SPECIAL REPORT

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Taking Control of Regulated Content and Data

New compliance strategies, quality metrics, and the emergence of the regulated cloud

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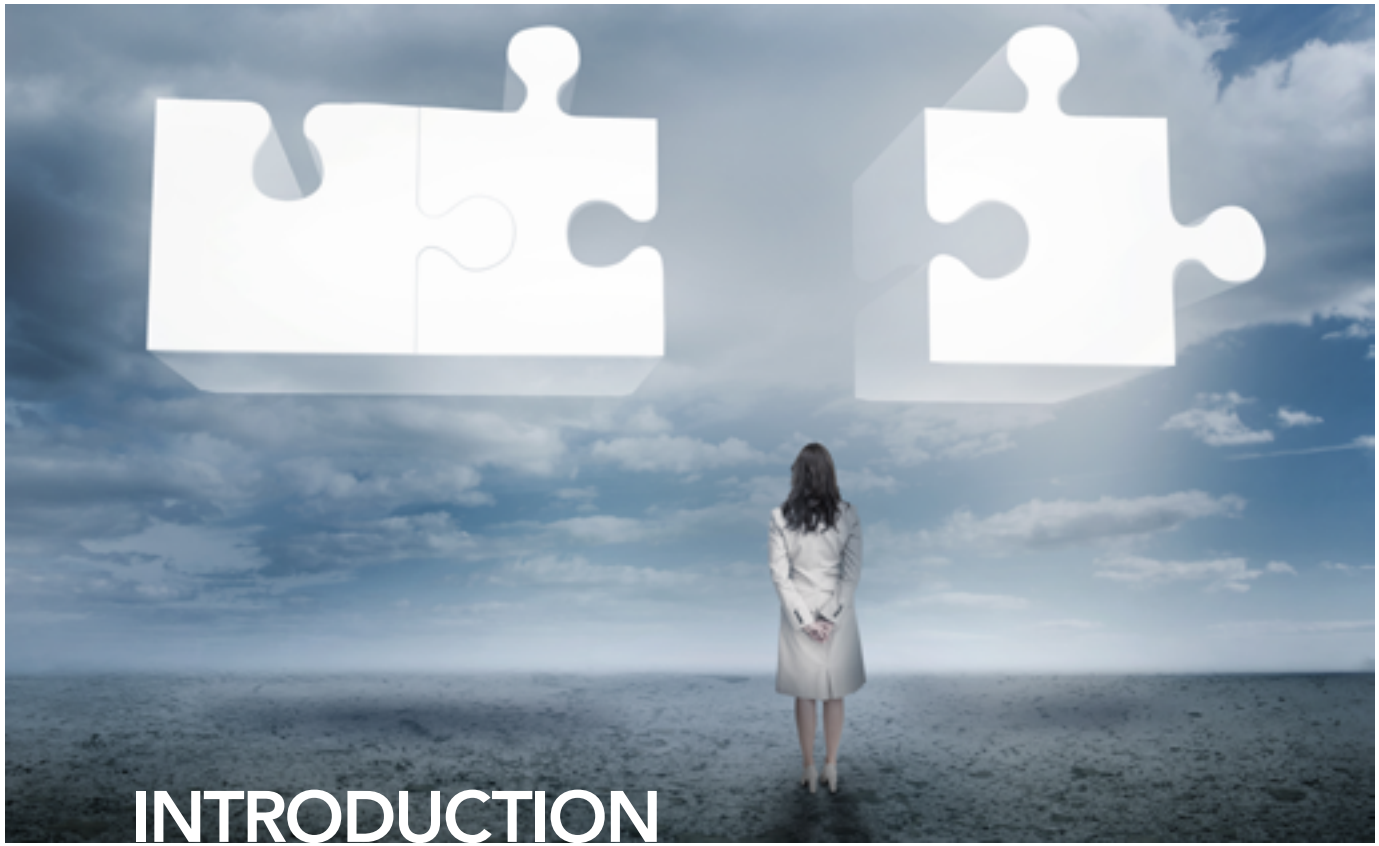


INTRODUCTION

MOST LIFE sciences companies rely on antiquated solutions to manage data and documents—systems built when companies were less impacted by globalization and had fewer regulatory requirements. Today, many more parties are involved in the end-to-end production of a drug, making the supporting processes more complex. Simultaneously, regulatory bodies are demanding more upstream visibility to drug development. Burdened by legacy systems and an increasingly regulated environment, many businesses struggle to maintain compliance. Where to turn? For life sciences data and content managers, modern, cloud-based solutions have become an attractive option, offering more than economies of scale, speed, and cost savings. They also provide greater visibility and collaboration with external parties. To help guide strategic thinking, the following articles offer a deeper dive into the benefits of content management applications in the regulated cloud and strategies for 21 CFR part 11 compliance.

Harnessing IT to Strengthen Relationships

Connecting key information systems assures your suppliers all pull in the right direction

By Doug Bartholomew

IT'S 2014. Do you know where your drugs are on that other guy's plant floor? You should. Unfortunately, pharmaceutical companies often lack the visibility they need to carefully manage their contract manufacturers and contract development organizations' performance.

That's surprising, considering the benefits pharma manufacturers can reap by connecting key IT systems enabling the sharing of critical information about product quality and manufacturing efficiency. First and foremost, meshing quality, manufacturing, laboratory, and other business information systems can help accelerate understanding of potential quality problems and support a faster resolution of plant floor issues. In other words, by expanding the flow of information between pharmaceutical companies and their contract drug manufacturers, both entities stand to gain. The payoff is greater visibility into operations, better information on which to make business decisions and easier tracking of manufacturing exceptions.

As pharmaceutical firms' dependence on contract manufacturers has increased, the need to expand and speed up connections with suppliers has intensified. While many of the most prominent pharmaceutical companies have connected business systems such as enterprise resource planning systems (ERP) with those of their outsourcing partners for supply-chain purposes, those that have connected other pharma-related IT systems — CAPA, LIMS, QMS, MES and enotebook systems — tend to be far fewer.

MINORITY REPORT

Of the 173 pharma industry professionals who responded to a Pharmaceutical Manufacturing magazine survey last year, only a minority reported that their firms had connected their various internal quality systems with those of their outsourced manufacturers.

For example, about one-fourth (24%) said they had integrated their corrective and preventive action (CAPA) systems with those of their suppliers. Only a limited number of respondents (13%) said they were using technology to connect their quality management systems (QMS) or similar IT platforms with those of their contract suppliers. Finally, one-fifth indicated that they had set up dashboards to electronically monitor key performance indicators (KPIs) for their contract partners.

Clearly, by strengthening connections with their contract suppliers through better, more extensive integration and application of various IT systems, pharmaceutical manufacturers stand to reap a host of benefits. One of the most obvious places to start is automating the workflows supporting various processes.

"The more you use technology, the better off you are in terms of efficiencies," says Tee Noland, chairman of Pharma-Tech Industries, a pharmaceutical contract manufacturer in Royston, Ga. "Connecting our ERP system with our customer Johnson & Johnson saves a lot of time for them, because we do a lot of the

supply planning for them. For instance, with Johnson & Johnson, we manage our inventory in their distribution centers," Noland says. "It saves a lot of time for them, because we do a lot of the planning. And of course, if they have a promotion, we have to boost our inventory to meet the increased demand."

