Enterprise ELNs as a foundation for preclinical drug development

To have real business impact within preclinical drug development, Enterprise ELNs (Electronic Laboratory Notebooks) must provide a secure, scalable and searchable data management backbone across all disciplines focused on development of both small and large molecules, in compliant and non-compliant environments. Through more effective capture and reuse of data and knowledge, we discuss how Enterprise ELNs improve inter- and intra-departmental collaboration, and support quality initiatives such as 'Quality by Design'.

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ELNs were originally intended to reproduce the paper-based lab notebook process that has been the basis of data capture and scientific Intellectual Property (IP) protection for centuries. They have evolved through widespread use into enterprise systems: sophisticated data capture, management and reporting solutions capable of spanning a wide variety of departments/domains[1]. The resulting Enterprise ELNs are able to support collaboration not only within teams, but now between teams as well. Each individual team has a solution based on its specific needs, but there is a common core allowing cross-domain data sharing and therefore more effective collaboration.

The early ELN systems focused on electronically capturing results from a laboratory with data from Excel®, PowerPoint®, emails and domain-specific applications, and were often in a chemistry-focused environment[2]. Such systems were only orientated towards the documentation and capture of patent-relevant IP and essentially replaced using paper-based notebooks with cutting and pasting information electronically, providing a 'sticker book' approach. These early systems had little regard for data and knowledge sharing between teams, or with reuse of corporate learning, because they were only designed to provide 'page'-like reports: they did not provide a rich data source that could be easily mined and shared.

Over the past five years the use of ELNs has spread into biology-related disciplines such as pharmacology, drug metabolism and pharmacokinetics (PK), and process-driven disciplines such as bioanalysis, formulations, analytical and pilot manufacturing. To support such diverse needs, ELNs have developed into enterprise systems that provide more flexible and broader data capture and sharing and IP capture. In this context, IP means corporate knowledge or data, ie important historical data and know-how that could be a potentially competitive advantage. Certain ELNs support both contextual and structured fact data capture that enables the creation of a Corporate Knowledge Store – a searchable, mineable resource that can be leveraged across the organisation.

The remainder of this paper will look in more detail at how these advanced Enterprise ELNs can deliver significant business impact, and what capabilities are required for their application to both large and small molecule preclinical development organisations.

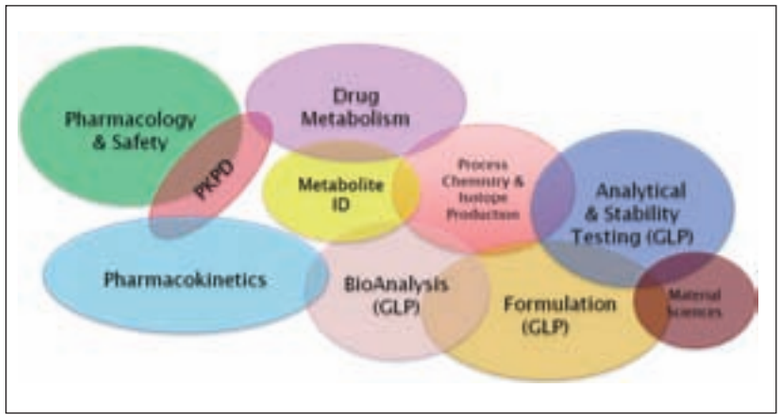


Figure 1
The preclinical environment presents multiple challenges for an Enterprise ELN. It must bring together data and interpretation, and enable collaboration between many varied groups

