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From data integrity regulations to Pharma 4.0

A vendor's perspective on recent trends in regulations and the potential future direction for the industry

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Introduction

The drug making process has increased in complexity over the last two decades, driven from globalization, cost saving demands and a specialization of suppliers in only one or a few subparts of the process. The separation of key process steps such as Active Pharmaceutical Ingredient (API) creation, clinical trials or outsourced manufacturing into different locations—often even different companies—and distribution of these steps around the globe has been a driving force to mandate better traceability of data and an overall improved quality for the drug making process. The first step that regulatory agencies implemented in reply to the increasing challenges was to establish data integrity guidelines and enforce them during inspections around the world.[1-4] Adherence to these guidelines helps provide higher transparency and traceability across the distributed nature of the drug production lifecycle.

But it does not end with data integrity—that is just a first (notably significant) step as part of a broader quality initiative, that thought-leaders from the regulatory agencies are demanding, which may end up in a transformation of the pharmaceutical industry. This is being referred to as "Pharma 4.0".

In this white paper we are outlining a scientific instrument vendor's perspective on the impact of the changes that one of their largest customer industries will undergo and what influence this will have on the evolution of software required to operate analytical instrumentation and the underlying handling of data.

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Increasing (quality) challenges in drug manufacturing

The pharmaceutical industry has been significantly shaken by reinvigorated regulatory guidance, drug shortages and the ongoing transition to more biological entities as active drug components.

- The enforcement of data integrity regulations has created an increasing overhead of validation and on-going, regular and periodic data review processes that must be executed to maintain guideline adherence
- Challenges in the delivery and supply chain, specifically in ensuring the availability of enough APIs for drug manufacturing, have resulted in drug shortages for both over the counter (OTC) and more advanced drugs
- The emergence of drugs based on biological entities continues to grow. In 2019, the U.S. FDA approved a total of 70 therapeutics. 48 new medicines and therapeutic biologics through The Center for Drug Evaluation and Research (CDER) and 22 new biological agents through The Center for Biologics Evaluation and Research (CBER). In total 46% of the approved therapeutics were of biological origin; including recombinant proteins, vaccines, cell, and gene therapies. This shift comes with an associated increase in the complexity of making the drug and keeping the process under control. Many of the medicines the industry now makes are becoming specialist therapies that require different, and often more complex, manufacturing and distribution techniques from those used to produce conventional small molecules.

These challenges may initially look somewhat disconnected, but they all have a common theme: The demand for an improved quality of the drug making process. The data integrity regulations released from the United States Food and Drug Administration (U.S. FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) in the last three years are a step towards transparency of the underlying data across the entire drug making process. The U.S. FDA clearly explains this as the primary goal of the data integrity guidance released in 2018 and the former U.S. FDA Commissioner Dr. Gottlieb highlighted this. He stated that quality was the major focus for regulators and failure to ensure data integrity by pharmaceutical manufacturers was contributing to poor quality products. Improved quality in the end-to-end process will help to increase consistency and reduce variations in the drug making process resulting in fewer out-of-specification investigations, an increased operational efficiency and higher reliability in the quality of drugs.

U.S. FDA Commissioner Dr. Gottlieb M.D.

"[…]Our policies and guidance must also evolve to ensure that quality standards are maintained, and to assist companies in building a culture of quality. To that end, one area we've focused new attention on in recent years is data integrity. Our goal is to ensure that the data associated with drug manufacturing are complete, consistent, and accurate, and therefore reliable. […]"[5]

Efforts to cope with increasing quality issues in drug production: From batch production to ongoing manufacturing

Challenges in drug production

The traditional way of producing drugs is batch processing followed by final lot release testing that ensures adequate quality of the final product. Most drug makers are still reliant upon batch processing, in which a pharmaceutical product is made through a stepwise process. The batch production process is supposed to create a steady output, but it is slow because it is a serial process—each step must be completed before the next one can start. Another challenge with the batch production process is an increased risk to the quality of the drug. Due to the serial nature of batch production, the process is subject to quality issues arising from degradation of substances or contamination and general human error. Every transition between steps presents a potential source for quality issues impacting the final drug, and the more time that elapses between the steps, the higher the risk.

Batch production versus continuous manufacturing

There are increasing challenges with the batch production approach and some industry thought-leaders are exploring a continuous production process as an alternative.

In contrast to batch processing, continuous manufacturing sends raw materials through an uninterrupted, nonstop process until the final product is completed. This approach is a faster manufacturing method; the U.S. FDA estimates that some drugs which normally take a month to produce using conventional batch processing, may only take one day to make using a continuous manufacturing setup.

Continuous manufacturing—which is the standard method in several other sectors, including the automotive, food and electronics industries—is still in a ramp up phase for pharmaceutical drug production. This is partially because of its high startup costs, but also because it requires a deep understanding of the entire production process and demands for more online monitoring capabilities with a

corrective action plan to immediately react to process variations. There are, however, several driving forces that will support the adoption of continuous manufacturing to produce pharmaceutical drugs.

