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Critical Aspects and Risks in Implementing Single-Use Technologies in Flexible Facilities

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The Paperless Laboratory: A Way Into Process Optimisation

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Study of Pharmaceutical Drug-Excipient Interaction by FTIR and Raman Spectroscopy

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The Paperless Laboratory: A Way Into Process Optimisation

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In this article, I will share experiences and observations how the scientific high-tech community, can benefit from adopting paperless processes in the laboratory. Is it because paper doesn't require any significant investment budget, or is it the low barrier to access, since paper even works without power or the need to have access to an information infrastructure, or is it just simply that the "what's in it for me" question hasn't been answered satisfactorily for the scientists?

Cross-functional collaboration between research, development, quality assurance and manufacturing is all about optimising and integrating multi-discipline distributed processes from start-to- finish. A paperless electronic record keeping system will add significant value to support these goals. LIMS, SDMS, LES and ELN products all reduce variability, transcription errors. Do we believe that traditional paper based systems could ever support these complex processes?

Think Exponential

Traditional mainstream LIMS will face new challenges. LIMS has been a brilliant tool to manage predictable, repeatable planned sample, test and study data flows, creating structured data generated by laboratories. In R&D environments, unpredictable workflows creating massive amounts of unstructured data showed that current LIMS systems lack the capability to effectively manage this throughput. Alternatively, Electronic Laboratory Notebooks (ELN) are great tools to capture and share complex scientific experiments, while an underlying Scientific Data Management System (SDMS) is used to manage these large volumes of data seamlessly. For example, many ELN applications include LIMS like native instrument interface capabilities to increase procedural enforcement and decrease transcription errors.

Paperless or Less Paper?

The paper versus paperless discussion is as old as the existence of commercial computers. In the 70's, just after the introduction of the first personal computer Scelbi (SCientific, Electronic and BIological), Business Week already predicted that computer records would soon completely replace paper. We all know that it took over 35 years before paperless operations were generally accepted and successfully adopted in our daily work. While paperless operations in electronic banking, airline check-in, patient and healthcare, and retail industries, have been accepted as the preferred way of working, in our scientific high-tech world, they lag behind. In research and development laboratories, adoption has been significantly slower, with several large pharmaceutical companies still predominantly paper-based. Even with the enormous potential for compliance and efficiency gains with fully electronic labs, significant barriers to a successful paperless lab implementation remain. McKinsey stated that operations performance in the pharmaceutical industry compares poorly to other industries, most notably in overall equipment effectiveness, labour add-time (20 versus 70 percent) and direct/indirect labor.[1]

Data-intensive science is becoming far more main stream. Research is increasingly collaborative and complex, leveraging multiple technologies to get a systems level understanding of diseases and organisms. Data integration is crucial for enabling virtual knowledge sharing and the exponential rise in the scale of (big) data being generated, combined with increased collaboration, has resulted in the need to rethink how data is cost-effectively stored, analysed and shared (Figure 1). Communication is a common dominator and often underestimated as a significant point of failure in multi discipline laboratory automation projects. Lack of capturing metadata creates eliminates the ability to re-use and find previous knowledge from experiments. Tacit knowledge (as opposed

Figure 1. Impact of data standards simplifies user experience.

to formal or explicit knowledge) is the kind of knowledge that is difficult to transfer to another person by means of writing it down or verbalising it. We store this information in our brains. This makes it difficult to share. However combining explicit information, stored in computer systems, with tacit information is where inventions and knowledge are created and shared. Technology is set to change the dynamics of how scientists work together.

The Informatics Journey…

The journey begins with the transition from paper to digital, which includes both the transfer of paper-based processes to "glass" and the identification and adoption of information and process standards to harmonise data exchange. The completion of this step propels organisations down a path towards clean, tractable data, drives out human variability and improves data integrity. In its simplest form, an Electronic Laboratory Notebook (ELN) can be thought of as for an electronic embodiment of what is currently being done in a paper laboratory notebook (Figure 2). It is a tool that facilitates the workflows that play out in your particular laboratory. Having said that, Laboratory Information Management System (LIMS), Electronic Laboratory Notebook (ELN) and Lab Execution System (LES) applications all support this basic definition, to a greater or lesser extent, as they exist within various laboratory environments. So what's the difference between these applications?