Pharma-Tech, which uses an ERP system from Syspro, depends on it for a variety of information essential to the company's successful providing of services to its customers. "Our ERP system gives us information on inventory, scheduling, production, production efficiencies, and materials ordering, as well as financial information," Noland explains. "We also have our own homegrown databases to track quality issues and any non-conformances."

Each shipment from Pharma-Tech to Johnson & Johnson is accompanied by an electronic notification that the shipment is en route. In a similar fashion, once each week, Johnson & Johnson sends Pharma-Tech an XML-formatted file containing a forecast for the products the contract firm needs to provide. "I take their forecast and import it into our system, and we use that to schedule our production," says Kristin Brown, customer service and planning manager at Pharma-Tech. In the next step, Brown uses the electronic forecast to do the materials planning for the customer. "We receive the forecast file and then go in and do the planning for them," she says. She connects with the Johnson & Johnson SAP system through the pharmaceutical company's SAP portal. "We see their inventory and sales, and then we do the planning and supply chain work for them," Brown adds.

Still, many of Pharma-Tech's customers are smaller drug makers that continue to use purchase orders, sales forecasts, and other non-electronic means of communicating with the contract firm. For quality-related issues, Pharma-Tech's quality department sends the appropriate forms to the customer's website or portal.

"For the most part, with our smaller customers," Brown says, "they email us their purchase orders, and we manually type them into our system. For a broad supply chain view, it's better to have all the information imported directly into our system.

"Overall," she adds, "If we had more electronic connections with our customers, it would bring improvements, including better planning, better decision making— for our own company and for the customers as well — greater visibility, and the ability to order in bigger chunks. And it gives us better flexibility in scheduling the workload."

Pharma-Tech also is able to share certain financial information with customers. For instance, the company shares pricing data for raw materials used to manufacture their products. If the cost of raw materials goes up during the year, Pharma-Tech is able to recover the variance in the purchase price by pulling the purchase information out of its database into a spreadsheet that displays the variances. "If there are price changes during the year, we want to get the money back if the cost of goods went up, or we may have to reimburse them if the costs were lower," Brown explains.

Another factor driving the increased use of technology for information sharing between pharma companies and contract manufacturers is the need to provide serialization of products to facilitate tracking and tracing. For instance, some larger pharma companies are using their ERP systems to provide the serial numbers to be used by CMOs, which in turn, communicate back to the pharma OEM a status report.

"The CMO will provide an overall 'statusing' of which codes were used, which were not used, and which were for products that were pulled for quality sampling, or where the labels did not come out right and the product was scrapped," says John Danese, Senior Director of Life Sciences at Oracle Corp., one of the leading ERP vendors.

Another factor driving the increased use of technology for information sharing is the need to provide serialization.

Despite the apparent benefits, many pharmaceutical companies have been somewhat slow on the uptake to embrace the sharing of various kinds of information with contract suppliers. "I think the bus is about half full, with some pharmaceutical companies yet to get on board," Danese observes. "For some CMOs, their idea of advanced communications is a fax. There is a broad spectrum of maturity among companies in the way they deal with their partners."

PREVIOUS NEXT

Looking ahead, Danese believes that in the next few years, the industry will more fully embrace the electronic sharing of product quality information between pharma companies and their outsourcing partners. "The exchanging of quality information electronically is a bit down the road," he says. "I think we'll see a larger uptake in the next three to five years."

In fact, the sharing of quality data has historically been an area where pharma firms have lagged. While most pharmaceutical firms have a CAPA system in place, those systems' lack of connectedness or integration to larger systems such as ERP has been a serious stumbling block to information-sharing between drug manufacturers and outsourcers. One reason is that CAPA systems often are not connected with other plants or with systems that can measure overall process effectiveness.

Nonetheless, connecting CAPA with ERP promises huge potential benefits. The chief goal is to ensure that everyone who needs to know about — or act upon — production miscue or quality problems, has easy and immediate access to the necessary data. The ability to both trace a batch of material to the source as well as to access all documents associated with it through the production journey can be very helpful in correcting and preventing future occurrences of similar problems.

Compared to the pharmaceutical industry, the high-tech industry is light years ahead in terms of information sharing with contract partners. Of course, outsourcing has long been a way of life for electronics firms, which often have little or no manufacturing of their own, but instead depend on an entire ecosystem of semiconductor foundries, assembly makers, and test providers to handle production. Many high-tech companies outsource logistics and warehousing as well, and some even outsource every aspect of their business.

But in a highly regulated industry like pharmaceuticals, there is an even greater need for information sharing and stronger ties between manufacturer and CMO. "We see pharmaceutical companies sharing quality data both ways, manually and electronically," says Elaine Schroeder, vice president of sales at Pilgrim Software, a provider of quality and compliance management systems.

From a quality standpoint, OEMs must first certify the supplier through an audit to determine that the contract firm adheres to standard operating procedures and GMPs. For instance, if a packaging nonconformity has been identified at the CMO, the pharmaceutical company may require the outsourcer to report on the problem electronically. "Pharma companies that have a quality management system may require the packager to respond through their supplier portal," Schroeder says. "But some respond through faxes or other means," she adds.

"Usually if the pharma company issues a change in supplier materials, they will communicate this through a supplier portal," Schroeder points out. On the sharing of CAPA data, Schroeder says, "It's not all that complex to have one CAPA system feed another CAPA system."

Yet another challenge facing many pharmaceutical firms is, ironically, an internal one — too many versions of the same ERP system that have yet to be consolidated into one. This lack of consistency within an organization inhibits the smooth sharing of data with outsourcers. "We have a well-known medical device company with three versions of SAP that don't communicate with each other," Schroeder says. "Another client has more than 60 versions of their call-center software, so they are not even treating their customer complaints in any homogenous way."

Companies that have a manufacturing execution system (MES) in place have a leg up when it comes to collaborating with contract suppliers, Schroeder explains, because they have more detailed production data already on tap.

Certainly in the high-tech industry the use of an MES with web-based access at both the electronics manufacturer and the contract outsourcer provides:

- Demand signs to the contract partner
- A view of current production status at key points
- Quality data
- Data for measuring supplier performance

Much of the impetus to adopt these technologies in the pharmaceutical business can be attributed to action on the part of regulatory agencies. "I think the regulatory bodies are providing the push in certain sectors of the industry, such as in the medical device area," Schroeder says. Device makers are required to do electronic submission of product deficiencies or non-conformances to a regulatory agency, she adds.

"There is a great deal of interest in expanding connections between pharma companies and their contract manufacturers," Schroeder adds. "But the contract manufacturers look at it as a way to get a competitive advantage by having a QMS in place."

Still another stumbling block preventing the industry from fully embracing more IT systems for collaborative purposes is a widespread concern among pharma companies over exposing their proprietary information to others. "The pharma industry still has a real fear of exposing their quality systems to suppliers," says KR Karu, pharmaceutical industry solution director at Sparta Systems, a provider of quality management systems.

