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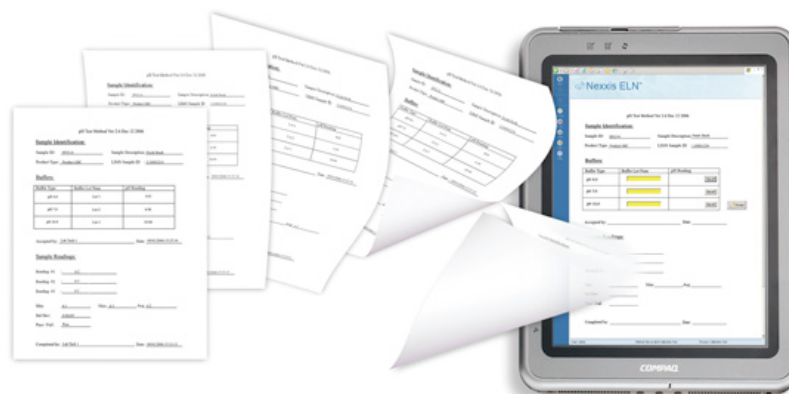
ELN

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Creating and archiving electronic records is riddled with difficulties. *Clare Sansom* investigates how the pharmaceutical industry is coping with these changes



ABOVE: Labtronics' Nexxis ELN employs a classic web-based architecture.

Despite the enormous growth in our understanding of molecular biology that has stemmed from genome projects and other 'omics technologies, the drug discovery process still generally takes well over a decade 'from bench to bedside'. A company embarking on a novel discovery programme in 2008 cannot expect to be taking the resulting candidate drugs through Phase III clinical trials until the late 2010s at the earliest. For the pharmaceutical industry, therefore, planning for the long term must be a priority. And this can seem a particular challenge when it is compared with the pace of change in computer applications, even simple ones. Will a document written in Word 2007 still be readable in 2020, for instance?

This may seem a trivial example, but scientific record keeping is far from a trivial issue. Chemists and biologists in the pharmaceutical industry are replacing old paper systems with electronic lab notebooks (ELNs). The advantages of these, in terms of reliability, reproducibility, and standardisation, can be immense, but the companies must make careful choices if they are to ensure that these applications, and the trail of records that they produce, are future-proof.

Companies must ensure that records keep their fidelity for regulatory submissions and to protect their intellectual property in the law courts. Fortunately, software companies in this field have so far been able to keep one step ahead, giving companies the confidence that the notebooks they select today will serve them well throughout and beyond the design cycle of what they hope will be their next blockbuster drug.

'Top five' pharmaceutical giant Pfizer chose IDBS' notebook systems two

years ago, beginning with a pilot project throughout Pfizer Global R&D. IDBS' product range includes: the simple, generic E-WorkBook; ChemBook, which includes additional chemical functionality; and BioBook, which includes an interface to molecular biology experiments. 'Currently we have 300 E-WorkBook users and 100 BioBook users, but we are aiming to deploy these products to all discovery biologists worldwide', says Graham Baker, associate director of primary pharmacology at Pfizer in Sandwich, UK.

Pfizer were already using a laboratory information management system (LIMS) before they adopted BioBook. 'We found that a LIMS wasn't flexible enough to cover the diverse needs of non-plate based biology, ranging from molecular biology to traditional pharmacology', says Baker. 'We needed a product that would allow our biologists to do data analysis in a Word-type environment: "MS Office for biologists". Another important requirement was for something that our users could work for themselves, without calling on computer experts or systems administrators,' he added.

After the initial pilot, Pfizer's senior scientists concluded that although BioBook was, indeed, a very strong contender, it fell short in a few areas, and recommended only conditional acceptance. 'Our outstanding issues with deploying the product concerned support and training as well as functionality. BioBook's relational spreadsheets are extremely powerful as analysis tools, but they are very much more complex to use than, say, Microsoft Excel. Our experience showed us that many users could develop templates, but that we needed a more comprehensive training and support package to accelerate them along the learning curve,' says Baker. Pfizer is working on these issues with IDBS, and version 7.0 of the software, released earlier in 2007, will be rolled out across the company nationwide.

These comparisons of ELN functionality with Microsoft Office underline the need for such software to be version independent if it is to stand a chance of outliving the design cycle of a typical drug. Andrew Pitt from the information and records management team mentions that 'eight or nine years ago we stopped accepting data on floppies, CDs or DVDs and moved to a fully server-based storage system to reduce the risk posed by media obsolescence.'

All IDBS' electronic notebook products, including BioBook, produce records in PDF format with the 'SAFE signature' option. Pfizer has already generated more than 10,000 of these globally, in its chemistry ELN, and they are archived with scanned pages from the paper notebooks that the ELNs replaced. However, the company has not yet adopted a single standard for archiving. 'We are working on this problem, but we should remember that this is a generic problem for all industries, not just for pharma. ISO needs to be involved; there is an ISO standard for long-term PDF storage of electronic documents,' says Pitt.

