IMPLEMENTING AND USING AN ELN IN VALIDATED ENVIRONMENTS

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John Leonard
Principal Scientist, Pharmaceutical Development
AstraZeneca

-One of the primary challenges in implementing an electronic lab notebook (ELN) is getting buy-in from the myriad stakeholders who interact with the experimental data being recorded. Nowhere is this challenge more pronounced than in validated environments such as analytical GxP testing and GMP manufacturing. In these areas, the need to comply with strict regulatory mandates about how methods, processes, and testing are documented and validated has led to even stricter internal controls that are codified in entrenched, paper-based workflows.

But the reality is that paper is more of a habit than a requirement. Groups at Bristol-Myers Squibb Business Services Limited and AstraZeneca discovered this when they aimed to introduce ELNs to improve the efficiency of their validated workflows for, respectively, GxP analytical R&D and GMP API (active pharmaceutical ingredient) manufacture. In both organizations, paper and its associated workflows were standard only because they were familiar and had been defined over time to meet the needs of scientists, process engineers, and quality control and assurance staffs.

When we first approached quality about introducing an ELN, we were told ‘ELNs were not designed as tools for GMP manufacture,’” said John Leonard, principal scientist, pharmaceutical development at AstraZeneca. “But the truth is, paper notebooks weren’t designed for this either—they were adapted to this purpose by scientists, quality assurance personnel, and compliance experts. It was this realization that motivated all of our stakeholders to collapse our paper paradigms and embrace new electronic ones that would allow seamless transfer of process information through all stages of R&D and ultimately to commercial manufacture.”

Leonard and Adele Patterson, senior research investigator at BMS, each delivered talks on their experiences implementing Symyx Notebook by Accelrys in validated environments at Symyx Symposium 2010 in Barcelona. This article is based on their presentations.

-Bristol-Myers Squibb Business Services Limited defined fully electronic processes for analytical GxP testing

-AstraZeneca eliminated paper-based workflows for GMP API manufacturing

-Refined processes improved overall quality assurance and compliance at both companies

-AstraZeneca observed a greater than 50% time savings on documentation—fewer documents produced, at higher quality
BUILDING SUCCESS THROUGH INTERNAL/EXTERNAL PARTNERSHIPS

To embrace the new electronic paradigms described by Leonard, the BMS and AstraZeneca teams had to not only convince internal stakeholders of the benefits of electronic over paper, but also select a system and a vendor with the potential to evolve an ELN that would successfully manage data in a validated environment. Both teams began looking at systems in the early 2000s, when most ELNs were deployed mainly in discovery chemistry. And neither group expected to find a system that would meet their needs right away. BMS, in fact, began by deploying two systems. “We initially brought in the Velquest ELN for routine GxP analytical testing and used Symyx Notebook by Accelrys for everything else, including non-routine GxP analysis,” said Patterson.

Leonard explained that the ability to develop a system that would help AstraZeneca bridge the divide between R&D and GMP manufacture led the organization to adopt an early version of Symyx Notebook by Accelrys in 2004. “We saw a lot of potential in that system and a real partner in Accelrys,” Leonard said. Leonard explained that the outcomes of the partnership benefitted both his company and the vendor. In getting the system it wanted, AstraZeneca was able to pass a lot of knowledge back to the vendor development team—knowledge that has since been reflected in the 6.5 release of Symyx Notebook by Accelrys.

AstraZeneca knew its primary goal in implementing an ELN: allowing seamless transfer of process information through all stages of R&D to commercial manufacture. An ELN would eliminate transcription between different document types: from process chemistry ELN records to templated Word-based process description recipes; from printed process descriptions to paper notebook-based batch records for early manufacture campaigns; and back to templated Word documents for batch and campaign reports. Envisioning the solution at the outset, however, was difficult.
you have to take a deep breath and step back to determine which steps are really value-added—what is the purpose of a particular step. Our assessment gave us the time to do this analysis and convince all of the stakeholders that we had the right processes in place to stay compliant.”

ASSESSING GxP REQUIREMENTS FOR ANALYTICAL R&D

The most frustrating assumption that Patterson and her team had to refute was scientists wanting to completely reproduce paper notebooks electronically, an approach that she referred to as paper on glass. Debunking this assumption required the team to step back from how things were being done on paper in order to determine the true requirements in various GMP areas. Once these were defined, the team could begin to develop electronic processes that would be followed during the pilot. Table 1 outlines the assessments BMS made in each area.