"When it comes to the business systems, there is a back-and-forth of data sharing between systems," he says. He cites just-in-time ordering data utilizing shared inventory information, shared purchasing information and other supply-chain data that is routinely provided by pharma companies to their outsourcers, and vice-versa. Not so, however, with product quality data, which often is kept within the manufacturer's systems.

By contrast, Karu points out, "In the high-tech world, the electronics firms' partners are in their systems as if they work there." Although most pharma companies adopted quality management systems years ago for use inside their own firms, few were willing to share that data with their contract suppliers. The result has been that many drug companies now find themselves handling quality issues the old-fashioned way. "Now that the industry is moving to more of a real supplier base, pharma companies are dealing with quality problems through phone calls, faxes and emails," he says. "There are quality issues falling between the cracks, I am sure, as a result."

The gains to be had by sharing quality data, however, far outweigh any concerns over data security, asserts Sparta's Karu. "For example, when you have a manufacturing deviation, you are not sure what the cause is, and having all hands on deck throughout the supply chain is important," he says. "You need visibility and transparency across the organization. If you have a supplier that fails, you need to know right away, so you can find another supplier somewhere in the world who can provide this service."

Standardization of data is another key area for collaboration between the pharma firm and the contract provider. "One of the top life sciences companies is working with us to take standard procedures and standardized data so that everyone is doing things the same way," explains Ken Rapp, managing director and senior vice president at Accelrys, a provider of lab execution and management systems. "As a result, we are now getting real transfer of process data between systems."

This kind of connectivity between systems at different partner companies has been extremely difficult up until now, Rapp asserts. "It's been nearly impossible to get the job done in the past, but I think there is change afoot," he says. "Today we have tremendous pull between the supply side and the partner side to get this done."

As an example, Rapp cites a pharmaceutical client that depends on Accelrys to keep close tabs on what's happening at its suppliers' labs. "We have a customer with three contract suppliers that they monitor closely. They run a dashboard every day to see what's going on with the manufacturing process at their three partners," he says.

"It's become a critical need for our customers to know what's going on," Rapp adds. "They want systems that include process informatics, and they want them faster, easier to deploy, and with shorter times to get to the benefit. We need to broaden the number of companies that can take advantage of these systems."

ABOUT THE AUTHOR

Doug Bartholomew is a journalist specializing in manufacturing, technology and finance. His articles have appeared in New York Magazine and Los Angeles Times Magazine, and he is a former senior technology editor for IndustryWeek and senior writer at InformationWeek.

Ensuring Data Integrity

21 CFR Part 11 might really be called the Data Integrity Act. Here is a high-level look at what is needed to ensure compliance.

By John Avellanet, Cerulean Associates, LLC

DATA INTEGRITY is critical to regulatory compliance, and the fundamental reason for 21 CFR Part 11. This article outlines and summarizes strategies and requirements.

First you must understand what FDA requires in terms of data integrity, and what the real-world costs are, whether you are taking proactive or reactive steps. FDA uses the acronym ALCOA to define its expectations of electronic data. The "l" originally stood for legible, which dates back to the time when FDA was dealing with scanned documents. I've updated it to "long lasting."

Attributable
Long-lasting (legible)
Contemporaneous
Original
Accurate

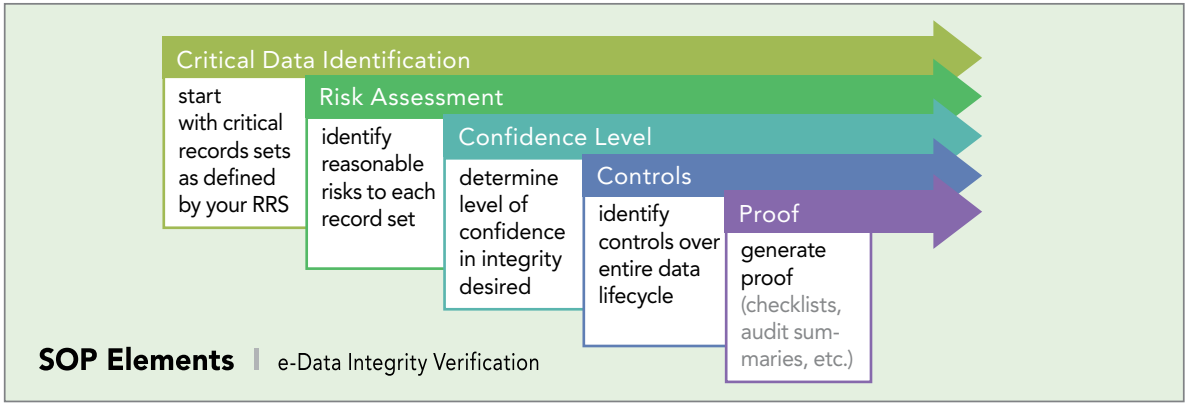
In addition, this is the definition of data integrity that FDA uses for internal training: "Data are of high quality if they are fit for their intended uses in operations, decision-making and planning . . . as data volume increases, the question of internal consistency within data becomes paramount…."

Following are the regulations that are critical to pharma and biopharma manufacturing.

- 21 CFR 11
- 21 CFR 58
- 21 CFR 201
- 21 CFR 202 & 203
- 21 CFR 210
- 21 CFR 211
- 21 CFR 600 (biologics only)
- 21 CFR 601 (biologics only)
- 21 CFR 610 (biologics only)
- 21 CFR 820 (combo devices only)
- 21 CFR 803 (combo devices only)
- 21 CFR 806 (combo devices only)
- Application Integrity Policy (AIP)

The Application Integrity Policy is what FDA pulls up when it has questions about a manufacturer's electronic data. Note that electronic information includes everything, such as emails, adverse events reports, complaints, batch records, quality control records—everything that's stored electronically.

When FDA invokes the AIP, the Agency is, in effect, saying, "We have concerns. We want to review everything this company has submitted, whether an additional application request, or request for a change in manufacturing." If FDA invokes this policy, you can expect an inspection. Not only will you have an inspection, but that inspection will focus closely on how you are controlling electronic records—i.e., it will focus on Part 11.

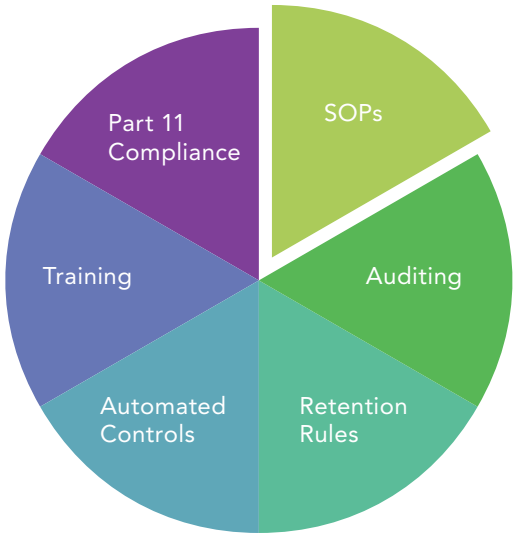


WHAT WARNING LETTERS TELL US

Some excerpts from FDA Warning Letters provide a better understanding of what the Agency is driving at with data integrity.

