to deliver perfect containers, labels and inserts, on time and on budget.

To render a 100% vision quotient, your supplier must offer a strategic combination of key components. Here's how your vision quotient adds up, stated in terms of key benefits:

- Secure and verified content is 100% accurate before going to market
- Automated vision inspection systems require less rework, saving on material,

and require less labor to address corrective actions
- Projects flow efficiently, opening greater capacity

The benefits of 100% vision inspection may seem obvious ("perfect will be fine"), but let's take a look at how vision inspection actually works. Next, we'll trace the evolution of vision technology. Finally, we'll examine the packaging industry's ready state to help you determine your brand's vision quotient.

HOW VISION INSPECTION WORKS

With 100% vision, a constant stream of electronic information flows from prepress through printing presses, folder-gluers and packers. Capturing the information in milliseconds, these are the eyes and brains that process your packaging requirements. Customizations enable the system to analyze data based on a predetermined set of criteria.

Using vision inspection technology, the customer establishes quality assurance (QA) parameters to detect characters, pixels, patterns, shapes, edges, presence (or non-presence) and location of glue, barcodes, labels or inserts. Irregularities, flaws or defects determined to be outside the parameters of the QA standard are flagged in pass-fail fashion and segregated from the lot.

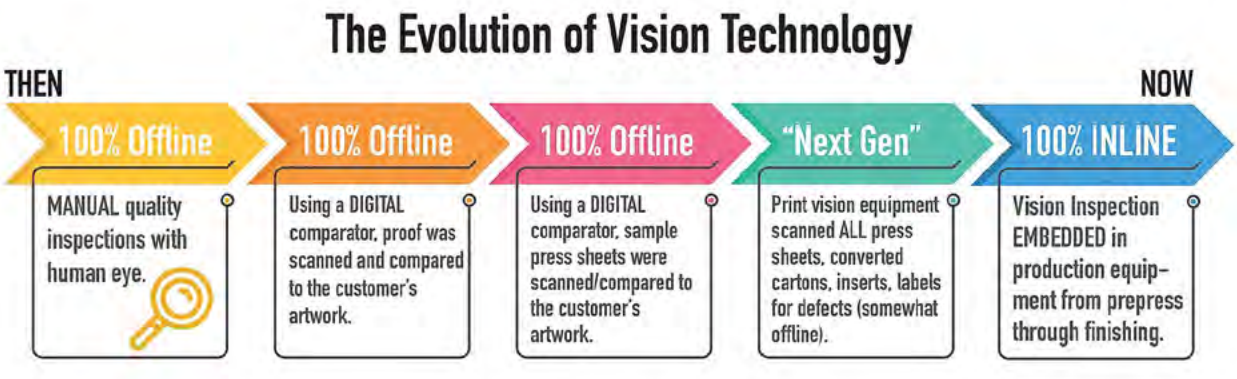
THE EVOLUTION OF VISION TECHNOLOGY

Would you be satisfied with an 80% quality quotient? Quality studies from the 1970s found that human inspectors were detecting only 80% of defects in manufactured parts, assuming the defective 20% would "squeak by." Not to mention, these 20th century offline inspections slowed production.[1]

In the days before computers and digital technology, manual quality inspections

FIGURE 1.

Vision technology then and now



Failure to comply with regulations can cause delays in product launches and fulfillment, customer complaints or product recalls.

relied on the human eye for proofreading and detecting errors or print flaws in packaging production runs. This process was not only time-consuming, but also self-limiting when applied to high-volume production of millions of pieces. At best, only a sampling could be expected to pass through a detailed inspection for quality (Figure 1). When you add together the human factors of distraction, fatigue, inconsistency and multiple sets of eyes performing inspections at varying times, the quality quotient of past processes is dubious.

THE VISION SYSTEM PROCESS

Prepress

Prepress represents the first point of entry for digital file comparison. The vision system digitally inspects and remembers the customer-approved file alongside the file to be ripped for proofing.