The biggest supporting factor is the demand for higher overall quality. Continuous manufacturing, with its inherent deeper, holistic process understanding, is seen as the means to reduce variations in product quality by introducing a Quality by Design (QbD) concept into the product's lifecycle. Also, along with it being a faster, more efficient way to manufacture pharmaceuticals, continuous processing could also be safer compared to batch methods. By eliminating steps involving human intervention, the risk of error could be substantially decreased and, as many of the issues with contamination occur during the manufacturing process, it is important that drug makers implement the best possible production process to limit the risk of recalls and protect consumer safety.

One of the adoption barriers here is the higher complexity of the drug making process for new biological entities (NBE). The process is more involved and requires a higher degree of process monitoring and, unlike the conventional chemical synthesis route, biologics require the protein-producing 'machinery' only found in living cells. However, biopharmaceutical industry thought-leaders have already started to take on the challenge to find procedures to establish continuous manufacturing for biological entity-based drugs. A new International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) workgroup (Q13) began work on guidance for continuous manufacturing in 2018. Key enabling technologies for better understanding and controlling biopharmaceutical production are Process Analytical Technology (PAT) and the Multi-Attribute Method (MAM).

Overall, the evolution of pharmaceutical production will provide several new challenges that the industry and suppliers will have to address:

- It may require evolution of the currently established "tried and tested" QC Batch release approach, to become much more adaptable to a variety of therapy delivery approaches
- High quantities of products must be produced in a short amount of time with a very narrow tolerance for error
- An increase in the creation of analytical and scientific data will be driven from a shift to information rich instrumentation, such as mass spectrometry (MS), and an increasing number of measurements throughout the lifecycle of a drug. This increase in volume and complexity of data needs to be managed effectively so that the underlying processes are transparent and traceable.

In this white paper we will focus on the last item from this list and outline supplier-driven (software) activities to assist in dealing with and analyzing the increasing data volume. We will use data integrity and the inherent need for meaningful review of audit trails as an example of how a supplier can assist adoption of new demands and trends in industry by evolving their product(s) in line with the industry drivers. Finally, we will provide an outlook on a potential long-term transition of the industry to Pharma 4.0. Pharma 4.0 is characterized through the (system-guided) analysis of the ever-increasing amount of data created during drug production together with the highest possible degree of process automation. As such, it is expected to specifically reduce the number of human interventions, reducing errors and enabling more insightful analysis of data, specifically over a longer period of time. In a very simplistic way, the answers to the demands for increased quality in drug production could be described as (system-guided) data visualization and automation accompanied by a widespread willingness to do things differently and embrace such technological advances.

Supplier strategic efforts to assist in quality improvements

Data integrity as an enforcement tool to improve drug quality

The increased focus from regulatory agencies on overall drug quality presents an evolution of past, mainly process-adherence driven, GMP/GLP (Good Manufacturing Practices/Good Laboratory Practices) guideline implementation. With the release of the 21 CFR Part 11 regulations on electronic records in 1997, the focus on data created during drug development and manufacturing had already increased. Chromatography Data Systems (CDS) have become a focal point of interest and investigation, in relation to drug production and their ability to control analytical systems. The initial focus was mostly looking at processes and questioning are there documented processes for validating computerized systems and are they followed? Are security measures and processes in place to ensure completeness of data over the data

retention period? In the late 1990's many application software packages did not have logon protection, which gave rise to basic questions relating to access, security and traceability. Consequently, hot topics for CDS inspections involved version-controlled storage, technical and physical data security (central storage in a secure server location) and the nature of any associated audit trails.

From 21 CFR Part 11 to data integrity

Computer-generated audit trails were one element to ensure adherence of computerized systems to GLP and GMP guidelines, but they were not the only one. In fact, the initial emphasis to generate reliable and trustworthy electronic records was more focused on ensuring completeness and security of the electronic records than on the content and quality of the audit trails.

One hard learning from the first 15 years following the release of 21 CFR Part 11 was that enforcing process adherence for computerized system validation does not automatically deliver better product quality. Evidence is provided through the shortage of standard drugs in the last ten years and the increasing level of regulatory findings during inspections as shown in Figure 1. VAI stands for "Voluntary Action Indicated". It means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action because the objectionable conditions do not meet the threshold for action at this time. OAI stands for "Official Action Indicated" which means regulatory and/or administrative actions will be recommended.

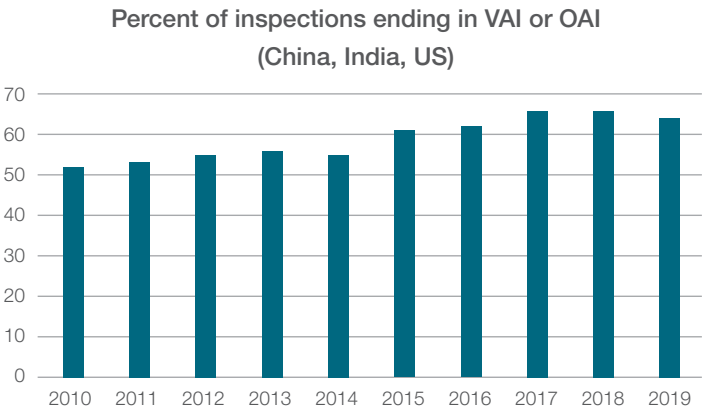

Figure 1. Number of inspection findings in large pharmaceutical industry countries.