- "It was observed that the data stored on the computer can be deleted, removed, transferred, renamed or altered [without control]."
- "There is no audit trail or log of data changes that are made to the information in the database. Data cannot be verified against source records, since such records are not maintained."

In such cases, data can't be verified because the original source records (e.g., certificate of analysis) have been scanned in and then thrown away. As a result, I have no way of knowing whether or not this is the original. Anyone can go into Adobe and change the record. Thus, FDA says, you have no tracking or controls on this, so we cannot rely on it.



Components | Mix procedural and automated controls

Below are excerpts from some more recent Warning Letters, from last year. Note the focus on record accuracy:

- "Your firm failed to check the accuracy of the input to and output from the computer or related systems of formulas or other records or data and establish the degree and frequency of input/output verifications."
- "Your firm's laboratory analysts have the ability to access and delete raw chromatographic data . . . Due to this unrestrictive access, there is no assurance that laboratory records and raw data are accurate and valid."

In the last example, FDA says there is no assurance of accuracy or validity. . . . The Agency has to stand in for the public, and cannot trust the data.

What the Agency is driving with Part 11 is the need for data to be trustworthy. Here are some of the questions that FDA inspectors are trained to ask about data control. They are all framed in common sense:

- Are original data entered directly into an electronic record at the time of collection or are data transcribed from paper records into an electronic record?
- Are there edit checks and data logic checks for acceptable ranges of values?
- How are the data secured in case of disasters, e.g., power failure? Are there contingency plans and backup files?
- Are there controls in place to prevent, detect, and mitigate effects of computer viruses on data and software?
- Are there records of critical computerized systems maintenance?
- Are there written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data?
- Are there records describing the names of authorized personnel, their titles, and a description of their access privileges to the data?
- How are the data transmitted from the firm to/from its suppliers?

Remember that Part 11 was introduced quite a while ago, before FDA could envision computing's limits. Today, Apple's iPhone contains more computing power than all of the computers worldwide in 1990. Remember that regulators are not concerned with technology integrity, but rather record integrity.

SITTING IN STORAGE

One of the most important things to understand is that we need to take a lifecycle approach to data integrity. Remember that adverse events records will have to be stored for 10 years, and batch records for seven or eight years. The key is to focus on the record.

Documents and e-data spend more than 80% of their lifespan in an archived (e.g., stored) state, according to ARMA [Authority on Managing Records and Information].

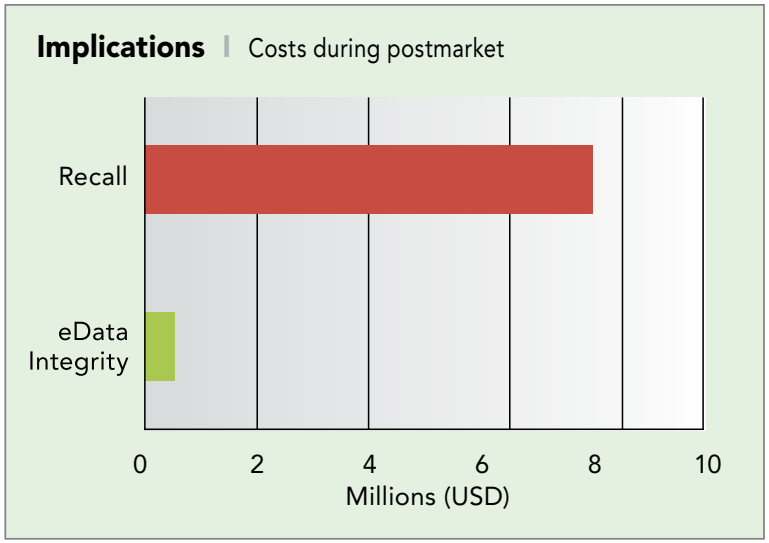
It's important to recognize that the records we've created and used are going to spend most of their lifetimes sitting in storage, with nobody looking at them. This is absolutely critical to understand, because if you don't build in controls to spot check those archived records, you may find that they're gone.

Carnegie Mellon studied data storage and found that, on average, two percent of data we store electronically literally vanishes—portions of hard drives are gone. Consider your CDs. After years pass, you'll see holes where data has evaporated . . . the key point to understand is that we have to build in controls.

You don't want to have to tell an FDA inspector that "you don't know" where the two percent of data went.

Following are some proactive and cross-functional best practices for ensuring data integrity.

- Form a cross-functional e-data working group
- Clearly define accountabilities vs. responsibilities
- Rely upon your records retention schedules
- Take advantage of and reuse IT controls
- Plan for at least one data migration during record lifecycle
- Incorporate e-data archive audits into internal quality audits



- Verify progress (and identify gaps) with a Part 11/Annex 11 mock FDA audit

Do not:

- Overlook the record lifecycle and focus on systems
- Rely on one-time validation of a system
- Assume e-data is "safe" in storage
- Turn it over to IT or to Validation or to Records Management
- Avoid tracking regulatory expectations in your regulatory intelligence program
- Forget that e-data is your proof of safety, efficacy, and compliance
- Lose sight of the costs–minimum 12:1 ROI

Remember that you need procedural controls. The following are the components of an effective data integrity SOP: Start with critical records sets, as defined by your RRS [record retention schedule]. Identify reasonable risks to each records set. Determine confidence level in integrity required. Set controls over the entire data lifecycle, then generate proof (checklists and audit summaries for instance).

Remember that the final SOP needs to fulfill FDA's ALCOA acronym.

Here are other SOPs companies ask about. All of these might be things to consider, depending on how you manage data, who is involved, and how many people are involved. Obviously, the requirements for a 10-person virtual company will differ from those for a 5,000-person operation.

Additional SOPs should cover:

- Virtual Data Storage Verification ("cloud computing")
- Secure Archived e-Data and Media Handling
- Data Maps–Creation and Maintenance
- Data Integrity/Controls Matrices–Creation and Maintenance
- Data Migration Protocols
- Data Transfers and Verification
- Maintaining Long-Term Confidentiality and/or Privacy
- Data Sampling and Archive Auditing
- Scanning of Paper Records for e-Data Archival
- Transfer and Retrieval of Long-Term e-Data Archives
- Secure Disposal of Clinical Patient & Adverse Event e-Data
- Qualification of Record and Data Storage Providers

FOCUS ON FAQs

Below are questions that I am often asked. Each of these is very particular and the responses will be very specific to the company and context involved, but they are important to think about:

- What if we don't have a records retention schedule?
- How much detail do we need in our data maps?
- Should we do a data-integrity/controls-matrix for each product or each system?
- Can we configure our network and computers for default data integrity?
- When can inspectors ask for system access?
- Do we have to keep all of our electronic raw data?
- How do we translate "data integrity" into budgets and projects?
- What are records that prove "safety and efficacy"?
- How do we document controls associated with records and personnel system usage?
- How best can we take advantage of IT, records and archival, quality management, and regulatory affairs?

It can be useful to take a very concrete "kick start" approach to ensure an effective Part 11 compliance approach within your organization.

1. Show sample enforcement actions that have cost and humiliated other firms.
2. Discuss how data integrity controls can limit risks and costs, with a focus on ROI.
3. Suggest next steps such as a management workshop to build momentum, talk to management and get a sponsor.

