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THE DIGITAL LAB

Integrating and standardizing lab data, resources and processes to improve operational excellence, collaboration and time-to-market

White Paper

THE CHANGING ROLE OF INFORMATICS IN THE SCIENTIFIC PRODUCT LIFECYCLE

Many leading life sciences companies have introduced cost-reduction initiatives to automate routine, non-value-added tasks related to data capture, cataloguing and documentation activities as products move from discovery through development to late-stage quality control, manufacturing and commercial operations. In most regulated companies, the key documentation needs in discovery and early development relate to intellectual property (IP) protection. Approximately 70% of laboratory resources from later stage development through commercialization are focused on meeting compliance requirements.

The drive to "go paperless" is a strategic initiative that offers demonstrable operational benefits in improving productivity, reducing cycle times and enabling organizations to leverage experimental and operational data generated along the entire research-development-manufacturing continuum. For example, quality and pilot plant data generated during late-stage commercialization can accelerate early product, process and analytical method development by facilitating better Quality by Design (QbD) experiments that are based on real-world conditions, experience and insight. Likewise, the proper management and exchange of data captured throughout the product lifecycle creates enterprise-wide intelligence that accelerates product development cycle times.

Today's digital environment drives improved "Scientific Product Lifecycle Management," delivering technology infrastructure capable of integrating and automating critical processes and enabling scientists to capture and share critical information and data across the product lifecycle. This environment requires a scientifically aware informatics foundation that integrates critical capabilities with existing systems and information sources—speeding "science to compliance" for organizations that rely on scientific innovation to differentiate themselves.

This approach is equally applicable to the laboratory environment. Removing paper from the processes, integrating laboratory capabilities and applications through a "laboratory"-aware informatics foundation will improve operational excellence, support collaboration and help shorten time-to-market. Continuous data, information and parameter transfer throughout the lab-to-plant lifecycle supports collaboration and innovation as well as product and process improvement whether you are handling structured or unstructured data. By institutionalizing flexible, procedure-driven processes, the "Digital Lab" contributes to the overall business goals of an organization, improving competitiveness and reducing risk.

This white paper reviews relevant aspects of the Digital Lab—an overall laboratory informatics solution that spans the lab-to-commercialization product lifecycle, using data standardization/harmonization technology and electronic lab notebook (ELN) capabilities to streamline technology transfer and support operational excellence initiatives. The paper also addresses the usefulness of a single, unified, scientifically aware environment in accomplishing technology handoffs along the lab-to-plant continuum, and the importance of consistent, standard procedures for managing data and processes from lab to commercialization.

INDUSTRY CHALLENGES TODAY

Today's science-based organizations are challenged to improve product quality, productivity and compliance, while at the same time speeding innovation, collaboration and decision making to shorten time-to-market. These challenges will be compounded over the next few years as more pharmaceuticals lose patent protection and companies struggle with anemic product pipelines and the growing complexity of extended externalization strategies. Globalization in emerging markets and new competitive forces are capturing the attention of senior management concerned with achieving and maintaining revenue growth and profit by winning and defending markets, minimizing reputation risks and reducing time-to-market. As a result, organizations are re-evaluating the entire product lifecycle process from research through development to manufacturing looking for true transformation, especially with a view to adopting advanced information technology (IT) systems that are capable of supporting their changing business ecosystems.

One significant challenge is the already large and continuously increasing amount of data being generated across enterprises in support of Research and Development (R&D) and Quality Assurance / Quality Control (QA/QC) activities. If leveraged in the right way, this data explosion

can be a valuable asset to positively impact the future development and scale-up of new therapeutics, as well as enterprise operations. Unfortunately, much of this data is contained in paper systems that are difficult to access or in "silo-based" electronic systems that make data difficult to integrate and aggregate. Furthermore, increasing externalization is resulting in even more paper and additional electronic systems that can jeopardize the success and value of collaborations.