The data integrity guidelines were launched in order to establish a more holistic approach for traceable data handling in the drug production process. Their intent is ensuring that data is controlled, secured and under complete traceability—thereby proving integrity—over its entire lifecycle. As Janet Woodcock phrased it, "the U.S. FDA wants drug manufacturers to move beyond simple process adherence to achieve compliance and focus much more on improving overall quality".

This was confirmed in the U.S. FDA Press Release distributed with the launch of their data integrity guidance in 2018 with a quote from U.S. FDA Commissioner Dr. Gottlieb[6]: "[…] One critical way to help ensure product quality is to prevent data integrity lapses in the first place. That's why we've worked to provide industry with clear guidance, so manufacturers have the tools and systems in place to prevent adulterated products from entering the U.S. marketplace [...]"

'Evident' challenges with demonstrating data integrity

The most impactful challenge to arise from latest data integrity guidance relates to audit trail review. Audit trails act as the body of evidence to distinguish altered or invalid electronic records and are considered part of the history of their associated data. Data integrity focused inspections by regulators have brought to the forefront that not all data are being considered in lot or batch release decisions. In the worst cases, the information that was not considered was either falsified or failed specifications. The latest guidance has made it clear that audit trails, along with the electronic data they support, must be reviewed as part of the data verification process.

Best described by the ISPE GAMP® RDI Good Practice Guide; Data Integrity—Key Concepts, an audit trail review is not simply a confirmatory check which, for instance, verifies that the audit trail record is capturing and collecting entries consisting of what and when, and why where necessary. It is also about making an assessment of the records within the context of the business process, which in turn relies upon having a solid understanding of that process and the systems and procedures supporting it.