Printing

Vision systems monitor the quality of the entire print job throughout the run. The print run may include detecting flaws or defects in printed paperboard folding cartons, informational inserts with complex folds and flexographic printed, pressure-sensitive labels. Errors are detected in real time, enabling the operator to take corrective action and limiting waste or downtime. The system limits waste by setting predefined, region-specific inspection priorities.

With the customer proof or .pdf providing the standard, many characteristics are assessed for quality: text, multiple languages, braille dots, graphics, foils, color variations, registration, filled in or missing characters, print flaws, variable data, and 1-D and 2-D codes.

Finishing

The finishing step detects mixed, missing or skewed copy; barcodes; jams or double feed; feed counts; base counts; and batch counts. Further, it ensures the presence of glue on each carton, as well as the glue line's position on a target area of the carton. Only 100% conforming materials are delivered to the customer.

CURRENT STATE

For the secondary packaging market, quality inspection is an integral process

throughout the entire manufacturing operation. Strict labeling and packaging requirements govern consumer packaged goods, health and beauty and, especially, the pharmaceutical industry. Failure to comply with regulations can cause delays in product launches and fulfillment, customer complaints or product recalls. Branding errors or mistakes regarding dosing information or other consumer instructions can damage the brand or, worse yet, endanger the consumer.

Current applications for vision inspection include positioning, identification, verification, measurement and defect (or print flaw) detection.

In highly regulated industries like pharma, vision systems software must conform to applicable industry standards and guidelines such as ISO 9001, GMP and GAMP 5. Vision software must also contain functions required for validation according to U.S. FDA Title 21 CFR Part 11 guidelines.

WHAT'S YOUR VISION QUOTIENT?

Has your secondary packager invested in these key components: up-to-date processing hardware, software to render and communicate results, sensors, cameras and an industry-compliant environment? Automated vision inspection systems accelerate the secondary packaging process by ensuring speed, accuracy and consistency, while supporting your company's commitment to sustainability by reducing waste. Removing defective parts before packaging arrives at the customer's production or fill line drives a more positive customer experience and a safer, more reliable end-user experience.

Improve your packaging quality quotient with 100% vision technology for better quality, higher yields and lower downstream waste.

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Simplifying batch record review

How a centralized data location improves the lot life cycle process and speeds historical data analysis

By Ethan Smith, General Manager, Life Sciences, Nuvolo

Advances in pharmaceutical manufacturing don't need to be complex to make an impact. Small, incremental changes can streamline your most cumbersome, yet important, processes significantly, including reviewing your batch records. Quality's batch review process is time-intensive for good reason. For starters, ensuring that pharmaceuticals are produced in a controlled, consistent way is essential to public health. Plus, the industry is extremely regulated, and having protocols in place ensures manufacturers standardize their processes, identify any deviations and deliver products of the highest quality consistently.

With that said, timing is everything. The sooner that batches are reviewed, the faster a company gets the products out the door to patients. When the batch review process gets held up, companies risk delays, expirations, shortages and lost revenue.

WHAT GOES INTO A BATCH REVIEW?

Batch records help keep manufacturers accountable throughout the production process. They help companies write good procedures, follow the procedures and record that they followed them correctly every time. Executed batch records include information such as the product name; the weight, count and lot of the raw materials necessary to manufacture the product; a list of all processes and procedures to follow; the equipment used; and the expected yield of each batch, along with information on the employees running the production. The batch review process includes checking all documentation that applies to a production run, which can get complicated when all of the information is decentralized.

This often is the case because many teams are involved in getting products released for human consumption. Each piece of the production process may be managed by a different team using a different system (including spreadsheets or pen and paper).