As new products emerge from Discovery and Research into Development and advance further into commercial operations, FDA guidelines on electronic records and electronic signatures (Title 21 CFR Part 11) and QbD, including recommendations of the International Conference on Harmonization (ICH), are placing additional demands on organizations, especially in the highly regulated pharmaceutical and biotechnology industries. These regulatory demands provide a compelling rationale and framework for improved quality systems and electronic records. Key to the new strategy is a risk-based approach as defined by impacts on human health. While most Discovery and Research areas are low risk, the QA/QC functions and even Development —at both the clinical materials and product release stages within the production and pilot arena—clearly fall into a "high risk" definition.

ENABLING SCIENTIFIC PRODUCT LIFECYCLE MANAGEMENT

As a result of these challenges, the Life Sciences industry has been seeking a unified scientific informatics foundation to facilitate and optimize the management of both R&D information and QA/QC data. Many companies have patched together disparate IT systems in an attempt to meet these demands; however, at best, the result has been interminable custom-coding processes with excessive total cost of ownership and validation/compliance shortcomings. A unified approach should significantly advance both QbD and Operational Excellence initiatives across global business networks.

The solution many organizations consider as the ideal approach is a unified foundation for scientific information management, essentially a Scientific Product Lifecycle Management approach enabling organizations to capture, manage and share product and process information including R&D, Chemistry, Manufacturing and Control (CMC), bioanalytical and formulations data; bioprocess and process chemistry; pilot operations information; and QA/QC data in an all-electronic environment allowing movement of procedures, recipes, methods, data and results across boundaries. Ideally this foundation is based as closely as possible on international industry standards ANSI/ISA-88 (covering batch process control) and ANSI/ISA-95 (covering automated interfaces between enterprise and control systems).

Next to the foundation it is also important to define a standard way to represent any analytical method and method schema. The schema should be independent of any particular software, hardware or type of method so that methods can move seamlessly between tools, vendors, organizations and geographies. This standard should be specific and robust enough that a wide variety of methods can be represented and when transferred, little or no detail and clarity will be lost. Fundamental to achieving this is the ability to express a decomposition of laboratory operations (lab unit operations, parameters) with sufficient detail. In addition, it is essential to capture the sequence of operations, dependencies and optional branch points.

THE DIGITAL LAB

Over the last few decades automation initiatives have been driven by the need for precise control of production processes and cost savings. Typical Supervisory Control and Data Acquisition (SCADA) and Manufacturing Execution System (MES) implementations are good examples of such automation. The development and early manufacturing stages of new products are also under scrutiny for opportunities to cut costs. The laboratory is one of the areas where non-value-added paper processes are still in place and are negatively impacting productivity. "E-lab" initiatives have received attention as one of a small number of critical-path issues that, if solved, will yield significant operational and cost savings.

As scientific documentation moves from research through development to commercialization, the fundamental informatics requirements change dramatically—evolving from a free-form, open structure for initial ideation, through a more structured (but flexible) experimental

set for optimization, to a rigid SOP-based method execution platform for quality control in manufacturing. In this lifecycle, there is a need to rapidly acquire and share scientific insights across the continuum from lab to manufacturing.

Several capabilities are relevant for the Digital Lab including:

- Managing, planning and scheduling laboratory tasks and resources
- Executing and documenting experiments, methods, procedures and tasks in the laboratory
- Storing, sharing, and protecting laboratory data and results
- Managing chemicals, materials, equipment, personnel and related processes
- Developing, adapting and managing recipes generated throughout the product lifecycle, from product development to manufacturing.

The extensive capabilities of the Electronic Laboratory Notebook (ELN), especially those involved in documenting the execution of laboratory processes, have been receiving special attention for their potential to positively impact productivity, collaboration and time-to-market.