To start, the majority of publications comparing ELN, LES or LIMS are product centric. Would it not be more appropriate to start with the end user in mind and look at the application from a user-centric perspective? (Table 1). Let's begin with looking at the world from the perspective of a researcher. The scientist should be able to record scientific data, make observations, describe procedures, include images, drawings and diagrams and collaborate with others to find new chemical compounds, biological structures, etc., without any limitation and not bound by any predefined process. In a research environment, workflows are often methodical but unscripted. Qualitative characteristics are often most important and require a free

	Research ELN	LES	LIMS
Where in use	Chemistry & Biology Research & Development	Analytical Testing laboratories	Analytical Testing laboratories
Main purpose	• Intellectual Property Protection • Knowledge re-use • Research efficiency	• Electronic SOP's • Compliance • Error reduction	• Secured laboratory information hub • Compliance • Reoccurring processes
Database focus	• Document centric	• Transactional	• Transactional
Typical IT infrastructure	• Windows workstation • Web client • Cloud • SaaS	• Windows workstation • web client • Tablet • App store	• Windows workstation • Web client • Client/Server
Application behavior	Experiment centric	Sample/Process centric	Sample/Process centric
User Interface behavior	• User centric • Free form & adaptable	• User centric • Procedural • Natural language	• Organisationally centric • Procedural • System defined
Related Applications	Scientific databases	LIMS, ELN, Instruments	LES, ERP, SDMS, CAPA
Licensing models	• Named user • SaaS	• Named user • Concurrent user • Instrument	• Named user • Concurrent user • Virtual user • Enterprise
Compliance support	+/-	++	++
Sponsors	Legal departments Academia networks Scientific communities	QA directors Lab managers	Production managers QA directors

Table 1.

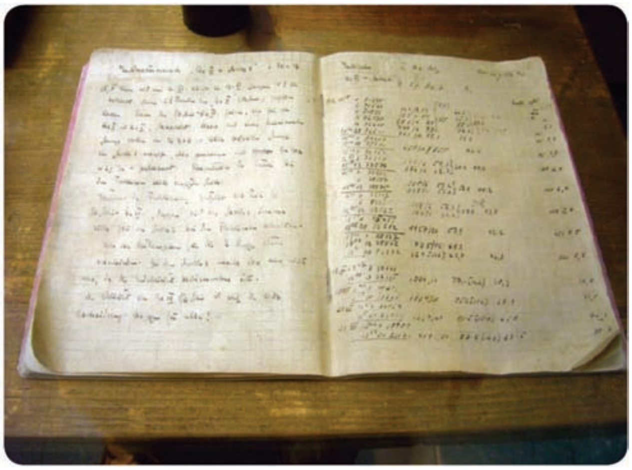

Figure 2. Otto Hahn's laboratory notebook 1938 © J.Brew.

format, often referred as unstructured data process. Complex chemical and biological searches and cloning experiments produce a significant increase in the research efficiency for the scientist. Intellectual property protection needs to be well implemented to support legal departments, and to assure protection of the new inventions as corporate assets. Audit trail features such as time/date stamps and user authentication are a must in this regard. The modern scientific researcher has become much more collaborative than ever before. Communication capabilities will also be complemented with new technologies to support virtual collaboration capabilities. These are IT-enabled services that allow groups of people to interoperate synchronously and asynchronously include collaborations tools like Electronic Lab notebooks and other scientific knowledge systems. Researchers like to be in the laboratory where the experiments are performed. It is therefore, no surprise that mobile computing platforms such as iPad's and other tablet devices are increasingly becoming popular. Because researchers tend to want to evolve and adapt relatively easily, the software and hardware platforms that support them should quickly adapt as well. Thus, for the researcher an ideal research ELN is one that provides the most flexibility and freedom– a blank page that allows the researcher to do anything that they would in a paper notebook, while adding the benefits inherent to an electronic medium including the ability to collaborate without boundaries.