Table 1: BMS Paper-based and Electronic Requirements for GxP

<table>
<thead>
<tr>
<th>GxP Functionality</th>
<th>Requirements</th>
<th>Paper Process</th>
<th>Electronic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Controlled/centralized</td>
<td>Fully traceable book allocation with the unique identifier tracked centrally.</td>
<td>Similar to paper system. Electronic request form is completed by the author, who receives a unique book number.</td>
</tr>
<tr>
<td></td>
<td>Unique identifiers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Security</td>
<td>Attribute actions to a given author or reviewer. Ensure appropriate access rights, backup/archival, and disaster recovery</td>
<td>Authors sign and date against all entries within the book. Authors seek appropriate reviews and signatures. Physical notebooks stored in fire proof/secure locations. Microfilmed on completion or two yrs from issue, whichever comes first.</td>
<td>Check in/check out and secure log in provide author traceability. Audit trail based on versioning. All versions retained. E-signature/e-workflow used to track/record data review. Individual records archived on completion. Daily backups.</td>
</tr>
<tr>
<td>Data entry</td>
<td>Secure Traceable Accurate Contemporary</td>
<td>Authors sign and date against all entries within the book. Handwritten records and cut and paste from instrumentation with annotations as required.</td>
<td>Secure access to system (read-access only for non-authors). Un-editable, configurable time/date stamps. Manual or electronic annotations used where necessary.</td>
</tr>
<tr>
<td>Attachments/inserts</td>
<td>Traceable Legible</td>
<td>Cut and pasted into notebook</td>
<td>Directly included in ELN through import functionality.</td>
</tr>
<tr>
<td>Corrections</td>
<td>Who made them? What was changed? Why was it changed? When was it changed?</td>
<td>Put line through it, sign and date, add reason.</td>
<td>Procedural controls define process for edits (changes with scientific effect vs. “textual edits” or typos that don’t impact science). Audit trail tracks who made the changes using un-editable, time/date stamps.</td>
</tr>
<tr>
<td>Cross referencing</td>
<td>Enable researchers to build on colleagues’ work</td>
<td>Book/page references</td>
<td>Two-way electronic handshakes (associations) tie data together</td>
</tr>
<tr>
<td>Signing</td>
<td>Final step in validation</td>
<td>Author provides reviewer with all relevant pages, procedural controls around timings.</td>
<td>E-workflow in place to notify authors/reviewers of actions required. Procedural controls track timing.</td>
</tr>
</tbody>
</table>
we had to find a way to distinguish between typos and changes that actually impact the science conducted." Patterson explained as well that BMS put in place processes to ensure that all requirements would continue to be reviewed as more users were brought on board and additional software functionality becomes available. "It's important to acknowledge that the implementation and procedural control of an ELN is going to be an iterative process, subject to frequent reviews and revisions," said Patterson.

THE STAGE NOTEBOOK: A REPOSITORY FOR MANUFACTURING RECORDS

Like BMS, AstraZeneca reconsidered every aspect of technology transfer in transitioning from paper-based processes to electronic ones. Figure 1 depicts the overall workflow that AstraZeneca follows to transfer processes from synthetic chemistry R&D through manufacturing. When the e-batch records project started, managers proposed that perhaps a single "method of manufacture" document could be used to describe all manufacturing requirements. But Leonard’s team realized that this proposal was based on paper metaphors and, in fact, created a workflow bottleneck.

"In the electronic world, you don't need one document," said Leonard. "All the records created to describe a process can be collected together in a single folder, where they can be easily found and referenced. This was the breakthrough—realizing the value of Symyx Notebook by Accelrys as a central point for managing and distributing records and making it a key element of our GMP system made our workflow more logical and efficient."

The core of AstraZeneca's workflow is supported by a simple folder structure that contains all manufacturing documents, including non-ELN (Word, Excel, etc.) files. Each manufacturing campaign has a separate folder containing an individual stage notebook for each stage of the campaign.

Overall Workflow for Manufacture

Figure 1: AstraZeneca's overall manufacturing workflow requires the transfer of experimental and analytical data to process chemistry. Rather than trying to develop a single document to encompass all of this information, AstraZeneca used a single folder—the stage notebook—to keep all the relevant documents in one place.
The stage notebook is a repository that comprises

- **The process description.** This is created in the stage notebook by the process R&D chemist, usually from a clone of an experimental procedure carried out in the laboratory. The process description is improved by developmental manufacturing chemists and contains comments, observations, and hold points. An electronic approval workflow allows a line manager to approve the process description.

- **The master batch record.** This is initially prepared by cloning the process description. Check-in points, which provide audit trail points during manufacturing, are added at important processing steps and at the conclusion of each significant set of unit operations. The final master batch record is again approved by e-signature to create a permanent pre-manufacture version in the audit trail.

- **Individual batch records.** These documents are cloned from the master batch record. Material amounts are scaled to the required batch size and populated automatically by the ELN, which ensures accuracy and provides a considerable time savings compared with manual methods. The procedure section is simply annotated as the batch is manufactured, and actual amounts, deviations, and minor process excursions are updated as necessary. Once the batch is completed, final comments and learning points are added to the document, which is finally checked in for review and approved by line and quality assurance managers.