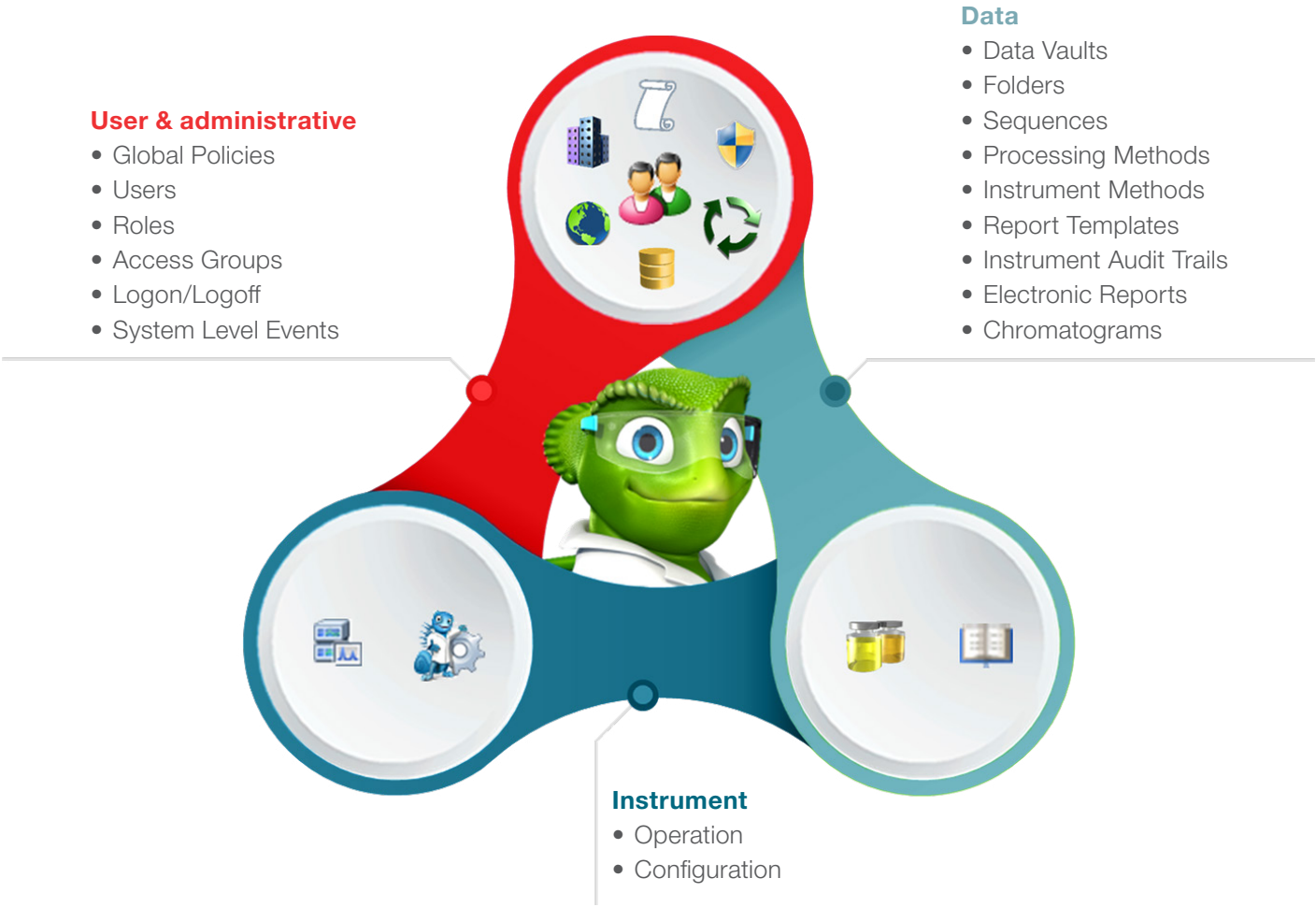

Figure 2. Overview of Chromeleon CDS Audit Trails.

To assist with this understanding, Thermo Scientific™ Chromeleon™ CDS's extensive audit trails (Figure 2) are categorized by the main components of a chromatographic data system including instruments, data and users and administration. They are then segregated further, according to their relevance, which gives them a clear context to the element they represent, for example instrument configuration or data objects, etc.

This approach in combination with Chromeleon software's audit trail ability to interact and search the audit trail information (Figure 3) allows for easy retrospective focused analysis of the audit trail itself. The audit trail functionality provides filtering using "find as you type" text entry or grouping via simple drag and drop operations. A time period filter can also be defined, different versions of objects can be compared where applicable, a free text entry can be searched for, the audit trail information can be sorted by one or multiple columns, and the information can be reported maintaining any filters, groupings, sorting, etc. that may have been applied.

As an illustration, a reviewer can easily conduct a review of all data audit trail events and records to establish when Chromeleon CDS sequences were started by grouping by 'Type', and then using the "find as you type" text filter to only include entries that have a "Started Run" 'Operation'. The reviewer can then go on and amend the 'Operation' filter to show any sequences in which there was an "Aborted Run". Further investigation of these two searches may then reveal that one or more analysts have been repeatedly restarting and then aborting an analytical run. Depending upon your operating procedures these actions may signify a risk to data integrity. The next stage in the review process could be to establish if there were any faults with the instrument by reviewing the audit trail records for the instrument involved over the period the analytical run was started and aborted, and in so doing, also determine via the audit trail records if it was in a qualified state.