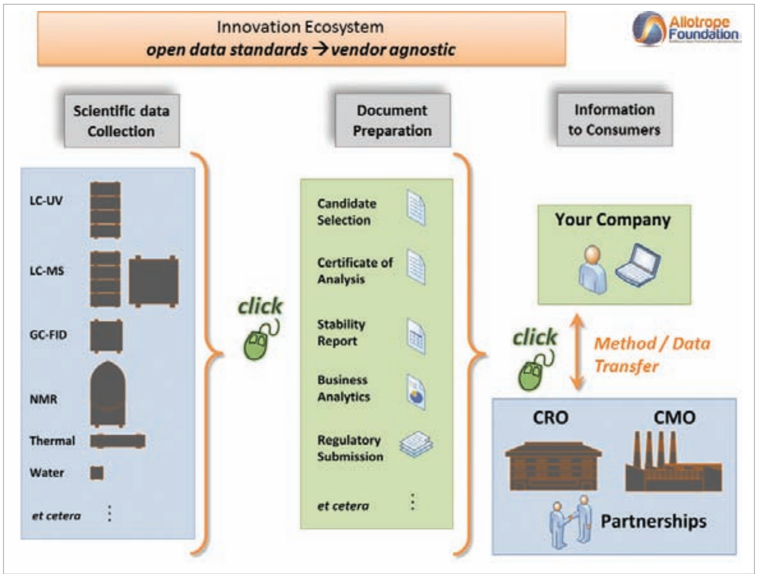

Figure 3. Benefits of open data standards – Courtesy of the Allotrope foundation.[3]

Adopting Standards Simplified

The Electronic Laboratory Notebook (ELN) is evolving to adopt compliance with international industry standards such as ANSI/ISA-88 (covering batch process control) and ANSI/ISA-95 (covering automated interfaces between enterprise and control systems), both of which are commonly used in manufacturing. By incorporating these standards and structuring data in a fully searchable format, the ELN enables scientists to mine information from development and manufacturing for improved process and product design. In addition, information is more readily transferable between systems (Figure 3). For example, a recipe delivered in early development can be rapidly transferred to a Lab Execution System for API manufacture and then to a Method Execution System for mainstream manufacturing.

For the QA/QC laboratory analyst, the requirements for an electronic laboratory notebook are quite different. In labs where a routine sample-processing paradigm dominates, workflows are more repeatable and data are often much more structured & quantitative. Analysts, therefore, need a structured and robust platform to ensure that proper procedures are followed, that the progression of samples through the lab is tracked, and that discrete measurement data are captured and reported reliably. Analytical services and quality control laboratories frequently deploy systems to automate high-volume workflows and to ensure compliance. In addition, many of the same needs and characteristics hold true for analysts working in core sequencing & genotyping laboratories that support R&D. Clinical diagnostics labs, and the like. Traditionally, in these laboratories LIMS has been very successful. In recent years, however, another category of ELN has emerged and is gaining significant popularity. This category of ELN products is often referred to as Laboratory Execution Systems (LES), and they range in functionality from simple to quite complex. These LES products are designed to support the analyst's daily workflows in a natural language form, and typically provide the analyst with a User Interface (UI) that closely resembles existing laboratory worksheets and/or Standard Operating Procedures (SOP's). Ultimately, whether they appear as electronic laboratory worksheets augmenting LIMS functionality, or as standalone applications, the LES category of ELN products serve the laboratory analyst by guiding them through reproducible workflows, managing the associated data, and helping to ensure compliance. Automatic instrument calibration, stability study reference data as well as environmental monitoring are the key most important user applications.

Pay Attention To New Consumes Of The Scientific Data

The initial objective was to support the laboratory manager with tools to create simple reporting capabilities to enable the creation of simple certificate of analysis (CoA) reports. These systems were initially designed to support a single consumer category, namely the scientists and lab managers. In today's world, consumers of laboratory data can be found across the entire product lifecycle, and may even include external organisations, such as CROs and CMOs. A different mindset to adopt the expanded view of the world is mandatory. It is critical to first analyse who these new lab data consumers are and to get an understanding of what their objectives are. Often forgotten, but as important, is to also investigate their usability perspective. The newcomers may be a non-technical audience! (Table 2).

Here are a few data consumer versus data creator examples:

- For the scientific researcher, the ability to record data; make observations; describe procedures, including images, drawings and diagrams; and collaborate with others to find new chemical compounds and biological structures without any limitation, requires a flexible user interface. For the QA/QC analyst or operator, the requirements for an integrated laboratory are quite different. A simple, natural-language-based platform to ensure that proper procedures are followed will be liked.

- To professionally support a client complaint, the customer care manager requires a quick and complete dashboard report to look at metrics for all cases,

Data Consumer	Objective	Impact / benefit
Patient	Assure secured instant access to medical data for doctors.	Better healthcare @ lower costs
Laboratory	Ability to re-use and easier find scientific evidence.	Better service to lab data consumers.
Scientific researcher	Re-use experimental data and leverage learnings. Higher efficiency and quality. Consistent meta and context data	Higher efficiency and quality
Legal	Protect company IP	Consistent externalisation processes (CRO's)
Finance	Understand overall life cycle cost of operation	Holistic overall view
Customer care	Ability to research product complaints and product investigations	Consumer service to secure branding image of company
Regulation	Faster responses to compliance inquiries	Simpler mechanism to audit heterogeneous scientific data
Management	Identify areas for continuous improvement in process. Reduce costs	Risk based information across heterogeneous data systems
Stability labs	Simpler mechanism to create e-submissions. Ability to submit standardised e-stability data packages	Faster responses during studies, Increased efficiency
CRO / CMO	Focus on lowering cost/analysis by decreasing IT complexity and overhead	Acceleration to move from paper to "paper-on-glass"
IT	Reduce bespoke/customisation efforts. Consolidation of systems. Reduce costs. Integrate with other IT systems	Enable holistic management view. Reduce costs. Simplifies IT processes