Supporting interdepartmental workflows in preclinical development

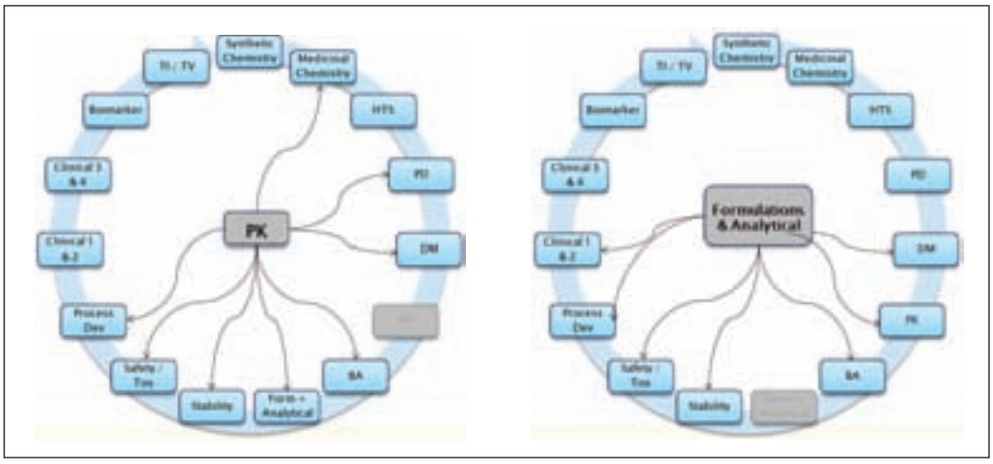
Each department in preclinical development needs to be supported by efficient data capture and knowledge management, to enable information and results to be used in project teams and regulatory documentation. A successful Investigational New Drug (IND) application requires a large range of department level solutions, each delivering specific elements of data and interpretation (see **Figure 1**). Each discipline needs to be supported, and each has different requirements of what an ELN must do and how it should work, for example:

- Formulations need to capture the design of batches, processes and dosage forms, calculations, test results and batch records, and deliver cross-domain reports to project teams.
- Analytical groups need to manage requests for testing, capture method development and validation details, integrate with clinical data systems (CDS) and laboratory informatics management systems (LIMS), and provide structured data capture and reporting of results.
- Pharmacokinetics (PK) need to manage studies, co-ordinate dosing and sample collection, integrate with instruments, import and manipulate data, provide summary analysis and integrate with domain tools such as WinNonlin®.

At the R&D macro level, using the same ELN platform for each area means that departmental solutions can combine to form a comprehensive view of compound/biologic progression. It also enables each discipline to see not only their own data, but also the relevant information from other departments. With Enterprise ELNs, both the capture and viewing of data can be tailored towards each user, based on their specific department/domain needs (see **Figure 2**). For example, a formulator looks at results from a batch perspective, but a bioanalyst who conducts the work sees the data from a worksheet and test perspective. This means that the concept of good data management is of paramount importance. Systems must consider the consumption of data as well as the capture, as data use is often aligned with the working practices of other groups. This fact alone is responsible for limiting the impact of new systems that only provide an ELN to a single domain and focus on replicating a paper system.

Careful review is required in assessing what data is to be promoted to management oversight level and what remains a departmental view, with consideration also given to differences in terminology[3]. The resulting executive-level view improves research oversight and portfolio management by giving an integrated up-to-the-minute view of all research activities.

Figure 2
Each preclinical department should be able to view, from its own perspective, data from many different groups across the organisation; in this case, formulations and analytical have a different but overlapping data landscape to pharmacokinetics



Supporting bioprocess

While the specific techniques used in the development of small and large molecule drugs are very different, the need to capture data and the associated analysis, interpretation and reports is the same. The increasing use of laboratory automation around purification and analytical techniques is resulting in a data explosion – similar to that experienced in the small molecule world over the last few decades. Labs are generating much more data than previously, and with the advent of new techniques such as next generation sequencing and protein mass spectrometry, the rate of growth is also unprecedented. This evolution and 'data deluge' only heightens the need for data management solutions to help scientists protect and leverage corporate knowledge.

Fundamentally, bioprocess organisations develop and implement cell, production and purification platforms. The data and knowledge cascade required to develop these platforms is dependent on many different domains being linked together and each domain having a specific view of that data: precisely the same high level requirement as small molecule development. The precise techniques, data types and science in biologics drug development such as molecular biology, cell line manipulation, fermentation, purification and formulations are all quite different to the small molecule domains. However, the collaboration, development and validation practices, regulatory oversight and the existence of data providers and consumers are identical. This means therefore that the foundation to support these practices can be the same – scientific information being preserved in an Enterprise ELN as part of the company's knowledge base[4].