For example:

- Manufacturing execution systems (MESs) manage the actual shop floor process and operations of the production line in real time.
- Quality management systems (QMSs) link all relevant documentation in the process, including work instructions, standard operating procedures (SOPs), electronic forms, batch records, test results, etc., and manage the processes of incidents, investigations, and corrective and

Step	Future State
Capacity planning and lot creation	Analyze equipment capacity and reservation history proactively
Plan/schedule manufacturing production run per lot	Maintain consolidated view of assets and capacity
Reserve manufacturing equipment and space	Reserve required equipment and auto-generate 'last-used equipment list.' Reservation and capacity data informs capacity planning
Ensure all equipment is maintained, ready and available	Auto-generate report of all reserved assets and receive automated alerts if any asset is not usable
Execute manufacturing run	Auto-associate batch number and the manufacture date to the audit trail of all equipment used
Review manufacturing records (EBR, etc.) to ensure quality	Auto-generate validated equipment report for the batch
Release batch into inventory	Simplify batch review process

preventive actions (CAPAs) when quality issues occur.
- Enterprise resource planning software (ERPs) or warehouse management systems (WMSs) manage the physical inventory and supply chain of the ingredients required to produce the end-product
- Enterprise asset management systems (EAMs) and computerized maintenance management systems (CMMSs) house the historical information of how and when assets and equipment are maintained. For batch record review, there needs to be a record of how each piece of equipment is used, cleaned, sanitized or sterilized. Maintenance records also must show the name/signature of the person who performed the maintenance work. However, there can be multiple asset records as different teams may service the equipment.

Because all the information required to review a batch record is decentralized, quality teams have a manual, time-consuming process for reconciling the sources of data and identifying any deviations from standard operating procedures.

WHY IS IT SO COMPLICATED?

It's no surprise that the pharmaceutical industry moves slowly. While some companies have adopted electronic batch records (EBRs) and interoperability among the various systems is on the rise, many paper-based and disparate systems remain in use. One such area is asset management.

Batch records typically do not include information on the specific assets involved in a production run, but rather note just the type of equipment needed for each step. The current process for reviewing this information is inefficient and can be improved dramatically by automating the asset review process. In many cases, teams manage manufacturing equipment using multiple systems, including an ERP, an MES and third-party vendor applications. With the lack of transparency on each asset, unplanned availability often delays production runs. As a result, there is often no single system that houses the necessary data, and reconciling all of the information extends the time to get the product batch to market.

BABY STEPS TO A MORE STREAMLINED PROCESS

It is possible for companies to align their quality and manufacturing processes to allow manufacturers to deliver products quickly while maintaining the highest levels of quality. Ideally, manufacturing equipment, execution records and quality documentation can be aligned in *one place*.

By connecting asset information (including manufacturing equipment and space records) with each executed batch, drugmakers can auto-generate validated equipment reports per batch. They don't need to manually verify the status of the equipment and whether it was in working order and calibrated properly. Instead,

In the future, companies will be able to receive a validated, comprehensive and consolidated report of all equipment and space used.

this information is compiled automatically, ensuring the complete documentation of manufacturing execution records and simplifying the batch review process.

Here's how aligning records in one place can help improve the entire lot life cycle process, streamline batch review and eliminate disparate systems in each step of the production process:

In this future state, companies will be able to receive a validated, comprehensive and consolidated report of all equipment and space used, which will become a part of the executed batch record.

By capturing all data in one place, you ensure complete documentation of manufacturing execution records, which cuts the time it takes to reconcile disparate data and streamlines investigations in cases of recalls or product complaints which can be automated via integration to your QMS. Historical data and trends of production issues, delays or quality concerns can be analyzed at the product level by having the batch numbers of every batch each piece of equipment has produced in its audit history. This data will be expanded and enhanced overtime with AI to enable predictive performance management of assets.

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Simplifying pharma through digitization

Manufacturers that are digitalizing lab information management can improve quality and streamline operations

By Kevin Finnan, Marketing Intelligence and Strategy Specialist, Yokogawa Corporation of America

As pharmaceutical manufacturers pursue quality enhancements, management is realizing many opportunities for improvement in laboratory information management and workflow processes.

Traditional methodologies are error-prone and can complicate compliance. As quality improvement teams turn to digital methodologies, they most commonly are challenged with:

- Improving the efficiency of data collection and analysis
- Improving the efficiency of quality control management
- Improving overall business efficiency
- Overcoming problems with human errors and document management

To overcome these challenges and enable improvements in laboratory data management and workflow processes, many pharma manufacturers are turning to digital

laboratory information management solutions (LIMS).