Swedish company Biovitrum, founded in 2001, is at the other end of the industry spectrum from Pfizer. It is a small biopharma company with 500 employees. Yet its needs for electronic lab management, documentation and archiving are not dissimilar from those of the giant companies. It has chosen a

hybrid solution, using an ELN from Contur but archiving secure records on paper using Amphora's PatentPad. The relationship between Biovitrum and Contur is an interesting one, as Ludvig Moberg, a senior scientist at Biovitrum, explains: 'When we were looking for a new ELN system, back in 2002, we couldn't find a commercial product that met all our requirements fully. We contracted Contur to build a system for us; after they had delivered it, they realised that it had more generic applications and began marketing it elsewhere.' Contur's customers range from speciality chemical companies such as Johnson Matthey, and biotechs including Affibody and ACE BioSciences, to the public sector: the University of Edinburgh has recently implemented ConturELN in its prestigious new Cancer Research Centre.

Contur's electronic lab notebook can be implemented across the entire R&D department and enables scientists to record text, images, Microsoft Office documents and data in many formats. The final experiment record is stored and archived in PDF format along with author and witness digital signatures. Original files are also stored in multiple formats.

'We do work with Microsoft Office, as that is the dominant office-based application,' says Contur's Thomas Rozlucki. 'But we readily recognise that we need to work round its limitations. If you want to read an Excel spreadsheet generated today in 10 years' time, you will need to have Excel on your desktop, and it will need to be able to read files produced by today's version. Microsoft's products are historically poor at 'backwards compatibility' and a fully-featured ELN like ours shouldn't depend on commercial applications. We use generic formats where possible and provide alternatives where necessary. Take Excel – ConturELN stores platform independent JPEG and text versions of the data as well as the original spreadsheets.'

Rozlucki believes that the solution to future-proofing both electronic notebooks and the records they produce will be procedural as well as technical. 'ELN technology offers a certain amount of future-proofing, but companies also need to have firm policies and procedures in place to determine how their data should be archived, transferred and stored. They need to minimise the chances of human error of, for example, data held on a central server being deleted by mistake. And it is all too easy for a small company, in particular, to become dependent on one systems manager who is bound to leave one day.'

Moberg explains further that PatentPad, from Amphora Research Systems, provides them with a straightforward and secure paper-based method of archiving the experimental records that are generated in their ELN. 'Had we been developing our archiving system now, rather than five years ago, we would probably have gone for a fully electronic version, but these products weren't mature enough for us to consider then. We are looking into using digital signatures with PatentPad papers as the next step towards a fully electronic system.'

Advanced Chemistry Development (ACD/labs), based in Ontario, Canada, is a company that specialises in providing software for analytical chemists. 'Over the last 10 years, analytical chemistry within drug discovery has gone from

being a centralised Analytical Department to something that almost all chemists are expected to do for themselves on Open Access Analytical Instrumentation,' says Andrew Anderson, director of channel partnership and western US Sales for ACD/Labs. 'Historically, chemists would literally "cut and paste" output from analytical instruments, such as NMR spectrometers, into their paper notebooks, and used this as the legal basis for proving their compounds' structure and purity. We can provide an electronic equivalent, integrating analytical reports into an ELN.'

Modern pharmaceutical companies collect chemical and biological data from a wide range of apparatus, and almost inevitably they will have a variety of vendor-specific interfaces to them. It is always a challenge to integrate these together and into a notebook product. A standard, XML-based format for NMR spectroscopy data files, developed through the JCAMP initiative, is now widely used. Using this, it is possible for software companies such as ACD/Labs to integrate NMR data into their ELNs and make it fully searchable.

Looking ahead 10 to 15 years, Anderson sees that the ever-increasing complexity of analytical techniques used will generate an increasing variety of complex datasets. It will be a continuing challenge to integrate these into a single notebook environment, particularly as instrument vendors change their file formats from time to time. Furthermore, the 'discovery' and 'development' phases of a pharmaceutical project use slightly different types of analysis. The regulatory agencies, the FDA and EMEA, require data for the validation of drugs in late phase clinical trials that is not generated in discovery chemistry. 'If an impurity that hasn't been seen during the development phase comes up during Phase III trials, a project team might want to go back and look at data generated in earlier synthetic lots, maybe even back into discovery,' he says. 'This will typically be from different equipment from that used later, and also from tests made well over five years ago. A well-designed ELN can make this easier by integrating all types of output data together, but making sure the software remains future-proof is going to be difficult.'