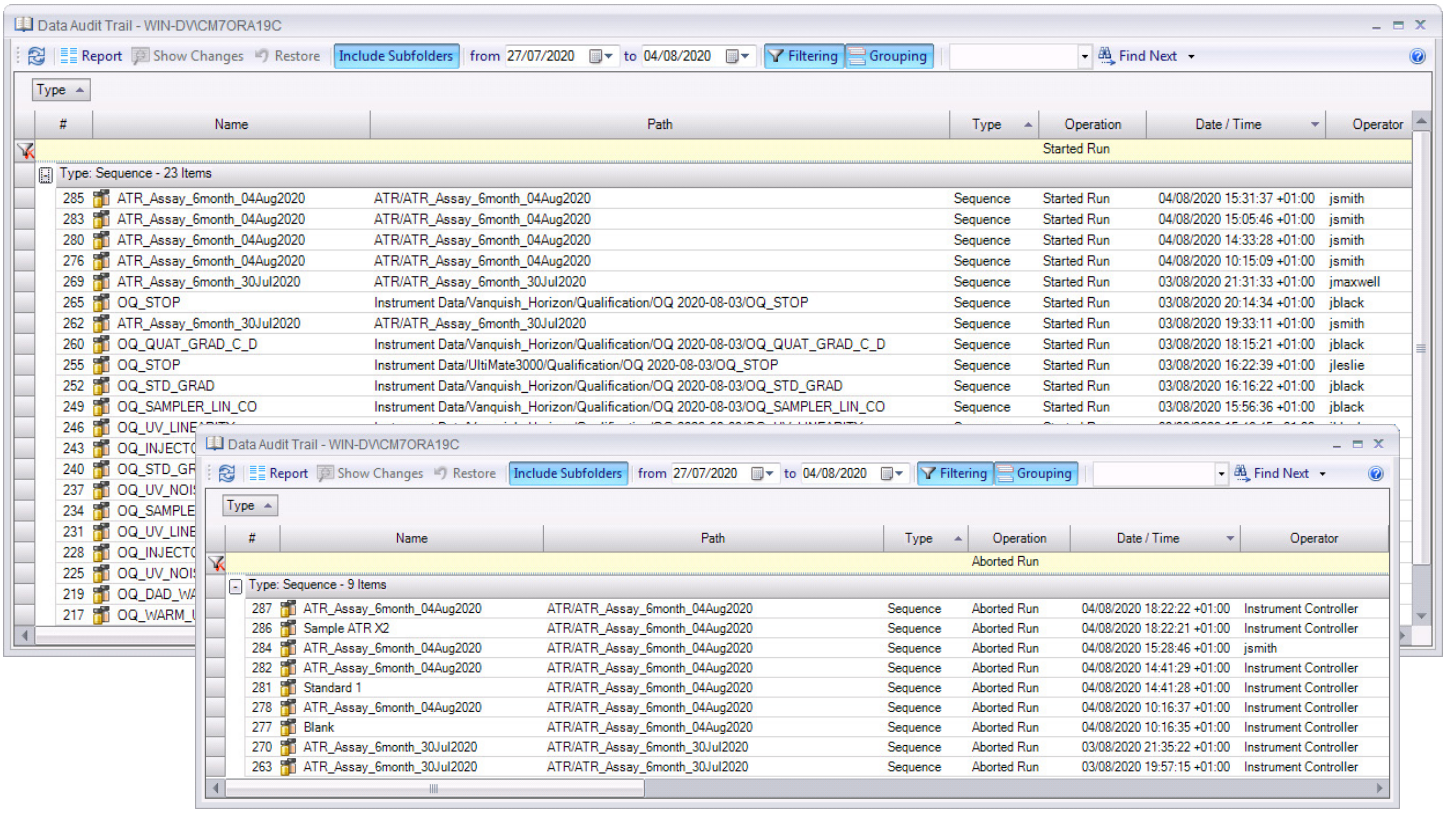

Figure 3. Ability for filtering and grouping of audit trail entries to establish sequence of user events.

In the previous paragraph and as illustrated by Figure 3, the point that is reflected in the ISPE GAMP guides-specific operations and events logged in the audit trail do not always lead to the identification of data integrity violations. While operations and actions such as data alteration and deletion are clearly identifiable and understandable, other potential data integrity infringements rely on the reviewer's ability to recognize patterns and to connect several apparently innocuous entries over a period, which when mapped against the business procedures, are in fact collectively a non-conformity. So next we will outline how these challenges can be alleviated with an innovation in the latest version of Chromeleon CDS.

For more information about adhering to data integrity audit trail guidelines, with Chromeleon CDS, please refer to the following white papers: Data Integrity: Technical Controls that Demonstrate Trust and Data Integrity: Audit Trails with Ease of Review.

Disentangling innovation for data integrity—the Chromeleon Audit Trail Review Framework

Audit trail review is inherently challenging with chromatography data systems. They are first and foremost a scientific tool that manages a versatile technique which comes in many variants. And although there is a reasonably well-developed framework in which the different chromatographic techniques operate, there are many other supplementary processes either created in support of, or built, around the CDS. The axiom of CDS is that they are not designed to collect and manage data about business processes. With many advocating an exception reporting process driven by the system, for audit trail review it becomes a difficult balance between recognizing what are scientifically justifiable actions and events that may or may not be exceptions to expected behavior.

This was highlighted when exploring common user challenges to providing a meaningful and comprehensive audit trail review within a CDS. It was expressed by many that the information in audit trail entries was not easily identifiable, and by their very nature they contained vast amounts of data that needed to be understood before a focused review could be conducted. Audit trails are also not conducive to "ask indirect questions" about the information contained within. The overall consequence is that proper audit trail reviews are time consuming and could result in increased data integrity failures if the review fails to fulfill the regulatory guidelines and requirements.

Analyzing these challenges and mapping them against Chromeleon software's architecture and logical structure led to the development of our Data Integrity Review Framework which was introduced to the market in March 2020 with the Chromeleon 7.3 CDS release.

The Data Integrity Review Framework makes use of Chromeleon CDS's sequence-oriented application hierarchy and adds new functionality for more efficient and faster audit trail reviews within the software. Key elements of the Data Integrity Review Framework thus far are as follows:

Ability to query audit trails

With pre-populated query fields that list the audit trail entry terms, questions can be formulated and asked of the audit trail, eliminating many of the steps and reasoning for each step that were required before. Reverting to the scenario in the previous section, using the query tool it is possible to determine Sequence "Started Run" and "Aborted Run" operations as one, making the review much simpler and the search more understandable. With Chromeleon software's ease-of-use grouping and filtering, it also prevents the possibility of incorrect cross-referencing between two searches where the same entity is involved in both operations (Figure 4).

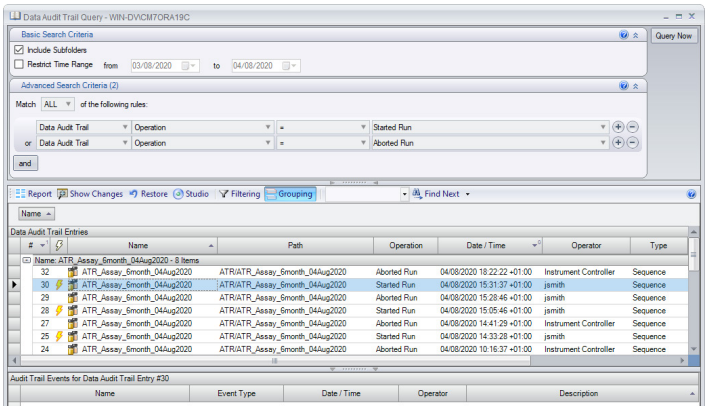

Figure 4. Chromeleon Audit Trail Query Builder interface.