There is a further implication for pharmaceutical companies developing both small and large molecules. For an Enterprise ELN to be capable of supporting both macro domains, consistent data management, analysis, reporting and validation approaches are required, which can simplify and streamline interactions with regulatory bodies, potentially reducing the total cost of ownership and maintenance of the system.

Table 1: Summary of key requirements for Enterprise ELNs

Scientific adaptability – support for study design with flexible protocol templates across many domains	Protocol templates need flexibility to support multiple, domain-specific design configurations. For example, *in vivo* protocols need to dynamically support multiple treatment regimes, randomise subject allocation to treatment, and add additional observation points or sampling times during the course of a study. Formulation requires the ability to easily vary excipient composition, process parameters and number of samples taken for in-process analyses. Modification of the design during the lifetime of a study should dynamically update associated calculations and analysis methods, as well as report structure.
Good data management – flexible views and data interrogation	An Enterprise ELN must be a full data management solution, ensuring that data is not held in static documents, but in a relational database specifically designed to take scientific data and support subsequent cross-experimental searching and data collation. In this way data consolidation and analysis across different projects and studies is automated for rapid reporting. This eliminates a tedious and lengthy process for the scientist and improves quality by reducing transcription errors. Multiple data views are essential to allow the researcher to easily pivot data without having to make changes to individual cells in nested Excel® worksheets. Viewing and interrogation is also part of the study reporting process, so the scientist needs to be able to report his or her findings easily.
Electronic signatures and validation support	Integrated and industry accepted electronic sign-off and witnessing (eg SAFE BioPharma[6]) are essential, and the ELN should also be a compliant system that can be validated without putting unnecessary complications and compliance overheads on the scientists. A granular security model is needed to allow multiple authors to contribute to a study. This must be done in an auditable and controllable manner.
Managing method libraries	Task flow and flexible multiple step experimental process control is required to support study execution, especially when working on projects requiring contribution from multiple scientists, often in separate departments or even locales. For example, the development of analytical methods requires great flexibility in an ELN; it also requires structured data entry once methods are validated for the lab. Capturing deviations and controlling vocabulary at the point of entry reduces error rates and makes support of regulatory workflows feasible.
Open and extensible architecture – integration with LIMS, instruments, statistics and analysis	Communication with laboratory equipment and LIMS is essential to enable sample orientated data to be automatically brought into the ELN environment. Access to compound registration systems, animal management systems and other internal data is also important. Enterprise ELNs must be developed using an open, industry standard platform and provide documented APIs and a modern web services framework to allow customers to easily add extensions and custom components, and to facilitate integration with other enterprise systems. This provides scientists with greater autonomy in the design and execution of experiments, and greater confidence in the results. This should not require any cut and paste or manual data transcription.
Collaboration	To ensure internal groups can effectively share information, an Enterprise ELN needs to support multiple teams working together on matrix projects, with suitable hierarchies and security restrictions. In addition, the system should be able to support sharing of data with contract research organisations (CROs) to enable new data to be uploaded directly into the appropriate projects using consistent data capture procedures. The growth in globalisation and outsourcing has required Enterprise ELNs to support collaborative environments where an ecosystem of CROs and internal groups are working together.

A foundation for quality by design

The growth in interest and application of Quality by Design (QbD) in the pharmaceutical industry requires a more systematic approach to achieving quality, and characterising acceptable variations in manufacturing processes[5]. This brings a different approach to regulatory submissions and manufacturing flexibility, but fundamentally necessitates a good data management approach to all data from the earliest stages of development.