The Regulated Cloud

Rik Van Mol, Vice President Veeva Vault, Europe, Veeva Systems

MUCH OF a life sciences company's most precious intellectual property falls into the category of regulated content, i.e., content that must be created, approved, tracked, stored and updated in accordance with specific government regulations. For the past two decades, companies have managed their regulated content by maintaining elaborate content management systems within their firewalls. Today, however, given fundamental changes in the healthcare landscape and companies' business models, these solutions are obsolete, inefficient and, in many cases, ineffective. The best practice in managing regulated content is to deploy solutions in the regulated cloud — an environment that conforms to the strict technical and quality standards established by global health authorities. Manufacturers may at first be hesitant to send proprietary intellectual property and regulated content off to the cloud and to use software that a vendor manages across multiple tenants.

A DEMANDING INDUSTRY

Perhaps no industry is as heavily regulated as life sciences, since laws dictate not only how various clinical and operational processes are performed, but also how they are documented and even how that documentation is handled electronically. Regulated content includes clinical trial protocols, safety reports, health authority submissions, manufacturing processes, formulations and promotional materials. Non-compliance with regulations such as 21 CFR Part 11 and EU GMP Annex 11 that govern the creation, storage and use of such documents can cause safety issues and result in criminal liability as well as civil and regulatory authority penalties or fines.

For years, life sciences companies have managed their regulated content using software designed for general, industry-wide platforms that is then modified for specific uses. These general-purpose tools, especially once customized, are complex systems to deploy, master and maintain. Consequently, they are no longer suited to the industry's current environment and business requirements.

A CHANGING CLIMATE

As it relates to regulated content, the life sciences industry has changed significantly since content management software was first introduced:

Companies are no longer autonomous. While life sciences companies once performed nearly all of their business functions internally, they now rely on a mix of external partners from CROs to co-marketers. They need to be able to exchange content and collaborate with their external partners, while maintaining system security, regulatory compliance and the integrity of their information. Any shared content management system must maintain tight security and at the same time allow users to be added quickly, provide easy role-based access to content and be intuitive to use.

Companies operate globally. To remain competitive and to serve a global marketplace, life sciences companies are doing business with partners and affiliates

around the globe. Their technology platforms and software solutions must therefore be flexible and affordable enough to serve even the smallest, most remote partners and affiliates. All users need the same easy access, speed and performance from the software that central offices enjoy, and the consistency of content must be maintained across borders.

Regulatory demands are growing. Regulatory restrictions and the pace of regulatory change are intensifying. In general, regulatory bodies have placed more and wider restrictions on the storage, distribution and tracking of content, as well as the validation of storage systems. Thus, any system for managing regulated content must accommodate constantly changing regulations, and system changes must be readily validated as compliant.

The budget is constrained. Declining revenues have forced companies to reduce costs — including those associated with mission-critical systems. Companies, therefore, need a more cost-effective alternative to implementing and maintaining the complex and solutions of the past, the cost of which can run into millions of pounds per year.

ANTIQUATED SOLUTIONS

Traditional content management software solutions are ill-suited to these new working conditions and no longer deliver what companies need, particularly when it comes to collaboration. Companies that maintain their regulated content within their firewalls have three options for sharing it with partners:

1. They can grant partners access to their internal systems through virtual private networks (VPNs) or by issuing company laptops, with all of the logistical complications that entails. This process can easily take up to three months to complete.

2. They can implement a second level of technology to share content externally. This model quickly degrades into an environment with uncontrolled sharing, version confusion and an inability to maintain a single master file that reflects the authoritative version of the truth.

3. They can take the path of least resistance and simply e-mail documents to partners or use an electronic drop box. Inevitably, this leads to the same uncontrolled environment described above. Existing systems are painfully difficult and expensive to deploy, update, maintain and support. Often, the hassles and expense involved mean that affiliates do not get the same functionality as headquarters, that smaller companies must manage their regulated content manually, and that companies fall behind in their upgrades. Failing to upgrade the software regularly can impact user acceptance, as performance and functionality are stagnant in the face of changing needs. Making even simple changes (such as adding new fields or document types) involves many elaborate steps in system validation, installation and deployment, requiring considerable IT resources.

TECHNOLOGY TO THE RESCUE

Fortunately, all of these challenges can be met by adopting new technologies. The first advance that can be brought to bear on managing regulated content is a very simple, intuitive user interface. Consumers using software on the Web, such as Facebook, Amazon and Google, can use these tools instantly, with no training, because the navigation and functionality is obvious. This same type of easy, user-friendly experience is now available to business users working with their regulated content management systems. The second is cloud technology. Cloud computing is an architectural model through which a vendor provides software to multiple subscribers, or tenants, from a single, shared instance of the application which is maintained centrally.

Consumers using software on the Web, such as Facebook, Amazon and Google, can use these tools instantly, with no training, because the navigation and functionality is obvious.

Users can access the software with an Internet connection and need no special hardware. Customers maintain full custody of their content, which is separated from others' by impenetrable partitions. This turnkey arrangement delivers a number of benefits over single-tenant instances of software that apply directly to the challenges of managing regulated content today:

Speed and adaptability. Administrators can configure and update an application using simple point-and-click tools. Thus, a change that takes months to develop and deploy with a hosted/on-premise environment takes just a few minutes. New users, both internal and external, can be added just as easily.

System performance and quality. The provider offers technology that would not be feasible for any one customer and can maintain a continuous stream of innova-

tion. The provider handles all system upgrades centrally, so all users are always working on the latest release. Additionally, the system can continue to sustain peak performance, even as usage increases.

Cost savings. The solution is hosted by the vendor who can achieve economies of scale and spread costs across multiple companies, so subscribers need not invest in any equipment or data center space. Companies pay only for the capacity and storage that they use. This makes content management affordable to even the smallest organizations or business units.

Flexibility and scalability. The system's capacity is elastic, so the vendor can adjust capacity for any subscriber as business parameters change. It is important to make the distinction between true, multitenant software implementations and software programs that are simply hosted off premises by vendors. The latter are still single-tenant solutions, meaning that each customer has its own dedicated server running its own version of the application, which the vendor configures and maintains for the client. Each time there is a change, the application must be redeployed for each customer — an expensive process with no economies of scale. Plus, the arrangement is subject to annual maintenance and support fees. It is the multitenancy aspect of an application, not strictly the off-premise hosting, that delivers the benefits of the cloud.

THE REGULATED CLOUD

When cloud computing is used for managing regulated content, the solution must go beyond what is required of non-regulated business applications. Given the security issues and validation requirements involved, the regulated cloud must offer:

- An environment that is both validated and auditable. For other applications, users do not need to know exactly where their information is stored within the cloud. Regulated content, however, should be stored in a fixed location that can be visited, audited and validated to the company's satisfaction. All software releases must be validated by a trusted system validation service.
- Adherence to Standard Operating Procedures for quality software development and system maintenance.
- A world-class security infrastructure. Multiple layers of firewalls ensure high levels of protection against intrusion, and security measures identify and close vulnerabilities.
- Robust and flexible security at the content level. Security policies must be user-based, and advanced controls are needed to enable user authentication, log user activity and define user profiles by document stage.
- Business continuity and disaster recover measures that match, if not exceed, what companies would maintain on their own.
- Data segregation for content files, metadata, full-text search indexes and application configurations. The exact location of each should be clear. Ron Calderone, executive director of Information Services and Management at Unigene Laboratories, maintains, "A system in the cloud is as secure as its host." When security measures include nightly backups, inherent redundancy, regular external security audits and a tested business continuity plan, he advises, "... the cloud can be a highly secure computing environment."