ELNS IN RESEARCH, DEVELOPMENT AND QA/QC

Since they first appeared in the late 1990s, ELNs have predominantly been utilized to document experiments and capture intellectual property. In fact, many of the early research ELNs were simply secure word processing and spreadsheet software products. Today's multidisciplinary ELNs have evolved significantly to the point where they now offer specific functionality supporting synthetic, analytical, (bio)formulations and (bio)process scientists as well as biologists working in areas from screening to preclinical and clinical development.

As analytical methods progress through the drug development process, the degree of "blue sky" flexibility versus "locked-down" execution will vary for different scientists depending on where they are along the lab-to-plant continuum (Figure 1). However, the final validated QC test and Certificate of Analysis (CoA) for both product and process in commercial operations are always the all-important outcome. By combining flexible ELN capabilities during the research and development phases of this process with procedure-based ELN capabilities supporting regulatory compliance during the development-to-commercialization phase, organizations gain a unified, highly automated, digital end-to-end lab environment from initial product ideation through development to manufacturing.

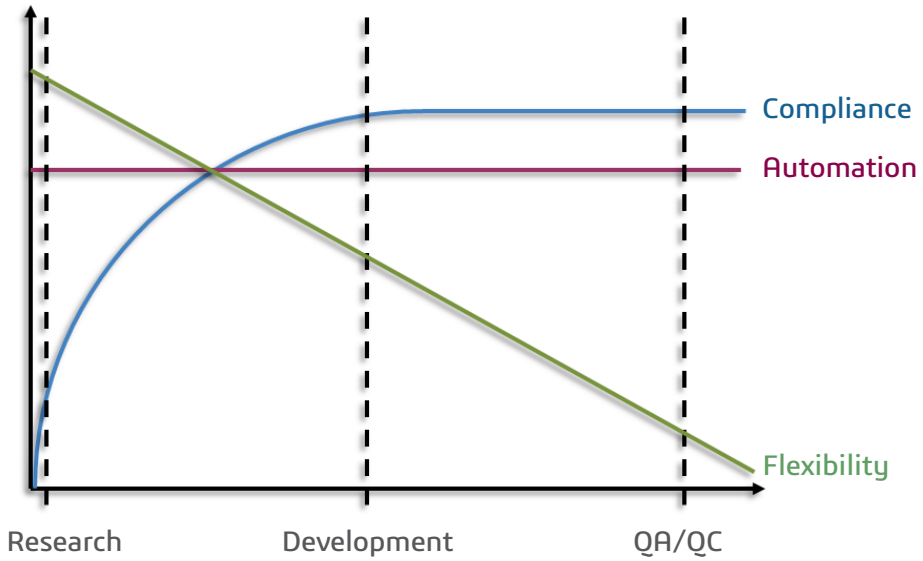

Figure 1: Laboratories in different domains have different specific requirements for documentation and workflow support with regard to flexibility and compliance, while all domains will benefit from a high degree of automation.

An ELN used in an R&D environment requires an open structure for handling general observations and experimental detail. This includes the flexibility to adjust scale, re-order process steps, substitute reagent components or change concentrations when developing analytical test methods. The research ELN enables scientists to capture both the processes they perform and the interpretation of experimental results.

In a regulated QA/QC environment, however, an open structure is not preferred and, in fact, is a compliance liability. A QA/QC ELN must be capable of handling highly structured, method-centric operational protocols with all lab systems (instruments, SOPs, reagents, etc.) integrated into the e-method, as well as large volumes of samples and associated information. Rigorous attention to compliance is essential for the QA/QC ELN. For example, reagents, instruments and devices used in the execution of test methods must be automatically verified for their "compliance state" prior to use, and QA/QC data must be validated in real-time. Figure 2 summarizes the major differences between Research, Development and QA/QC ELN capabilities.