Audit Trail Events

Audit trails have a 'digital shadow' which, although not pertinent to the entry itself, can provide information about connections between events or other objects or entities that may have or have had an association with an event. It can even be used to give greater emphasis to events. This means that additional information can be elicited, such as in our example illustration ("Started Run"/"Aborted Run"). Chromeleon software can now automatically identify when sequences are restarted and provide a record in the audit trail. In so doing it can also generate a real-time notification as and when these events occur. These are called Audit Trail Events (Figure 5). Other events, such as changes to linked objects of a Sequence including Report Templates or Spectral Libraries, give greater visibility to a reviewer and alerts them to actions and operations that are not initially visible to them from the current data set or object they are reviewing, but which could have had an impact on the result or outcome. Audit Trail Events simplify focused reviews giving greater reassurance through increased visibility and transparency, that a more complete and considered review has taken place. Audit Trail Events, like all audit trail records, can be queried, searched and reported using Chromeleon software's audit trail and reporting functionality.

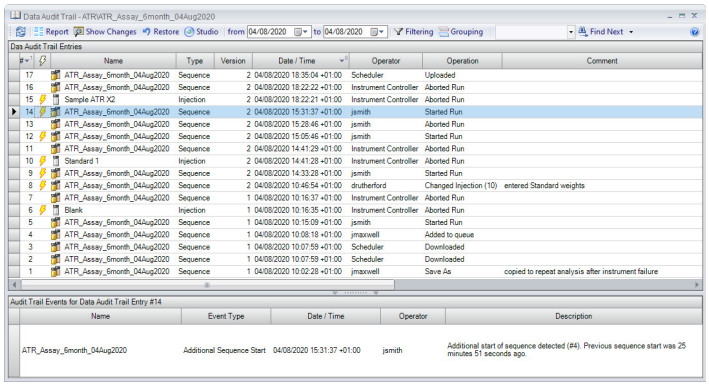

Figure 5. Display of new Chromeleon Audit Trail Events with detailed change information and flag.

Procedural policies

Ordinarily, policies within a CDS are introduced to prevent or restrict a user's access or ability to operate and execute actions within the system. The introduction of Audit Trail Events brought an enhancement to Chromeleon software's policies that in effect introduces a degree of cognizance of business operations and procedural requirements. With 'Copy and Apply' accession of procedural policies, a record of the business procedural control in place at a certain point in time is maintained with the record, while allowing all future records to be adapted to any business process improvements or revisions.

Improved quality using the Chromeleon CDS Data Integrity Review Framework

Regulatory agency and industry analyst findings indicate that most violations of data integrity guidelines are the result of inadequate processes and systems that fail to ensure reliable, accurate and complete data. Their response has been purposeful through actions that portend to drive deeper process understanding and "maturity" about the data the pharmaceutical operations generate. As suppliers to the pharmaceutical industry we have felt the reverberations of this drive and witnessed an upsurge in requests that en masse have the following common themes: Automation of steps that currently rely on operator's following written instruction, system led notifications that advise in a rational manner with full traceability, and greater preventative measures that can rule out human intervention.

The new Chromeleon Data Integrity Review Framework is a great example of supplier contribution to the demand for better traceability and thereby the integrity of data and analytical records. Providing means to easily explore the history of an electronic record throughout its entire lifecycle helps to identify and explain deviations from the expected outcome much more easily and more comprehensively than a combination of multiple manual steps.

When looking at the new Data Integrity Review Framework from the angle of the more system-driven, automated detection of quality issues, it becomes an enabling element. Audit trail review is a multifaceted and laborious task, requiring an experienced user to connect the isolated individual pieces of information to identify and assess the impact of potential data integrity violations. Consolidating information and automatically flagging high risk activities allows for a much higher degree of automation of the review. In the future, the software could automatically analyze audit trail content and propose an initial "no issues" or "needs review" assessment.

Automation is seen as a key enabler for an industry transition towards digitization of processes and to systems providing a more holistic quality approach driven from data insights and end-to-end process understanding. A higher degree of automation of routine processes—including but not limited to the audit trail reviews—will trigger a deeper understanding of drug development and drug production processes based on data. Better detectability of process deviations will enable better analysis of the root causes of such deviations and this root cause analysis will drive better understanding of the overall process and enable optimization. These better processes for method development and production process control will result in overall better drug quality. Eventually better process understanding will allow scientists to establish a more effective, more comprehensive pharmaceutical quality system.[6]

An industry in transition: Pharma 4.0 approach for an overall improvement in quality

Quality failings were one of the core findings by a U.S. FDA drug shortages task force. In their report from 2019 they quantified that 62% of drug shortages were caused by product quality problems. The regulators have found that failures to meet specifications have often gone uninvestigated or even unreported. The failure is to follow basic, universally accepted, GMP principles are concerning, and their conclusion is that simply enforcing compliance is not delivering quality. The report calls for a rating system to incentivize drug manufacturers to invest in improvements and for increased visibility of the level of maturity of the manufacturer's quality system. The intent of the rating is to help drug distributers reduce the potential of quality issues impacting their supplies. Since manufacturers with lower quality tend to have more drug shortages, a distributor can reduce the risk of an impact to their supplies by deciding to purchase from manufacturers with higher quality ratings.