THE PROBLEM WITH PRE-DIGITAL METHODS

Using traditional methodologies in which large quantities of data are transcribed, technicians find the raw data transcription to be subject to errors. Even the checking process introduces the risk of errors. Review processes often are cumbersome. It takes considerable time to check dilution calculations, blank calculations and reported values.

Analyzing and tracing historical data, particularly when test records are maintained as paper documents, also incur considerable time. There are inefficiencies in report generation. Sometimes, there is a lack of space for storing test records as paper documents.

Older methodologies also make compliance with U.S. Food and Drug Administration (FDA) 21 CFR Part 11 and other regulations more difficult. Such processes are prone to inconsistencies in recordkeeping, which could complicate audits.

'Pre-digital' methods further introduce difficulties when personnel outside the lab need to check on testing progress. Internally, the manufacturing and shipping departments most often need access to this information. It also takes considerable time to prepare high-quality information to respond to the requests of external parties such as customers.

FIGURE 1

The industry is digitalizing the pharmaceutical lab to improve quality.

DIGITALIZING THE LAB

Manufacturers that are digitalizing laboratory information management and workflow processes can realize numerous quality benefits (Figure 1). It is desirable to unify data management including the management of requests to external analytical laboratories. In a transformed operation, the unified information can be made available throughout the enterprise and the supply chain — and provided in formats that are best-suited to all individuals requiring access.

In addition, unified management of analysis data and analysis workflows meets customers' requirements for enhanced quality management and enables them to respond to recalls and complaints quickly.

To enable improvements in data management and workflow processes, manufacturers are turning to digital LIMS. The digital solutions support analytical and quality management operations and allow end users to establish test workflows to standardize and optimize laboratory operations.

Ultimately, the LIMS enhance quality by minimizing human error, improving laboratory information management workflows, increasing quality control reliability and ensuring compliance with such regulations as FDA 21 CFR Part 11.

Tight integration of the LIMS with enterprise resource planning (ERP) platforms and manufacturing execution systems (MES) of measurement results from analyzers eliminates the need for raw data transcription. Dilution, blank, other calculations and rounding of reported values are automated.

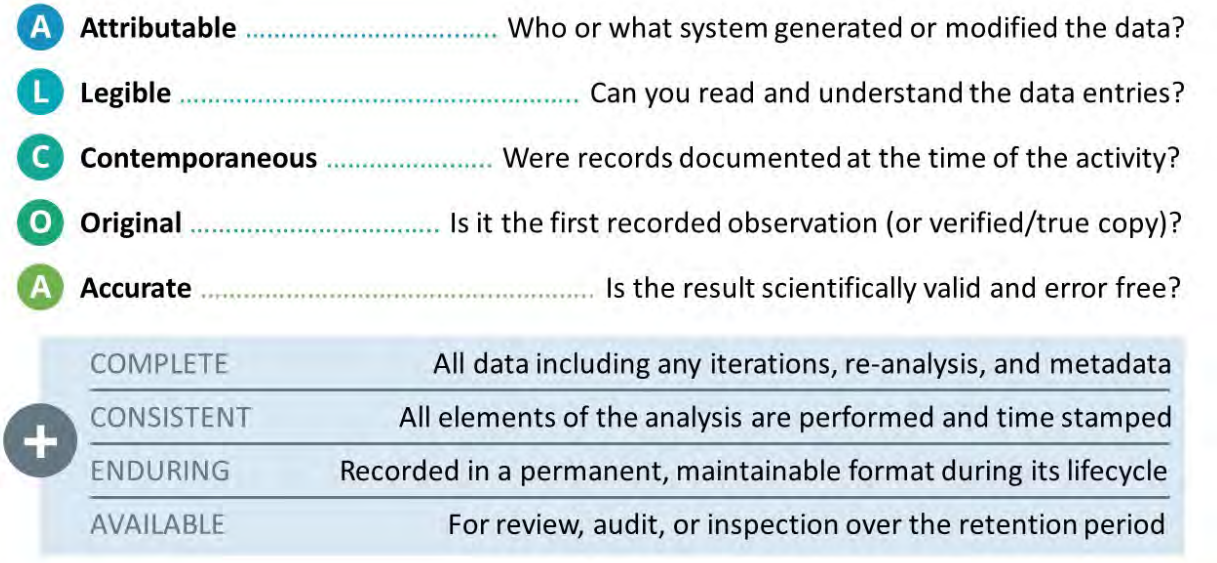
Automated lot-by-lot recording of test information such as the equipment in use and reagent or technician name facilitates traceability and data analysis. The LIMS manages the progress of each lot and enables the test progress to be viewed graphically from the manufacturing and shipping terminals.