	RESEARCH ELN	DEVELOPMENT ELN	QA/QC ELN
FOCUS	Experiment-based	Experiment and workflow based	Method and procedure-based
PRIMARY USER	Scientist	Formulator	Analyst/Chemist/ Operator
BUSINESS DRIVERS	Intellectual property protection and knowledge sharing	Tech transfer and compliance	Compliance and lab operations productivity
DESIGN APPROACH	Flexible, unstructured and project-centric; specialized scientific functionality; for recording observations and outcomes	Flexible, unstructured as well as structured and experiment-centric, while compliance-centric tool for developing QA/QC methods, recipes and procedures QA/QC	Highly structured; method-, execution-, and compliance-centric; for enforcing and documenting procedures and ensuring data integrity
SEARCH APPROACH	Projects, experiments, documents, results data mining, molecule/ therapeutic, personnel	Experiments, methods, recipes, molecule/ therapeutic, equipment, materials, personnel, results	Sample, manufacturing lot, equipment, methods, materials, personnel, results

Figure 2: Research, Development and QA/QC ELNs – Open vs. structured approaches

MOVING FROM DEVELOPMENT TO QA/QC

Transferring methods between the Development and QA/QC areas is typically an enormous burden for organizations, often requiring them to relocate the method development and process team to the pilot or production site for extended periods to ensure complete and accurate technology transfer (Figure 3). A technology and informatics foundation that allows this transfer process by enabling an interchange of method information reduces the time required to re-implement a method within the QA/QC infrastructure and enables better development and tracking of methods. This will significantly reduce product development and cycle times and at the same time reduce errors resulting from manual data transfer.

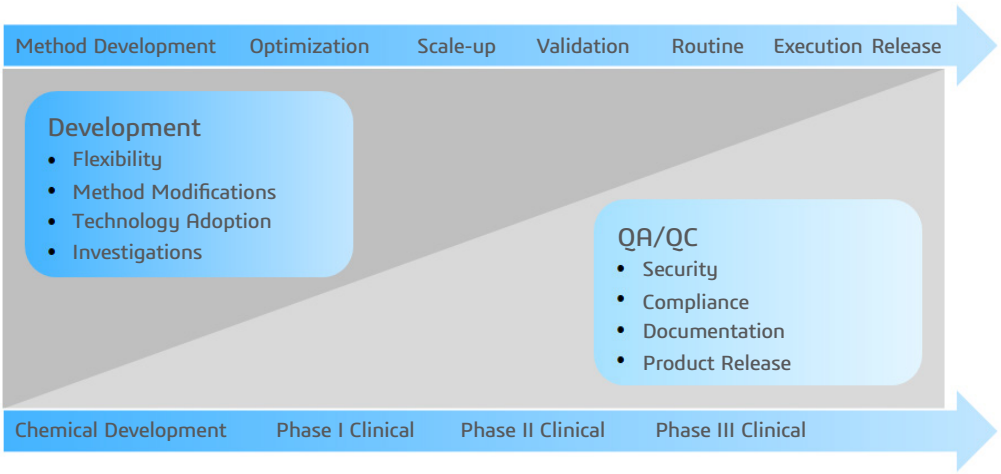

Figure 3: Development and QC labs – requirements for data and method exchange

During the Product/Process Development phase, the therapeutic entity is already known and research is focused on deriving the optimal formulation, manufacturing process conditions, testing and production environment to achieve the highest purity with the optimal yield at the lowest cost. New analytical test methods are being developed which require optimization and validation experiments to transfer robust procedures to QA/QC operations. Across this continuum, scientists require an electronic environment that supports both flexible "authoring" and structured "execution" to perform and document experiments and sample processing during the development stages of new entities. While these capabilities seem to be opposed, they can be implemented within a single solution through an integrational foundation combining flexible, parameterized development with rigid execution capabilities. In the end, when the product and technology are transferred to commercial operations, the validated QC analytical test method is already available and executable for routine QA/QC use in the lab.