Regulators are openly promoting change and improvements within drug manufacturer operations with a focus on making the data more transparent and expect pharmaceutical organizations to take more responsibility and demonstrate digital and quality maturity.

As Janet Woodcock phrased it, "we want drug manufacturers to move beyond simply adhering to regulatory requirements and achieving compliance, and to focus much more on improving quality".

The industry themselves have been embracing technological advances to improve their operations. The manufacturing process has been one area that has seen significant investment in technologies such as the digital twin that started the transition from batch to continuous manufacturing (Figure 6). Simply put, a digital twin is a virtual model of a process, product or service. This pairing of the virtual and physical worlds allows analysis of data and monitoring of systems to head off problems before they even occur, preventing downtime,

developing new opportunities and even planning for the future using simulations. Pharmaceutical companies have been applying this technology to their manufacturing plants where, for instance, they have introduced smart components into various equipment such as valves and traps. These have sensors to gather data about real-time status, working condition, or position. This data is recorded and then analyzed against business processes and procedural controls, and through data analytics they can predict potential issues and react to them to prevent variability in the manufacture of the drug product. Big Pharma have also used this technology to create plants that fit inside shipping containers that can be replicated to scale up or down production as required. Although developed for biologics these plants can also be used for mass production of small molecule drugs.

Digital twin technology has made the paradigm shift from batch to continuous manufacturing a reality. For over 50 years batch manufacturing, where there are various stages that rely heavily on operational procedures and process control backed up by rigorous testing, has served the pharmaceutical industry well. Adjustments at the various stages are made by human operators who often make subjective judgments which ultimately results in variability of the product. Continuous manufacturing is seen as the solution to this fundamental problem of variability in product quality by building the concept of QbD into the product's lifecycle. As the name states, it is end-to-end production processes that continually flow, backed up by the manufacturer's process validation, which includes continued process verification to maintain control of the process at all times.

Figure 6. Digital twin technology.

Other technologies and practices being used to improve pharmaceutical manufacturer's businesses include robotics, such as those used in aseptic filling to eliminate human contamination risk. 3D printing is contributing to the development and manufacture of complex biomedical devices while cybersecurity provides the protection of emerging networks, devices and computers automating the manufacturing processes and, with big data, the cloud is powering all the analytics behind it.

In the pharmaceutical industry all these developments and initiatives come under the term Pharma 4.0. In essence, it is the digitization of processes and systems and may very well bring about the end of paper records. Pharma 4.0 has the backing of the regulatory agencies because, for them, it delivers their priority of quality.

Pharma 4.0 is an adaptation of the term Industry 4.0 (Figure 7), which was coined by the German government, who wanted to enhance the competitiveness of its manufacturing industry and adopted the idea of digitization. In the broadest terms, the machines employed are no longer just something operated by a human, but rather, become an independent entity that can collect data, analyze it, and advise upon it.

Impact of Pharma 4.0 to method development and QA testing functions in the industry

So let's bring some perspective about the impact from the viewpoint of a supplier to the pharmaceutical industry, and in particular, laboratories that they serve. Enforcing compliance is not delivering the quality desired today, and the regulators expect pharmaceutical organizations to take more responsibility and demonstrate digital and quality maturity. Adoption of new technologies and practices has the regulatory agency's backing and are a perquisite to achieving a more mature quality approach.

While we have looked at most components contributing to this transition, in this last section we want to take a short look at the impact that this may have on the analytical demands for the drug development and production processes. It is evident that the shift to a more integrated production process will require a much deeper understanding so that processes can be stabilized and allow for a much higher degree of automation. Methods need to be optimized for both comprehensive information on the drug ingredients and evaluation of the long-term performance of the production process.