Table 2. Selected new Consumers of Laboratory Information Data.

assignments and progress in real-time, by task, severity, event cause and root cause. Significant increase in supplier risks requires full traceability and integrity of all data from start-to-finish. The devil is in the detail, and that's where the laboratory data may give significant insights.

- Patent/Legal: Instead of saying "we saw that a couple of years ago, but we don't remember much about it," sensitive information can searched and retrieved, including archives.

- Product innovation often relies on reformulating existing product offerings. Formulators will need the capability to mine data across projects, analytical methods or formulations to create valuable insights. Transforming unstructured scientific experimental data into a structured equivalent will be mandatory to perform these tasks.

- Organisations with a strong consumer marketing focus deal with data mining techniques providing clear pictures of products sold, price, competition and customer demographics.

- Adoption of new technologies is expected to have a significant impact. Wi-Fi, Bluetooth, barcoding, RFID, mobile devices are expected to be mainstream accepted in the years to come.

- Managing operating budgets will be redefined in the next decade. The days to purchase software as a capital investment (CAPEX) are changing to a new model based upon a "pay-as-you-go" philosophy (OPEX). CRM applications, such as SalesForce.com started this business model in the traditional enterprise business software segment. Popular applications, such as Photoshop and Microsoft Office 365, as well as Amazon, are rapidly following these trends. It is expected that scientific software suppliers will be forced to follow the same model in the years to come.

Paper is Cheap, Familiar and Comforting

People and paper have had a long and close relationship. Traditionally, researchers were individualists and working in their laboratories on their discoveries. A study showed that, although documents are current when printed, they "age rapidly during the day." Similarly, "versioning," occurs when multiple versions of a paper document exist, leading scientists to wonder which document has the latest information: "We feel it's safer to go to the original document or spreadsheet in the computer."[4] Paper documents hold static information that loses timeliness with age. Another study concluded that filing costs are averaging $20/document, each misfiled document costs approximately $125 and a lost document $600[5]. But, even more significant, is that when an employee leaves a company, 70 percent of his knowledge walks out the door. Paper documents are always at risk due to loss or damage. A simple spill or a careless

Laboratory Integration Killer app's	
Archiving	The perception of data archiving is often only related to store data only. The fascinating extension of having meta data standards as part of the archive procedure, we will be able to re-use data for collaboration between different instruments in or externally with CRO's.
Data finder and data viewer	The ability to full context searching across heterogeneous data sources, in and external data systems and archives and display in unified viewer.
Regulatory reviews	The ability to build and transmit to regulatory agencies a standard data package for inspection without altering the underlying information (e.g. regulatory submissions, stability studies).
Reduction in (re)-qualification processes	In GxP environment the ability to automatically update USP methods across individual instruments will significantly reduce the requalification process.

Table 3. Potential Integrated Laboratory killer apps.

misfiling of a document can result in hours of time wasted trying to find or recreate the test results. It may sound obvious, but destroying paper to comply with retention policies is more costly and cumbersome than we may think (Table 3).

Sustainability

With growing eco awareness, paperless processes also may decrease the environmental footprint. An increased number of global companies include sustainability plans in their corporate business plans. Studies showed that, for a typical mid-size 100 FTE company with an average of 1600 releases a year, a paper stack of almost 750 meter (1/2 mile) will be created, which is higher than the Eiffel Tower in Paris and slightly lower than the Burdish Chalifa in Dubai [6]! New studies are underway to identify the net impact of energy, paper and waste reduction targets.