Beyond these basic protections, the ideal software solution can support global collaboration, compliance with changing regulations and more cost effective operations. Users anywhere in the world can log into the secure environment using any device with an internet connection, a web browser, and a username and password, and then begin work with little or no training. Content is visible to all authorized team members (internally and externally) immediately, and documents stay in a controlled environment throughout the collaboration process. The logic behind document lifecycles, workflows, properties and actions is easily configured, yet strictly controlled. Updates are made within the underlying application by the vendor and are pre-validated before being released simultaneously to all subscribers.

New functionality is turned off by default and must be activated by the business administrators. By combining a user interface that is intuitive with a world-class infrastructure that is rigorously protected, cloud-based platforms offer companies the best of all worlds for managing their regulated content. Systems maintained in the regulated cloud are accessible to partners and affiliates globally, supporting collaboration between internal and external partners. Yet content remains in a secure, controlled, audited environment. The best solutions mimic the usability of popular, consumer software on the web — even while providing all the powerful features that users need for peak efficiency.

The multitenancy structure also means that upgrades are deployed automatically. Users are always on the most current release, business systems are validated and business practices remain current with legislation. The cloud platform also spreads costs across multiple clients and permitting companies to pay only for the capacity they need.

ABOUT THE AUTHOR

Rik Van Mol is Vice President Veeva Vault, Europe, Veeva Systems. Rik has over 15 years of business/IT consulting and regulated content management experience in life sciences.

21 CFR Part 11 Compliance Roadmap

ACCORDING TO some analysts, the cost of 21 CFR Part 11 compliance could vary from $5 million to $400 million, depending on a company's size and current state of systems. Companies with computer systems that are not compliant with 21 CFR Part 11 must prioritize which systems to upgrade first. They are now beginning to use a risk-based methodology to create a roadmap for compliance. This paper explains the 21 CFR part 11-system requirements, discusses a risk-based methodology to create a compliance roadmap and identifies popular first steps in the roadmap for most companies.

CGMP - THE BASIS FOR 21 CFR PART 11

Current Good Manufacturing Practices (cGMP) are mandated by the FDA to ensure that the products manufactured by the industries such as pharmaceutical, biotech and medical devices, meet specific requirements for identity, strength, quality, and purity. cGMP regulations are specified in 21 CFR Part 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General Part) and 21 CFR Part 211 (Current Good Manufacturing Practice for finished Pharmaceuticals).

In order to comply with cGMP, companies are required to record, track, manage, store and easily access various production documents and their detailed change history including:

- Standard Operating Procedures (SOP)
- Master Production Batch Record (MPBR) or Production Batch Record (PBR)
- Equipment Log Books

WHY 21 CFR PART 11?

Historically, all the quality documents including SOPs, MPBRs, PBRs and log books have been maintained on paper by companies in order to comply with FDA's cGMP. Even as companies automated their production and quality processes, they were still being forced to maintain and track paper records. The code of Federal Regulations (CFR) Part 11 was implemented in 1997 to let the FDA accept electronic records and signatures in place of paper records and handwritten signatures for compliance. The regulation outlines controls for ensuring that electronic records and signatures are trustworthy, reliable, and compatible with FDA procedures and as verifiable and traceable as their paper counterparts.

Hence, 21 CFR Part 11 also specifies a number of requirements for software systems to enable trustworthy and reliable electronic records and signatures. These software requirements must be met for the resulting electronic records to comply with FDA's cGMP. If an organization does employ electronic records and signatures, but fails to comply with these system requirements, the FDA will cite the firm for violating the underlying regulation. For example, if a drug company maintains its written complaint records, required by 21 CFR 211.198(b), in electronic form, but the agency finds for some reason that these records are unacceptable substitutes for paper records, then the FDA would charge the firm with violating 211.198(b) – "Master production records are generated from a computer as electronic records without any apparent controls to assure authenticity and integrity [21 CFR 211.186(a)]."

Click on link below to read more about software requirements and building a roadmap for compliance.

http://www.metricstream.com/insights/21CFR_Part11.htm

Into the Cloud: New Technology Blowing In Big Benefits to Regulated Content Management in Life Sciences

Jennifer Goldsmith, Vice President Vault, Veeva Systems

FOR MORE than two decades, life sciences organizations have purchased, configured and deployed a series of ever-expanding and complex content management systems. At first, these systems had to be heavily customized for the unique needs of life sciences companies. Over time, industry-specific applications that better support life sciences-specific processes have evolved.

These content management tools continue to tack on new capabilities, but they have failed to fundamentally change to meet the new business challenges facing the life sciences market: greater collaboration, fast-paced globalization, increasing compliance and stronger focus on cost reduction.

Despite these radical shifts in the business environment, life sciences content management systems have remained largely unchanged. They are built on the same basic platforms and technologies, and they are often only affordable to larger organizations with significant time and resources to invest in systems development projects and customization.

Consequently, many life sciences organizations have grown frustrated with the cost and complexity of implementing, maintaining and updating inadequate content management systems — a process that can often cost hundreds of thousands of dollars every year. Even worse, smaller

companies are left with few, if any, good options for the implementation of IT systems supporting their regulated content management processes.

The life sciences industry requires an entirely new solution, a content management technology that truly fits the new needs of all life sciences companies regardless of their size. One technology has emerged that may support this kind of change: cloud computing. (See sidebar.)

The Cloud: Open Collaboration, Secure Content

When cloud computing was first introduced to the mainstream, skeptics tried to find vulnerabilities in the security of cloud applications. However, these concerns were quickly dismissed as respected organizations — from Amazon to the U.S. Department of Defense —began adopting cloud computing for everything from the management of customer information to the management of sensitive government materials.

From a content management perspective, cloud content management solutions often include advanced access-control frameworks that enable secure authentication, provide advanced logging of user activity and allow administrators to control which users have access to highly sensitive documents. Multiple layers of firewalls also ensure high levels of protection against intrusion and identify and close security vulnerabilities.

Today, cloud applications are often considered even more secure than other systems because they enable access to world-class security infrastructures.

CLOUD COMPUTING FOR REGULATED CONTENT MANAGEMENT

Cloud computing may be the key to regulated content management in the life sciences industry. One of the biggest reasons is the fact that multitenant Software-as-a-Service (SaaS) applications built in the cloud enable the sharing of resources, resulting in massive economies of scale. It's this model that also provides many of the benefits hailed by pundits such as scalability, flexibility, fast implementation, low maintenance, simple integration, cost efficiency and easy configuration.

When it comes to content management specifically, the cloud enables life sciences companies to meet the needs of the current business climate to collaborate closely, connect globally, comply swiftly and manage costs effectively.