It provides functions such as operational history, identification records of analyzers used for measurements and technician identifications, which are compliant with FDA

FIGURE 2

ALCOA+ Principles

These guidelines help to ensure the reliability of data requested by regulators in Europe, the U.K. and the U.S.

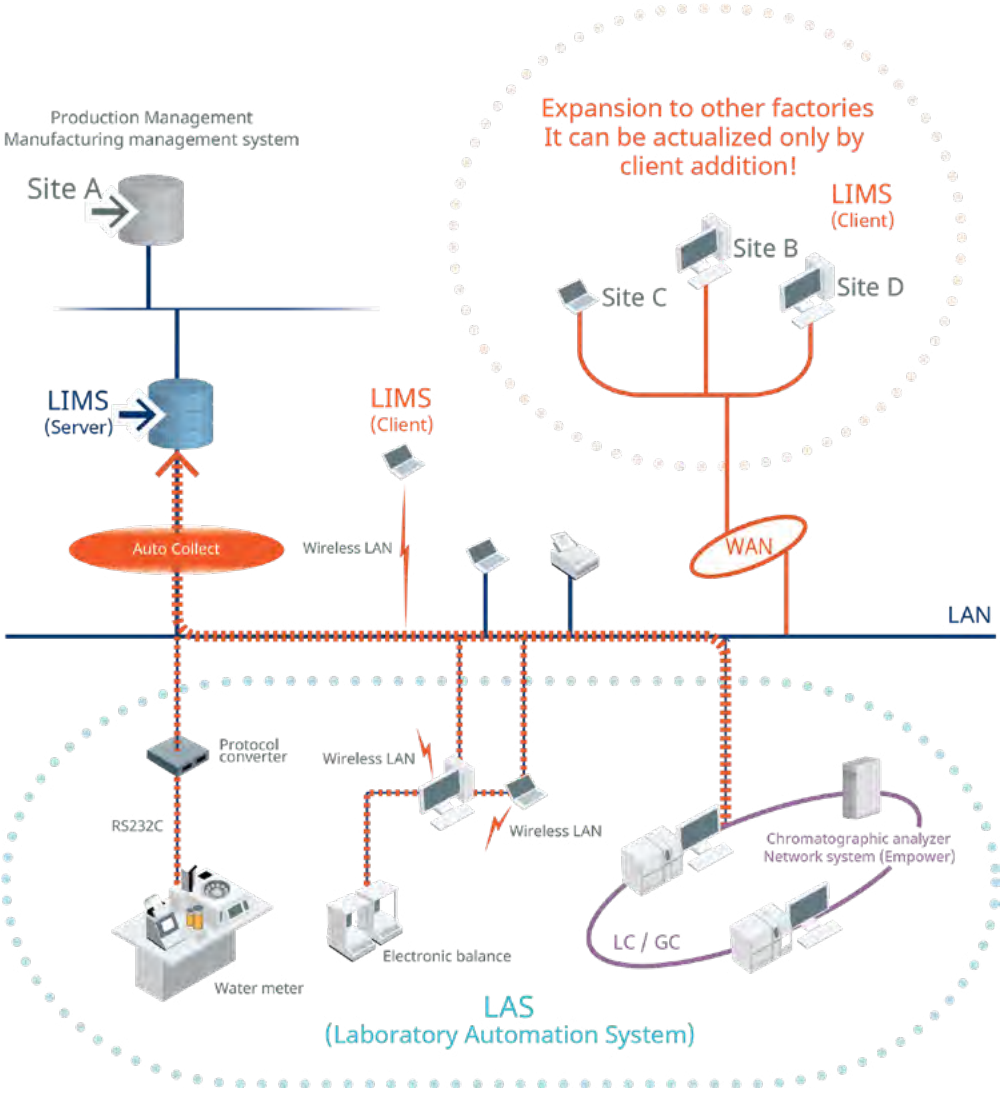


nonconformities in the industry. The unified guidelines provide best practices that are intended to avoid nonconformities and regulatory agency sanctions.

The FDA has issued five data integrity characteristics that are based on the accurate, complete and consistent recording and management of data or information, either on paper or electronically. In the "ALCOA" concept, the five data integrity characteristics *are attributable, legible, contemporaneous, original* and *accurate*. Figure 2 contains the definitions.

FIGURE 3

This example shows how a laboratory information management solution (LIMS) supports data sharing with other systems via a corporate network.



Further to the ALCOA concept, the PIC/S agency in Switzerland uses "ALCOA+," which has added four more characteristics for data to be considered intact: *complete, consistent, enduring* and *available.* These characteristics also are defined in Figure 2.

In an example, among the guidelines is a criterion that the data recorded from analyzers in a lab needs to be precise upto the last decimal digit. Typically, a LIMS includes a feature, which enables technicians to achieve the quantifiable benefits of automatic input for experimental data. This provides for a considerably reduced workload for double-checking records and reports. Users have found barcodes very effective and have helped to reduce workloads in reagent and analyzer management with increased efficiency of data traceability.

STREAMLINING ANALYSIS AND QUALITY OPERATIONS

In addition to meeting data integrity best practices is the need for quality activities in compliance with regulations such as Current Good Manufacturing Practice (CGMP). The agency "ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

The approval process for new and generic drug marketing applications includes a review of the manufacturer's compliance with the CGMPs. FDA assessors and investigators determine whether the firm has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.

In the industry, there is a growing need for high-mix/low-volume production, and conventional paper-based data management often can be overly complicated. A LIMS addresses the regulations by establishing a workflow for quality control to improve efficiency, save labor and centrally manage test data.

An LIMS also provides total support for the standard workflow of quality control, from receiving test requests and issuing instructions to approval of test results and factory release evaluation (Figure 3). It also covers all aspects of quality control, including automated data collection from analyzers, stability test plans, and management of reagents and analytical instruments.

By linking with existing MES and ERP systems, it is possible to visualize the entire enterprise, which significantly impacts improvements at all levels from corporate management to the plant floor (Figure 4).