Democratising Research

The Cloud, for example, is not just an IT initiative; it really changes the ways in which people and science can work together in virtual communities (Table 4). For example, it eliminates the need to wait for months for a particular scientific paper to be published. Building trust within relationships in order to create these teams' remains a people issue and when considering where active communication occurs in science, thoughts may lean towards scientific presentations and great papers. The cloud as an infrastructure gives researchers computational access on a subscription or pay by-demand cost structure. New LIMS and ELN applications are developed to be deployed in a modern native cloud environment. In manufacturing the acceptance of virtual services is still low/ In discovery and development, the acceptance is significant higher. Why? Instant access to computational power, significant lower administration costs, no capital spending headaches and no dependence of availability of IT resources are the considerations to deploy this approach. Software as a service (SaaS) is a software delivery model in which software and its associated data are hosted centrally in the cloud and are typically accessed by users using a thin client computer or tablet device, using a web browser over the Internet. Zero footprint applications imply that no software needs to be pre-installed on your client. This significantly helps to simplify installation procedures. A browser is all you need! To upload successfully large datasets, it is critical to have access to fast network infrastructures. Limited network bandwidth, especially in start-up phase, may result into frustration, and should be avoided. As a researcher you want to avoid thinking in computer terms. The table below summarises the overall nomenclature and major acronyms for the most common cloud computing service models: SaaS, PaaS, and IaaS. Licensing software in the cloud is different than traditional software licensing. A traditional software purchase involves in many cases a capital investment and comes with an annual maintenance and support plan. The SaaS model is solely based upon an operational cost model with monthly or annual subscription fees with all maintenance and support services are included. No hidden costs. No surprises. The two major areas where cloud services are being deployed in discovery are computational power to execute computer intensive (Biological) calculations and in electronic lab notebooks (ELN) to electronically capture scientific experiments and share knowledge across research teams. In table 4 you'll find a summary of the most common abbreviations and what they mean.

Conclusion

Very seldom does a company have the luxury of starting with a clean slate when it comes to making an ELN or LIMS decision. Due to the prevalence of Merger & Acquisition activity today, the need to rationalise your portfolio of applications in a holistic manner will almost inevitably be an essential part of your decision making process. In today's world, the cost/benefit analysis frequently needs to be done in a way that considers the functionality already being provided by legacy applications, and business justifications need to be based upon providing transformational benefits to the organisation. Overall, the scientific software industry is creating superb technology breakthroughs, but is often lacking behind, to translate these great technologies innovations into viable business solutions.

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Cloud 101 Abbreviation list		
SaaS On-demand software	Software as a Service – Software distribution model in which discreet applications are hosted by a vendor or service provider and made available to customers over the Internet.	• Easier administration • Automatic updates and patch management • Compatibility & Easier collaboration: All users will have the same version of software. • All operational costs. No capital investment. Pay as you go and subscription based
PaaS STaaS	Platform / STorage as a Service - External service who provides the hardware, operating system, software upgrades, security and everything else related to the day to day hosting of an (enterprise) application.	• Unification of programming development efforts. • Enabling geographically distributed development teams • Lower operational costs; cross-boundary, single vendor support. • Enterprise data integration and systems consolidation
IaaS HaaS	Infrastructure as a Service - Provision model to outsource equipment used to support operations, including storage, hardware, servers and networking components.	• Utility computing service and billing model. • Automation of administrative tasks. • Dynamic scaling. • Desktop virtualisation. • Policy-based services.
DaaS Virtual desktop Hosted desktop	Desktop as a service - The outsourcing of a virtual desktop infrastructure to a third party service provider.	• Service provider manages the back-end responsibilities of data storage, backup, security and upgrades. • All operational costs
XaaS Anything as a service Everything as a service	Refers to an increasing number of services that are delivered over the Internet rather than provided locally or on-site	XaaS is the essence of cloud computing.
Public Cloud	Standard cloud computing model available to the general public over the Internet.	• Inexpensive. Hardware, application costs are covered by the provider. • Scalable to meet needs. • No wasted resources; you pay for what you use • Examples include Gmail, Hotmail, Yahoo, SalesForce.Com
Private cloud Internal cloud Corporate cloud	Marketing term for a proprietary computing architecture that provides hosted services behind a firewall.	• Full control over data • Internally hosted • Traditional approach
Hybrid cloud	A hybrid cloud is a composition of at least one private cloud and at least one public cloud	Allows a business to take advantage of the scalability and cost-effectiveness that a public cloud computing environment offers without exposing mission-critical applications and data to third-party vulnerabilities.
multi-tenancy architecture	An architecture in which a single instance of a software application serves multiple customers. Each customer is called a tenant. Tenants may be given the ability to customise some parts of the application, such as color of the user interface (UI) or business rules, but they cannot customise the application's code	• Cost effective - provider only has to make updates once • Ability to take advantage of virtualisation and remote access. • High security - each tenant's data is isolated and remains invisible to other tenants.

Table 4.