COLLABORATE CLOSELY

Over the last five years, the number of external partners (co-development partners, clinical research organizations, co-marketing partners, ad agencies and more) that life sciences companies employ has increased by as much as 50% or more. The use of these partners has reduced costs and increased speed to market. However, this new model has also created significant content management challenges, specifically surrounding collaboration.

While traditional on-premise content management systems often support working collaboratively within an organization, they are not designed for external collaboration. It takes too long, is too complicated and too expensive to give secure access to all external collaborators.

Rather than deal with these obstacles, companies tend to simply pull content out of their controlled repositories and distribute it via e-mail or secure FTP. These methods, however, are inherently risky because they skirt the compliance checks and audit trails maintained by the core content management system.

In contrast, cloud-based content management systems allow life sciences companies to truly collaborate rather than simply administrate. New users, both internal and external, can be added in minutes, not weeks or months. By enabling secure access to appropriate content in real time via the web, life sciences organizations can work closely with their partners and affiliates around the globe, as well as with various departments across the organization.

Administrators simply provide a secure log-in. Content is visible by all authorized team members immediately and without significant IT intervention. Additionally, the documents stay in acontrolled environment throughout the collaboration process, providing a more compliant system and reducing risk.

CONNECT GLOBALLY

Annual global spending on pharmaceuticals is expected to grow to nearly $1.2 trillion by 2016, according to a report from the IMS Institute for Healthcare Informatics.

In addition, the IMS reported that annual global spending growth will increase from $30 billion in 2012 to $70 billion in 2016. This is driven, overall, by volume growth in emerging pharmaceutical markets and higher spending by developed nations.

Given this explosive growth, both small and large life sciences companies will be challenged with managing their content globally. Affiliates around the world, including geographies where affiliate offices have only a few people, will need the same system access, speed and performance that central offices have typically enjoyed.

Because the cloud is ubiquitous, cloud content management systems provide — for the first time— a truly global view of how content is created and used. Systems in the cloud are accessible from wherever users have an internet connection. Additionally, cloud solutions are cost-effective enough to deploy to even the smallest local affiliates.

This enables content access to participants around the globe, thereby eliminating the common, less secure approach where central offices email or FTP documents out to local affiliates to make their changes and then back again.

This approach resulted in a lack of visibility (for example, local content changes were not accessible to the central offices and vice versa), a proliferation of uncontrolled content copies and a sense of version confusion as people were unsure which document version was the most current. In contrast, by providing equal and immediate access for all, cloud content management systems avoid these issues, resulting in greater transparency and better communication.

COMPLY SWIFTLY

From product development to manufacturing, from drug safety to marketing, the rate and scope of regulatory change and reinterpretation are increasing exponentially. Across the globe, regulatory authorities are fundamentally changing the way in which life sciences organizations conduct business.

Because much of a life sciences organization's information is contained in the form of content such as safety reports, promotional materials and health authority submissions, the increasing rate of regulatory change presents a special challenge for today's content management systems. These on-premise or hosted systems are difficult and costly to change.

Even simple changes, such as adding new fields, tracking document distribution and changing security structures require elaborate system validation, development, installation and deployment. This can require thousands of dollars and as long as four to six months to implement. That's too long for teams that need to focus on creating, assembling and delivering content, rather than implementing and validating system changes.

In contrast, cloud systems can reduce the time to deploy and validate such changes by more than 50%. This is because cloud content management systems automatically receive updates as part of the underlying application structure, are easily tailored to meet changing regulatory requirements through simple configuration, and significantly reduce the time and effort of validation by sharing that burden across organizations. The result is less time spent on IT systems and more time spent on core business functions.

MANAGE COSTS EFFECTIVELY

Technology is notoriously expensive, and life sciences content management systems are no exception. But with an increasingly challenging global economic environment, greater competition, expiring patents and a shift from the blockbuster drug models of yesterday, companies must find ways of maximizing technology effectiveness while reducing overall costs.

Cloud computing makes content management affordable to even the smallest organizations or business units by reducing both up-front costs, as well as costs associated with ongoing system updates and maintenance. As a result, companies typically save anywhere from 30% to 50% over on-premise or hosted systems.

How? By completely avoiding the capital costs of servers, software and maintenance and, instead, adopting a highly predictable pay-as-you-go-model. Additionally, costly administrative tasks common with on-premise systems (upgrades and back-ups, for example) are eliminated with cloud technology since there is no hardware or software to manage on site. All upgrades and back-ups are handled by the solution provider.

FUNDAMENTAL CHANGE IN CONTENT MANAGEMENT

Collaborate closely. Connect globally. Comply swiftly. Manage costs effectively. These simple requirements are having a profound effect on how life sciences organizations need to manage their content today and in the future. It is no longer enough to patch, update and upgrade existing, on-premise systems.

Fundamental business change requires fundamental technology change. New cloud applications provide that leap forward – and, according to analysts, are the fastest growing technology. For the first time, companies of all sizes can meet the challenges of today and tomorrow, without the complexity, cost and uncertainty of traditional, enterprise on-premise or hosted content management implementations.

One Step Back, Two Steps Forward to Improved Quality Processes

By Jennifer Goldsmith

FDA HAS been encouraging drug manufacturers to tackle their batch-to-batch quality requirements for years, but is now getting serious about it. Historically reactive in its enforcement actions, FDA is now looking to proactively improve quality in the life-sciences industry. For example, rather than just punish companies for quality missteps, FDA is making plans to incentivize high-quality manufacturing in hopes that this will ensure better overall drug quality and a reduction in drug shortages. While FDA is still unclear on how this can be done, it knows which sort of initiatives it wants to reward."[We are] looking at ways the FDA, using our existing authorities, can recognize manufacturers that do a particularly valuable job," said FDA deputy director of regulatory programs Dr. Douglas Throckmorton.

One major step has already been taken. The Center for Drug Evaluation and Research has created a new Office of Pharmaceutical Quality that will support these efforts by collecting performance metrics and conducting trend analysis. Ostensibly, the office will focus on metrics such as manufacturing defects, cycle times, and overall batch quality. This makes sense except that these are all lagging indicators that measure the outcomes of what has

already happened. Leading indicators, by contrast, provide information that may directly aid in predicting future outcomes so companies can potentially prevent errors or identify bottlenecks before the damage is done. While they can be more difficult to capture, leading indicators can be spotted early on—before molecules are processed, capsules are formed, and batch reports are run. Months before the quality management system starts processing data, life-sciences companies can get a sneak-peak into potential quality problems by looking at the leading indicators hiding in the document management process further upstream. In other words, by taking one step back, organizations can jump two important steps forward.

DOCUMENT LIFECYCLE METRICS

Today, especially with the high volume of quality assurance (QA) related documents (standard operating procedures [SOPs], training manuals, etc.), life sciences companies can uncover trouble spots and bottlenecks just by looking at their documents from the authoring process to related training impact. Document lifecycle metrics (e.g., how much time it takes to review a change in training SOPs) can pinpoint various key leading indicators of quality discrepancies and compliance risk.