Much of the preclinical and early development environment uses paper and electronic reporting, with tabular data embedded in flat documents. This makes accessing relevant data from the typical document store very difficult, and limits reusability because it cannot be searched and extracted in a structured manner. Relying on these flat documents, which lack any data management foundations, as systems to support QbD is therefore challenging. However, the use of Enterprise ELNs in preclinical development enables each study/project, be it in stability, analytical or bioanalysis, to be easily retrieved at any time for:

- Assessment of current project design
- Use in regulatory submissions
- Analysis of post market issues

This enables Enterprise ELNs to form a foundation to support QbD, by providing the data and

knowledge management backbone across preclinical development, and bring significant benefits by:

- Improving data quality – by reducing and potentially removing the risk of transcription errors from paper binders, instruments and Excel® spreadsheets, the quality of data is improved and ensures there is a time-stamped, electronically signed record of all data and IP generated.
- Supporting knowledge reuse – scientists can reduce the time spent repeating studies by having a single point of access to a knowledge base that is searchable and retrievable.
- Supporting knowledge mining – allowing past data to be mined effectively enables predictive models to be built and multivariant analyses to be run, to characterise the variables with significant impact and requiring more analysis.

Key capabilities in enterprise ELNs

Enterprise ELNs are differentiated from earlier generations of ELNs by their data management orientated approach. Having a properly architected ELN, based on good data management practices, brings many benefits in terms of searchability and scalability, and moves the ELN from a simple patent IP capture tool to the portal environment in which scientists spend most of their time working. Some of the key capabilities for Enterprise ELNs are described in the following section and **Table 1**.

ELNs and regulatory compliance – review by exception

When ELNs are used in a regulatory environment, the capabilities required and implications of deployment change significantly. Enterprise ELNs must support the deployment requirements of good laboratory and manufacturing practice (GLP and GMP), with system audit trails, version control, process enforcement, real time data validation and e-signatures. When working in a GLP/GMP environment, an important function is to enforce and monitor compliance to Standard Operating Procedures (SOPs). The ability of an ELN to provide easily configurable, structured forms/templates that ensure user data capture conforms to specific business rules is fundamental. However, even with a GxP environment, there are exceptions to the rules, and when they occur it is important that the ELN not be prescriptive, but rather allow a user to complete a task with comments, and track such deviation for future reference and reporting. This approach improves data quality but remains flexible, by ensuring data was captured correctly at its source, and that any deviations are tracked in a searchable manner.

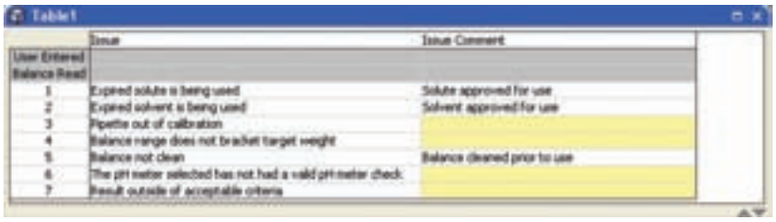


Figure 3
Exceptions can be used to provide QA teams with reports and alerts of deviations from SOPs, replacing paper log books and reducing the burden of regulatory compliance. The image shows a series of bioanalysis issues captured using IDBS E-WorkBook

At any point, a Quality Assurance (QA) reviewer or auditor should be able to generate a report on all process deviations or exceptions with a given scope of work – a notion called 'Review by Exception'. Such reports document all process exceptions and user comments, and provide links or references to the relevant experiment or record. Thus QA personnel no longer have to review all notebook content and associated paper binders for compliance, and instead only need to focus on documented exceptions. This significantly expedites the QA process and reduces the cycle time for study completion and issuing of reviewed reports.

Reuse of corporate data

The complexity of the preclinical and early development formulations process, for small and large molecules, means there is considerable difficulty in finding information on historical data. This means that the sample questions below are often difficult and time-consuming to answer:

- I need particle size and density data for each formulation containing API (Compound 1234, batches 01, 02, 03).
- I want to compare content uniformity and impurity data for all formulations using excipient X, Y and Z.
- Get me all instances of protein degradation and their associated excipient selection, responses and analytical method/instrument selection.