Another product aimed largely at the quality assurance market is Nexxis ELN, produced by Labtronics. 'Our key customers are in QA labs, although we also have some in R&D,' says Tom Curtis, vice president of product innovation. 'We work anywhere where there is a regular experimental routine; our system has huge efficiency benefits over paper-based systems in managing this routine.'

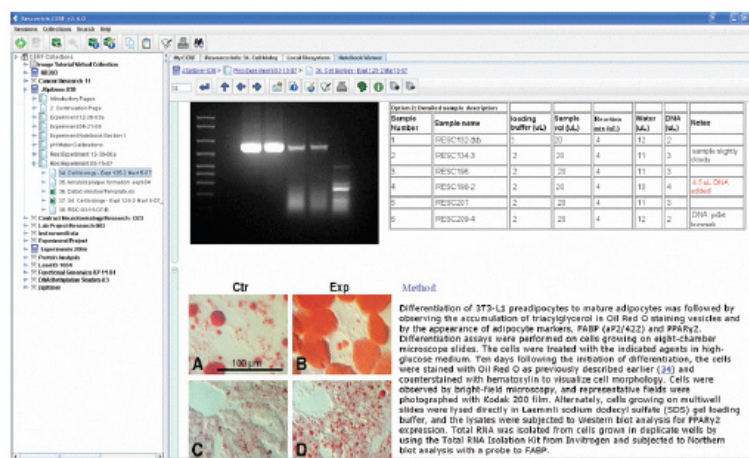
Curtis sees that one of Nexxis' advantages is its flexibility, as different levels of automation can be built into the system depending on customer need. If required, it can be configured to only allow experiments to proceed if certain checks have been made, only allowing progress if, for example, a balance has been calibrated and if its operator has been authorised to perform that particular experiment.

Nexxis employs a classic web-based architecture. 'This provides a degree of future-proofing to our application,' says Labtronics' marketing specialist Steve Bolton. 'For the foreseeable future, we see technology developments evolving from the current core standards of web architecture.'

Chemists looking for a notebook to integrate with cheminformatics may be considering Kalabie. This ELN was originally produced by the Klee Group, which was acquired in summer 2007 by Agilent Technologies. 'We bolt proprietary chemical cartridge software from companies such as MDL, Accelrys and ChemAxon on to Kalabie,' says Agilent's Alain Meller. 'Therefore, a company wishing to adopt an ELN need not walk away from their existing cheminformatics choices. Conversely, they are not forced to put all their eggs in one basket; they can pick an ELN outside their cheminformatics provider portfolio. Kalabie promotes an open architecture where clients can choose the best-of-breed products for the everyday work environment of their most valuable personnel.'

This 'bolt-on' approach is also useful to cheminformatics companies, who often work with many partners. ChemAxon is currently working with 35 partners, including ELN companies Contur and Rescentris. 'We focus on developing functionality so our partners and their users can rely on the cheminformatics remaining relevant,' says ChemAxon's marketing director, Alex Allardyce. 'Our Java-based delivery is straightforward for third parties to use.'

Rescentris, based in Columbus, Ohio, has developed an ELN specifically for interdisciplinary bioscience research, which future-proofs intellectual property and research data produced by academic institutes, government labs, and biotech. Their flagship product, CERF, the Collaborative Electronic Research Framework, won Best in Show from Bio-IT World 2007 in Boston, Massachusetts. 'CERF has been very successful in the academic research environments because it was designed as an open platform, built on XML standards, and can easily adapt to scientific workflows, data capture, and flexible record keeping,' says Eric Rentschler, Rescentris' senior sales lead.



ABOVE: The CERF electronic laboratory notebook from Rescentris is a fully functional data and content management system.

Biotech companies have taken to CERF because the Rescentris ELN is a fully functional scientific data and content management system. 'Biologists want to perform a wide range of tasks and operations during their working day and CERF's scientific content management support makes it possible,' says

Rentschler. One such company is Primorigen. 'As a start-up biotech company, complete and searchable records of our experiments are critical for our company's future success. CERF meets these needs in a user-friendly manner,' says operations manager Jennifer Fronczak. Unusually, CERF is platform independent, with both server and client applications running on both Mac platforms and Windows-based PCs. Rentschler adds: 'Many of our academic customers, in particular, work in Mac-only environments, and we want to be able to support them as well as possible.'

The ELN market in 2007 is a healthy one, with a wide range of products for companies to choose from. The companies involved are thinking carefully about how their products can be maintained throughout at least the decade or so that is the life cycle of a drug development project, and have largely come up with the same solutions: platform independence, adherence to accepted standards, and a reliance on common file and data formats, particularly PDF and XML. But the industry is urged not to rely on technology alone to future-proof their pipelines: good management practice has been shown to be at least equally important.