INTEGRATION WITH INSTRUMENTS

In order to achieve a fully digital lab and to benefit from a fully automated workflow, the implementation needs to include the integration of lab equipment with validated interfaces. The purpose of these interfaces is the automated transfer of test results from the instruments to the system, as well as transferring any sample-related information from the system to the instrument. Furthermore, the interface helps ensure that the instruments are calibrated and fit for use before acquiring data. This reduces deviations and shortens the review time since it is guaranteed that the instruments are calibrated and checked routinely. Overall these instrument connections will ensure the rapid, efficient and cost-effective replacement of paper processes in a fully automated, electronic lab environment - free of transcription errors - where all sample information is centralized for rapid reporting, data investigations and capacity resource management (Figure 4).

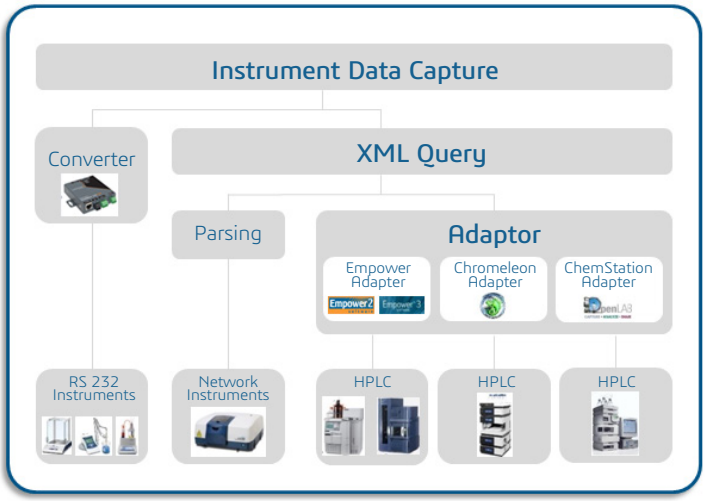

Figure 4: Automation of instrument data capture, processing and storage including direct raw data capture from the RS-232 port, file parsing from a file store or direct communication with the scientist's desktop software

The use of S88 and S95 ISA standards to manage methods and procedures from method development to sample analysis enables the accurate, uniform storage of enterprise data in a single centralized database. Uniform data accelerates data mining, reporting and sharing for continuous insight and process improvement.

Standard technology modules enable IT/IS and System Administrators to implement any of the instrument applications without the need for vendor or third-party resources, significantly accelerating installation/validation while also reducing or eliminating traditional Laboratory Information Management System (LIMS) customization/configuration issues. The ability to track and trace materials, samples, instruments, specifications, reports and data transfers in enterprise cGLP- and cGMP-compliant environments is of additional benefit.

SCIENTIFIC DATA-DRIVEN DECISION MAKING

Research, Development and QA/QC need to utilize lab data effectively so that scientists can extract full value for decision making and innovation. This applies to operational reporting and release processes as well as data mining, trending and feedback into QbD initiatives.

A common technology and informatics foundation will streamline data access and reporting across the enterprise by providing a unified "view" of underlying data and a standard process for extracting, transforming and loading data using a single common data structure and format (ETL). Querying and reporting components can be exposed as web services, enabling multiple applications or internal configured interfaces to access and display information in a manner most appropriate for various corporate "stakeholders." Business rules and quality checks can be built into re-usable components to ensure that data complies with necessary standards as it moves through the organization. A single foundation supports flexible data mining and query activities in upstream R&D, as well as the compilation of more structured therapeutic dossiers required for downstream regulatory submissions.