To answer these types of question, the ELN must have a combination of good data management and powerful search capabilities providing enhanced visibility of all past data around formulations, their analysis, excipients, PK and stability. By capturing and storing all data, corporate knowledge is fully searchable, promoting reuse of high value knowledge and enabling better risk-based decisions.

Report generation and regulatory validation

Once the cycle of formulations, PK and analytical

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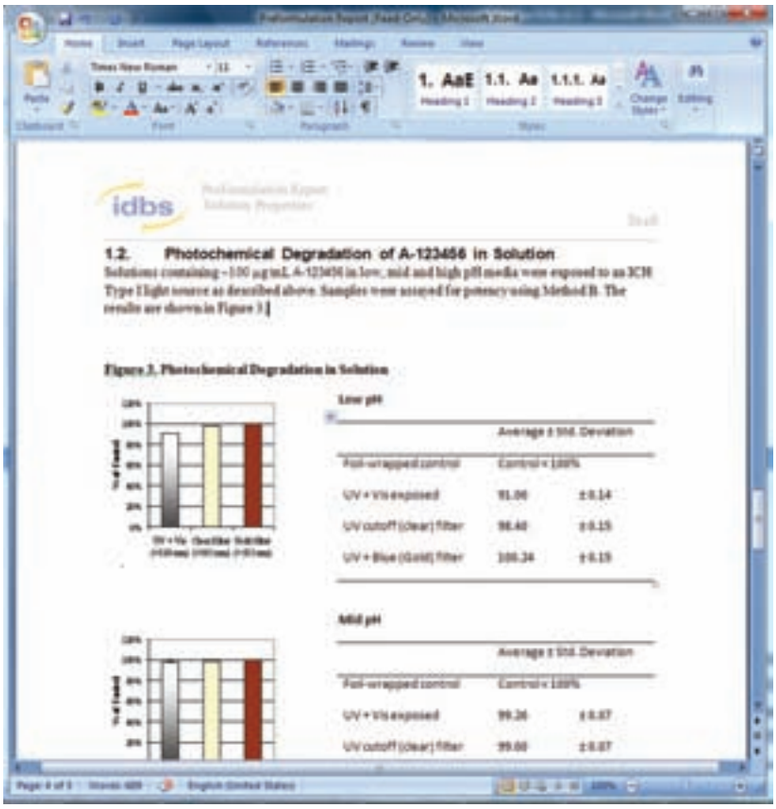

Figure 4
ELN data in Microsoft® Word can deliver study and regulatory documentation with robust and streamlined QA and auditing. Report generated using IDBS E-WorkBook

testing is complete, study reports and eventually regulatory submissions need to be prepared. It is common for the data to be distributed across multiple data sources, storing structured results and scientific interpretations. A challenge for all groups is bringing this information together and then validating that the content of a report is accurate and no transcription errors have occurred. Report content can take weeks to prepare and many more weeks to validate because everything needs to be checked across different departments against multiple electronic and paper-based systems. Researchers want, and generally need, to write reports in Microsoft® Word, so the Enterprise ELN must allow researchers to develop report templates that can automatically populate documents used throughout development, from study reports to regulatory submissions.

These validation and study reports need to be generated as far as possible automatically, using digitally signed experimental data with the reports having active hyperlinks back to the source data captured in the ELN to streamline report validation and QA. Consolidation of data to a single authoritative source allows simpler real time checking and validation of data, resulting in fully prepared, QA and validated reports in days or weeks instead of months – a significant breakthrough in efficiency for preclinical scientific and quality groups.

Conclusion

Many companies are now recognising that using ELNs as purely paper-based replacements means they are missing out on strategic long term benefits, and are now integrating LIMS and legacy ELNs with those that provide data- and context-centric architectures. The growth in use of ELNs in preclinical environments has resulted in major advances in functionality that are allowing them to become the *de facto* standard for data management and corporate knowledge capture. By employing these capabilities organisations can streamline the preclinical development, provide a foundation for QbD and reduce the burden of regulatory compliance.

Acknowledgements

Thanks to Jeff LoCascio, Chris Molloy and others at IDBS for sharing their thoughts on this area. DDW

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