If there is a spike in the number of corrective actions and preventive actions (CAPAs) submitted in a particular month (say a 25% increase compared to the typical run rate), for example, a company could expect an increase in the number of days to update affected SOPs or work instructions. Changes to these documents require a change-control process, and delays prolong completion of the documentation updates. This delay postpones checking the effectiveness of the resolution to the original problem and closure of CAPAs. An organization that has an internal goal to speed closure of change controls and CAPAs could find their metric has trended adversely. If the company, however, had been monitoring the status of documents in process and rebalanced document control resources to accommodate the influx of documentation updates, it might have been possible to avoid a performance decline, thereby closing change controls and CAPAs more quickly.

Looking proactively at the document lifecycle can reveal many leading quality-indicating metrics, such as how long it takes for a document to be routed from draft to review to approval and distribution to staff; or the amount of time it takes to train staff on a new or changed SOP. If a document gets snagged somewhere along the way, it could cause a production delay downstream, and if this is a common bottleneck, it could suggest a much bigger problem. If an organization must amend an equipment calibration SOP to meet new standards, but approval is stalled, staff training is likewise postponed, which directly impacts manufacturing. Such delays could even shut down drug production. But, if a company sees this bottleneck in the document management system, it can immediately take corrective action. Further, if the QA manager determines that a calibration SOP needs revision to improve manufacturing, but knows that SOPs traditionally 'get stuck' for two weeks longer, he can monitor the process and work to remedy the problem in advance, or otherwise expedite the review. Long term, the company can address the root cause to improve overall processes.

CLOUD-BASED MANAGEMENT SYSTEM

Horizon Pharma, a specialty pharmaceutical company that has developed and is commercializing products to primary care, orthopedic surgeons, and rheumatologists, adopted a cloud-based electronic quality document management system enterprise-wide in late 2012. Horizon had been using paper-based processes but needed a new, more efficient solution that was also scalable and accessible globally, to support its rapid expansion. Since implementing its cloud system, the company has leveraged it to identify areas that need process improvements, by tracking and monitoring product deviations. "We route all quality data and documents through our document management system for review and approval and then house all of this content in the same system, so everyone has visibility and access. With everything in one place, we can spot key performance indicators and improve the overall manufacturing process," said Cara Weyker, Horizon's vice-president of CMC Regulatory and Quality.

Weyker continued, "For annual product reviews, as an example, we look at how many investigations we've had, the types of investigations, and any recurring deviations by category and location. Running a simple report gives us immediate insight

into a potential glitch, and we can remedy the situation before it turns into a real problem. Fortunately, we haven't had any major quality problems since implementing the new system."

With an electronic quality document management system, the manager can easily run a quick risk assessment on documents in process, monitoring various metrics across the enterprise. Similar assessments can trigger a red flag so QA managers can help ensure effective documents are produced rapidly, and people are trained thoroughly and quickly, both leading to an efficient production line for a quality output. Configuring the system to automatically generate 'read-and-understood' reports broken down by user, department, and facility assessments gives a quick, visual demonstration that proper training has been completed to meet compliance audits, and provides valuable metrics by role and by function. In addition to driving more comprehensive compliance reporting, this creates transparency for all parties across all levels, empowering staff with performance data they need to identify areas that still need improvement.

By focusing on document lifecycle states and identifying bottlenecks or process anomalies found at different stages in the lifecycle, companies can also cross reference against other documents and processes to determine reasonable internal benchmarks for use across the enterprise. If one particular manufacturing plant is noted for having the lowest risk of non-compliance, for instance, and their standard for reviewing critical SOPs is four days, then 'four days' can become your organization's benchmark. When using a cloud-based electronic quality document system, specifically, the scope of these quality performance reports is compounded, because the application is easily accessible worldwide. At this level, drug manufacturers can compare SOP performance between different locations around the globe and gain meaningful insight.

Additionally, because the cloud is so ubiquitous, cloud-based systems enable life-sciences companies to establish universal quality and measurement standards, even when it comes to taxonomy, for continuity across the organization. Process data can, therefore, be compared side by side. If two or three other locations take six days to accomplish the same quality assurance review, the centralized quality group can examine the circumstances more closely and potentially solve a problem, or open up a roadblock. "Since implementing a cloud-based quality document management system at Horizon, we've been able to harmonize across the organization globally," added Weyker. "What used to be a manual process is now handled in a single, centralized system so that processes and document templates can be standardized. This reduces the risk of making errors or duplicating efforts and helps to ensure that the right people are reviewing the right documents at the right time."

GenomeDx, a genomic information company based in Vancouver and San Diego, recently migrated to a cloud-based electronic document solution to help improve manufacturing efficiency and quality. "Our document management system makes it easy for us to understand where a document is in its lifecycle, who's touched it, who has yet to do something about it, and where the bottleneck resides. It does so in a way that is intuitive and easy to follow," said Andy Katz, PhD, chief operating officer of GenomeDx.

Cloud-based electronic document management systems are also designed with a modern framework and consumer-like user interfaces (think Amazon) rather than legacy architectures that are notoriously clunky and difficult to use. An easy-to-use system encourages higher adoption and, therefore, captures more data, resulting in in improved accuracy and increasingly reliable leading indicators. It also aligns with the business world's move away from the desktop for greater flexibility and mobility—managers can review and approve documents from wherever they are, whenever they want, from any device, to improve efficiency. And, external partners such as contract manufacturers and subject matter experts who write SOPs can access and work with documents conveniently in a centralized repository, further fostering system use and greater data capture. With more data, companies gain visibility into leading indicators to thwart problems before they cause non-compliance or worse.

"We run reports on a wide range of document lifecycle metrics across the enterprise and are now able to anticipate potential bottlenecks or compliance risk well in advance," concluded Horizon's Weyker.

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CLICK HERE **White Paper -** Into the Cloud: New Technology Set to Deliver Heavenly Benefits

CLICK HERE **Collaboration Conundrum:** How to Share Content in Today's Global Life Sciences Industry

Moving the Life Sciences Industry to the Cloud

Veeva provides a suite of cloud-based applications built specifically for life sciences, making compliance with requirements such as 21 CFR Part 11 easier and facilitating better inspections. Designed to meet the needs of a highly regulated, global industry, Veeva's solutions improve the following key areas:

- **Gain Greater Visibility –** Information is gathered to support detailed audit trails and empower companies to make proactive, informed decisions with accessible data and insightful reports.
- **Build a Foundation for Information Sharing –** Cloud-based applications provide secure, easy access for internal users, partners, and other systems, facilitating collaboration for end-to-end quality processes.
- **Streamline Compliance –** Developed to address both current and emerging regulations, Veeva's solutions also include critical compliance features such as document control, workflows, electronic signatures, and more.
- **Create Efficient Processes –** Designed to align with life sciences business processes, these applications simplify workflows and make them more efficient.
- **Accelerate Validation –** Veeva's solutions are created with the rigorous validation process in mind, and provide tools to accelerate and simplify validation. These applications also undergo IQ and OQ validation to reduce the validation effort needed from life sciences companies.
- **Simplify Data Protection and Archiving –** Robust cloud infrastructures ensure applications are always available, data is only accessible to authorized individuals, and content complies with specific retention policies.

VEEVA GLOBAL HEADQUARTERS
4637 Chabot Drive, Suite 210
Pleasanton, CA 94588
Phone: (925)452-6500
Fax: (925)452-6504