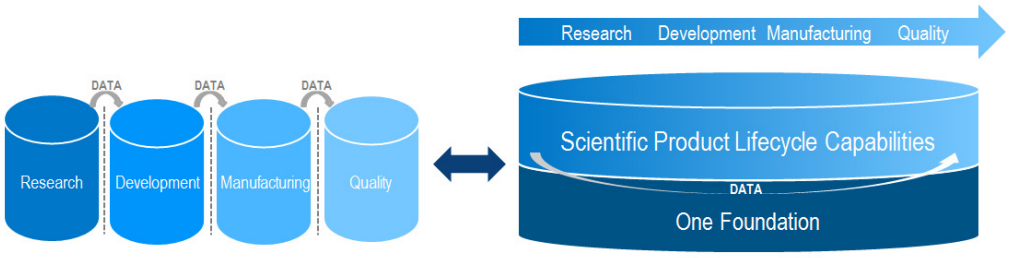

Figure 5: A unified technology and informatics foundation facilitates direct data capture from all instruments (via BIOVIA Instrument Data Service) while also providing a data querying/analytics platform supporting product and process design and decisions in development and QA/QC operations.

With all data centrally and consistently captured, analytical groups can quickly find sample information, compare and contrast information across multiple samples and investigate sample genealogies (Figure 5).

BENEFITS OF THE DIGITAL LAB

The Digital Lab provides research, development, analytical, and QA/QC laboratories a unique opportunity to remove paper processes while supporting end-to-end, analytical and process workflows. The Digital Lab supports:

- Collaborative and innovative research
- Early and agile development
- Optimization and validation of analytical methods
- High-throughput, compliant execution of sample analysis in regulated and non-regulated labs
- Automated, locked-down procedure execution via electronic batch records during late-stage quality control and manufacturing in cGMP environments

Common standards between systems ensure rapid transfer of data, information and parameters and new opportunities for data mining, analytics and visualization. A common Foundation based on these standards assists scientists in designing, developing, deploying and delivering critical tasks from upstream R&D to downstream QA/QC operations.

CLOSING THE GAP BETWEEN INNOVATION AND COMMERCIALIZATION

Faced with revenue erosion resulting from expiring patents and questionable new product pipelines, life sciences organizations are "sharpening their pencils" to improve operational excellence, control costs and drive innovation. For decades, most data has been paper-based, requiring numerous non-value-added checks to ensure end-to-end data integrity and quality from product development through product commercialization. These paper-based and legacy point solution systems are becoming even more difficult to manage as life sciences companies increasingly externalize operations.

Today's technology can eliminate these paper systems and replace them with efficient electronic environments supporting "science to compliance." Within any life sciences company there are three key laboratory informatics design issues depending on where scientists are working within the lab-to-plant continuum. Research scientists require an open-ended, free-form environment for experimental design, results capture and IP protection. QA/QC scientists in cGMP regulated areas need just the opposite—a highly structured, procedure- and method-centric operation with full instrument integration and data exchange capabilities with other IT systems (LIMS, ERP, MES, etc.). Between discovery R&D and manufacturing QA/ QC are the unique needs of the development groups. Here, flexible experiment design coupled with parameter variations are the key informatics documentation needs. The Digital Lab informatics environment enables quick technology transfer of ruggedized, automated test methods to quality operations as well as process parameters to pilot plants and manufacturing facilities. When a therapeutic goes into full commercial production, the Digital Lab enables recursive data access supporting QbD efforts and continuous product/process improvements.

With the Digital Lab companies can adopt an informatics approach that effectively connects innovation and commercialization cycles with high fidelity data that retains contextual information as projects move through R&D into manufacturing. Scientific Product Lifecycle Management supports this approach with a comprehensive, scientifically aware informatics foundation for capturing and harmonizing data along the end-to-end product lifecycle continuum.

By bridging the innovation and productivity gaps in research, development, manufacturing and quality and enabling successful technology transfer across new product development and production QA/QC operations, organizations adopting this proven informatics IT solution will experience:

- Enhanced productivity through integration and streamlined workflows
- Improved compliance through automated data transfer and support of execution and reporting
- Better collaboration within globalized R&D and across dispersed teams through easy data access and standardization
- Informed decisions through optimized experimentation and sample processing with real-time results
- Faster time to market through shorter cycle times and reduced latencies between cycles

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