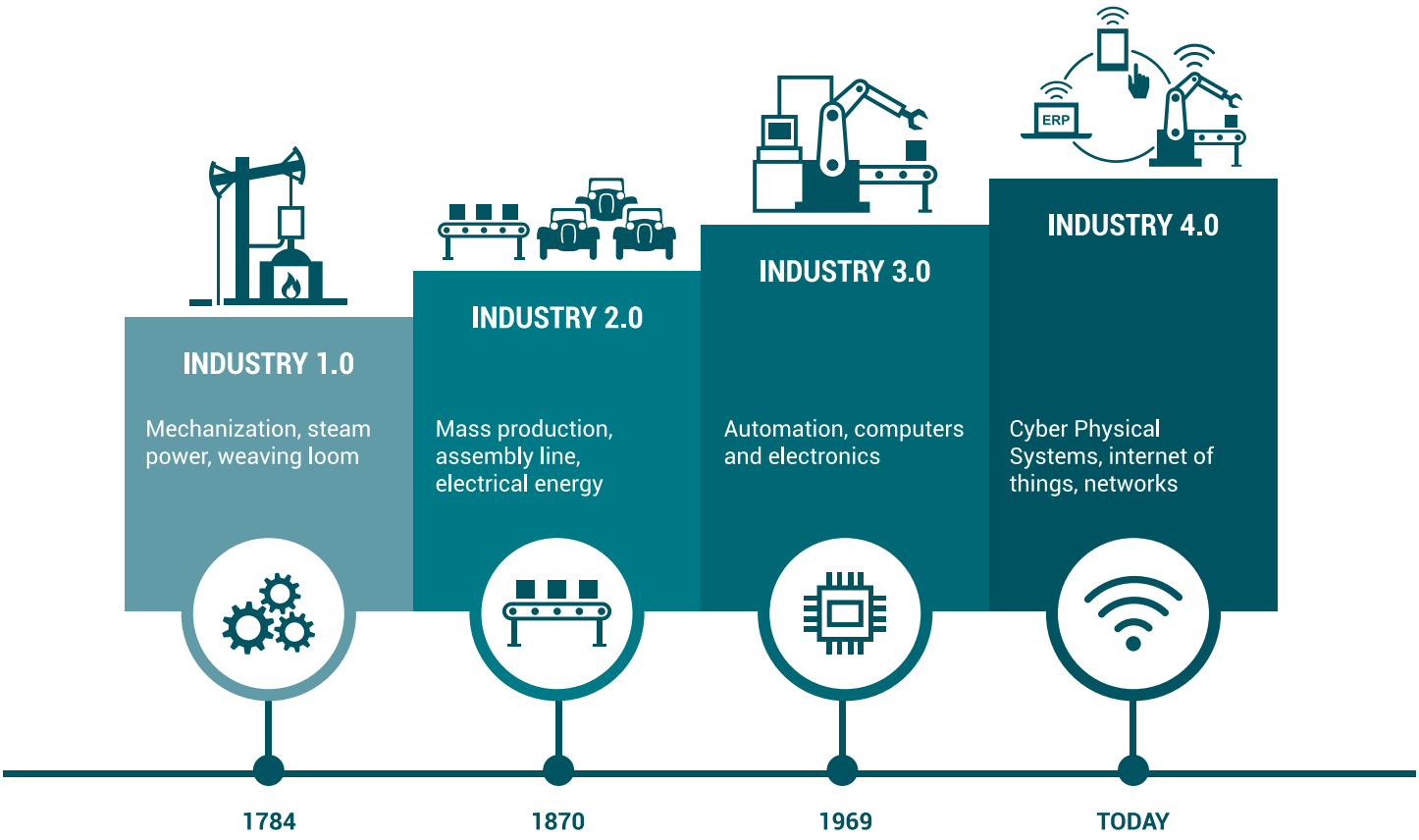

Figure 7. Industrial evolution from Industry 1.0 to Industry 4.0.

An important contribution from the suppliers is the availability of more qualitative analysis techniques, specifically MS/MS. MS/MS detection systems have become stable and mature enough to move down the development chain, even into Quality Control operations. MS/MS High Resolution Accurate Mass (HRAM) techniques can provide a much deeper insight into processes than traditional UV-based assays can provide. A great evidence of this capability is MAM as an MS based approach to conducting quality control of biological drugs. MAM was initially developed to increase the efficiency of quality control of biological drugs and it replaces a series of UV-based QC tests with a single MS/MS based assay to identify and confirm the critical quality attributes of the biological drug. The adoption of MAM has accelerated since the first industry filing to the U.S. FDA of a new drug describing its use as a quality control several years ago.

In addition, MAM provides a much deeper insight into the drug creation process compared to conventional techniques. The MAM technology can be utilized for different types of protein therapeutics delivering highly specific and quantitative information, which is invaluable during process development and essential for molecular characterization. Data has also been generated to support its use for release and stability in alignment with QbD principles.

The rise of MAM underlines the importance and value of using advanced MS/MS detection techniques in the development of biological drugs. While use of MS/MS technology for the analysis of “classical” chemical-based drugs has not yet shown similarly sized quality and efficiency benefits at least single quadrupole based MS detection techniques have already moved into late stage development and are on the edge of moving into QC. Overall, it can be expected that the need for a holistic process understanding will also drive increased adoption of such techniques into routine operations—specifically for quality control of continuous manufacturing-based drug production processes.

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Conclusion

The rationale and drive behind all the recent regulatory guidelines and future direction is to assert quality in the manufacture of drug products and safeguard the public. Advancements such as continuous manufacturing has been at the forefront and demonstrated that through a systematic approach, consistently high-quality products with minimal variability is achievable. The concepts learned now extend to Pharma 4.0 and emphasize that in order to transition there needs to be much deeper product knowledge and process understanding along with sound process control. This fundamentally means significant increases in information from several connected and ideally automated sources in order to fully characterize quality attributes and how they relate to safety and efficacy. Analytical testing is one of those sources and fast, information rich detectors, like MS have an important role in combination with evolving CDS software.

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