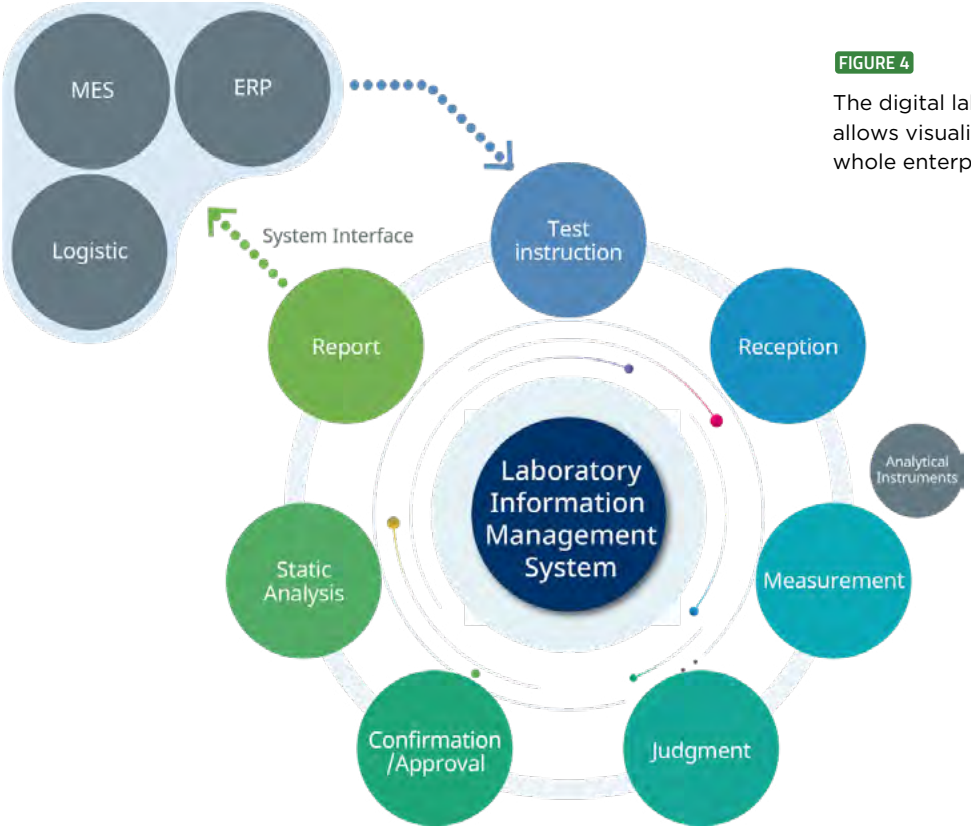


FIGURE 4

The digital lab workflow allows visualization of a whole enterprise.

A LIMS streamlines operations by establishing test workflows and provides 21 CFR Part 11-compliant electronic signatures. It also enables centralized control of test data through on-line connection with inspection and analytical instruments and allows visualization of internal operations in the plant through linkage with other systems.

BENEFITS OF DIGITAL LIMS

To enable quality improvements in pharmal operations from the laboratory through the enterprise, a digital LIMS offers numerous benefits.

- *Standardization of quality control operations:* Users can establish standard workflows to improve the quality and efficiency of analytical operations.
- *Workflow reductions through lab automation:* The platform allows technicians to connect online with a variety of analytical instruments and collect analytical data automatically. This has a significant labor-saving impact on data input and prevents transcription errors and data falsification.
- *Regulatory compliance through security and traceability features:* Operators achieve secure system operations by granting appropriate permissions to users through user ID and password at login and authorization. Also, as a traceability

To enable improvements in data management and workflow processes, manufacturers are turning to digital LIMS.

function, users can check the history of sample acceptance, approval of results and release evaluation.

- *Paperless operations and improved search speed:* Online input of test data eliminates hardcopy. Test data can be approved and released via an electronic signature. In addition, a database that includes test data and approval data allows searching at a much higher speed than paper-based data management would allow. Quickly comparing and analyzing past data allows management decisions on test data in real time.
- *Accommodation of a variety of forms:* The platform allows users to freely create form layouts. This can significantly reduce the engineering costs required for form creation.
- *Stability test plan preparation:* A stability test can be planned to evaluate the aging deterioration of drugs. Automated test requests are sent in accordance with the plan. This can prevent missed testing time points and analytical method errors.
- *Concurrent validation and retrospective validation improve data reliability:* The past and present test data can be referenced by the test unit. Users also can set permissions for editing test data and viewing the audit trail of any alteration.

LIMS provides a broad variety of both intangible and quantifiable benefits. Among the former are the elimination of human error in data entry, transfer and calculations and increased efficiency in analytical and experimental tasks via standardization. High data traceability improves customer satisfaction, and improvements in product quality and compliance operations lead to an increased reliability in company-wide quality management.

Quantifiable benefits include the automatic input of experimental data; a reduced workload for double checking; and a reduced workload for instructions, records and reports. Barcode scanning reduces the workload in reagent and analyzer management. The LIMS further enables integration with many other business systems and substantially increases efficiencies in terms of data traceability and audit preparation.

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