Symyx Notebook by Accelrys provides the validated, fully compliant environment containing robust, timed audit trails for storage of all manufacturing documents. AstraZeneca has also developed procedures to control the use of documents outside the validated environment. At the end of all the document workflows, publication provides a permanent, visible version of the documents in a centralized and easily accessible location.

**THE PROOF IS IN THE PILOT**

Both AstraZeneca and BMS ran extensive pilots to evaluate and confirm the functionality of Symyx Notebook by Accelrys, verify the efficiency of their workflows and procedural controls, and identify areas to refine. The analytical R&D pilot program at BMS was rolled out to 18 users at one BMS site in the United Kingdom. Stakeholders from analytical R&D, informatics QA, and global quality and regulatory compliance (GQRC) participated in the 10-week pilot. Several testing types were included in the pilot, such as release, investigational new drug (IND) stability, method development/validation, investigations, and formulation support. Testers accumulated 130 records and GQRC reviewed 24 documents during the course of the pilot.

According to Patterson, most of the concerns raised during the pilot were addressed by conducting additional targeted training or by revising and clarifying specific sections of the SOP. For instance, the team had to clarify the process for corrections and the order of reviewer approval. The pilot and early implementation of the ELN demonstrated the flexibility of Symyx Notebook by Accelrys. That, combined with the established procedural controls, began to blur the line between the Velquest system and Symyx Notebook by Accelrys. “Where each system was being used became a little less cut and dried,” said Patterson. “We are now using both ELNs for GxP analysis.”

AstraZeneca conducted extensive GMP trials over a one-year period. Metrics collected during the trial showed that the e-batch record system was considerably more efficient than the previous paper-based system. “We observed a greater than 50% time savings on documentation, mainly because the use of the stage notebook actually reduced the number of manufacturing documents produced,” Leonard reported. “Moreover, the overall quality of the documents was much improved over paper-based methods.”
Compliance and quality audits were also carried out by AstraZeneca’s R&D and operations QA groups. Leonard noted that the independent audit concluded that the system was “overall acceptable with regard to compliance.” The R&D QA group was particularly pleased with the transparency of the documentation, which made the QA assessment easy to conduct and helped process chemistry gain more insight into manufacturing processes.

Issues raised during the pilots led AstraZeneca to make broad revisions in how it approached previous practices for data integrity. An existing internal guideline for recording raw data was judged to be out of line with a modern external risk assessment-based guidance. The revision ensures that a conscious decision is made to commit a revision or change to a record, which is associated with a required audit trail event. The pilot also revealed some inadequacies in how previous versions of the ELN prevented changes in existing data during batch record updates. AstraZeneca addressed this issue by putting in place clear procedures and guidelines to minimize risk. Additionally, the company drew up a system improvement plan with Symyx to ensure that future versions of Symyx Notebook by Accelrys enabled “lockdown” of text sections in batch records. “The vendor was fully willing to collaborate to address our concerns,” said Leonard. “And we plan to share our conclusions with other pharma companies in order to establish cross-industry standards in this area.”

Some of the questions raised by AstraZeneca’s QA group during the trials helped drive more efficient working practices together with better quality procedures that could be harmonized across manufacturing sites. Additional efficiency benefits were derived by removing non-value adding procedures, and quality management was enhanced by clarifying the purpose and requirements for such things as in-process tests and controls. “The QA function recognized an opportunity to establish a defined business process for GMP manufacture of clinical trials API as part of a pharmaceutical quality system (PQS), all of which is in line with modern regulatory guidances established by the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use),” said Leonard.

**PARTNERSHIPS = SUCCESS**

Both Patterson and Leonard were adamant that without the input of their organizational colleagues and partners, their ELN implementations would not have succeeded. At AstraZeneca, for instance, assumptions that the e-batch record project was mainly designed to improve the technical efficiency of information transfer between R&D and development manufacturing could have derailed the project, as internal compliance was designed entirely to facilitate paper-based quality control systems. “Reformulating a ‘holistic’ project with improved quality management as a central goal enabled us to develop a positive engagement with QA and compliance representatives,” said Leonard. “Together, we recognized that a structured approach to recording manufacturing processes made it easy to generate a global business process, which the QA function saw as an opportunity to harmonize activities across sites and support PQS.”

“My advice now would be to initiate an e-batch records project with a PQS, business process approach, which is the best way to get all the key stakeholders on board and recognize the universal benefits of the work,” he concluded.

Patterson concurred. “It is really important to get all stakeholders on board early and to discuss remit of the system,” she said. “The challenge is that this work introduces a new paradigm, and many stakeholders initially think you need to generate an exact electronic copy of your paper notebook processes. You don’t—instead, you want to evaluate what is really value added. It’s iterative, and you’ll need a way to continually review the system and implement changes as required.”

To learn more about Symyx Notebook by Accelrys, go to [accelrys.com/eln](http://accelrys.com/eln)