Structuring Data Management for ELN in Formulations

S88 and S95 standards are excellent foundations for building an integrated platform

Pharmaceutical formulation is a complex process matching a composition of active and non-active materials with a method of production to create a safe, effective and manufacturable drug product. This product can undergo many iterations as it progresses from early designs for first-in-human (FIH) studies, to large-scale efficacy and effectiveness trials, and eventually to commercial production. Knowledge learned during the course of clinical trials may require changes to the formulation composition or its manufacturing process, e.g., evolving from a parenteral dosage form acceptable for FIH into a tablet or capsule for Phase III trials. At each stage along the path, the formulator is challenged with analyzing an ever-increasing mountain of data generated from a multitude of sources.

Formulations investment across the pharmaceutical sector is increasing to provide competitive advantages and improve bottom-line results. One reason for the growing attention is pressure from gener-
ics; new approaches are being explored to extend the patentable life of an existing active pharmaceutical ingredient (API). Another is time-to-market — the faster a drug product can be created, the faster FIH studies can begin. Additionally, unresolved issues of poor API solubility and permeability slow down cycle times and often end up on the formulator’s doorstep, requiring complex investigations and unique methodologies. As complexity increases, teams are relied upon to collaborate on solutions, requiring the sharing of data and information on excipients, APIs, and batches of formulated product.

Formulators are faced with data capture, look-up, comparison and visualization of data from a wide-variety of sources:

- characterization data on pilot lots of a drug substance coming out of process chemistry
- solid state screening data from pharmaceutical sciences
- design-of-experiment (DOE) models
- internal department experimental results on different stages of manufacture and compositions
- drug product testing on different lots such as dissolution, experimental stability, content uniformity generated by analytical development
- in vivo bioavailability results from animal studies performed by the pharmacokinetics department
- clinical trials results from clinicians
- Oo-line measurements from process automation technologies in the clinical supply pilot plant
- details on excipients and batch records stored within enterprise resource planning (ERP) systems

Since it is typical that each of the aforementioned departments has their own silo data management tools and processes, the formulator receives data in different formats and file types. For cross-data analysis — e.g., comparison of bioavailability to dissolution across several composition batches — data must be manually transposed to another tool, commonly Excel. Not surprising is that each formulator routinely has their own layout for their Excel templates. Paper lab notebooks are used for storing compositions, process designs, printouts of analyses and results commentary.
Therefore, the current state of independent silos, manual aggregation, formulator-specific spreadsheets and data management methodologies does not lend itself to meeting the objectives of accelerating time-to-market, collaboration, or the re-use of formulations knowledge. It is exceedingly difficult for senior scientists to roll-up data across formulations for materials science investigations. The ad hoc nature of managing process knowledge is at odds with quality by design (QbD) concepts promoted by the FDA. The rapid expansion in the use of contract manufacturing organizations (CMO) necessitates formal and consistent technology transfer packages rather than verbal information hand-offs, which is routine within a single organization.

**ELN AND FORMULATIONS**

The addition of structured data management capabilities to electronic laboratory notebooks (ELN) allows organizations to improve the current state. ELN can act as a library of formulation designs and a repository for assay results generated by the partner laboratories. The collaborative nature of ELN enables sharing and team-based task flow. Through integration, data can be posted to or obtained from other systems in the enterprise — such as an analytical laboratory information management system (LIMS) — increasing both resource efficiency and data quality.

Some ELN vendors offer a relatively simple platform that can be used for basic formulations requirements, while others provide a feature-rich solution suitable from early development through commercialization. For companies with a straightforward, routine and well-defined platform-based development process, simpler solutions may be adequate. Those companies with challenging APIs and formulations who desire a seamless information technology transfer into manufacturing may desire a system with more robust capabilities.

Three examples of solutions are shown in Figures 1-3. The first is an example from Accelrys, where the Pipeline Pilot scientific workflow authoring application is integrated with ELN. In this workflow, a DOE model is created in Pipeline Pilot, which creates multiple experiments in the ELN, each with a slightly different composition. Figure 2 from PerkinElmer shows how ELN can be used to summarize results from multiple experiments, comparing unit operation results. The next screen capture is from IDBS. Here, the
ELN system shows both textual results being displayed with flagging out-of-range results, but also photomicrographs and curves of particle size data. Lastly, Figure 4 highlights the application of Accelrys’ Electronic Batch Record (formerly known as VelQuest Smart-Batch) in downstream clinical supply manufacturing to review formulation batches and flag outliers.

One of the benefits of ELN is its flexibility; this is also one of its negatives. Where the need is to collaborate, compare and analyze formulation batches, letting each researcher continue to manage their spreadsheets as they always have prevents this. Just pasting the same spreadsheet template used before into the ELN (i.e., “paper on glass”) may help the individual organize their work, but does not enable the capabilities highlighted previously.

**S88 AND S95**

To create a common language, automate processes, and to expedite technology transfer from formulations through commercialization, several pharmaceutical companies are turning to the ANSI/ISA-88 and ANSI/ISA-95 standards (commonly referred to as “S88” and “S95,” respectively. See www.isa.org). S88 is a set of standards describing a process model for batch control through an ordered set of procedures, materials, stages, operations and equipment. S95 is a set of standards for the integration of control and enterprise systems. Both have an extensive library of terminology definitions. Though the standards were designed originally for large-scale batch manufacture, many of the concepts and vocabularies can be applied to formulations and ELN.

A key concept in S88 is a recipe analogous to a recipe used in a kitchen. Simply, it is a list of materials combined in a particular order using equipment to make a product. There can be different types of recipes from an early design where the equipment is in flux, to downstream recipes where equipment optimization is more critical. For researchers at the bench, the concept of a recipe can be foreign and take quite a bit of time to grasp. This is especially true in an organization where terminology can vary from person to person. But, once transitioned, they see the benefits of searchability, modularity and simplicity of creating required documentation.

S88 and S95 are easily applied to ELN, and Figure 5 highlights a high-level version of a formulations data model employing the concepts. This structure shows that a drug product is a physical manifestation of a recipe, where a group of materials, both active and non-active (a “formulation”) are processed (“manufacturing process”) with an ordered set of activities (“unit operations”). Unit operations are stages of activities such as blending, deglomeration, granulation, coating, etcetera. A batch of material can be created from a unit operation and may flow into another, eventually creating a packaged lot of a dosage form. This modular method enables the developer to create one formulation and apply different manufacturing processes or vice versa. Each of the objects in the model can be stored in a library for sharing across all scientists and locations.

A sampling of the formulation vocabulary definitions:

- **Formulation**: A description of a group of materials, including the active drug, and their targeted composition within a recipe to make a final product
- **Material**: The specific materials that are used in the production of a batch, including the quantity(s) of each. Reference S95 3.5 "Bill of Material"
- **Recipe**: The necessary set of information that uniquely defines the production requirements for a specific batch of material. It is the application of a specific manufacturing process to a specific formulation. Reference S88 3.48 “Recipe”
- **Manufacturing process**: A defined process that leads to the production of finite quantities of material by subjecting quantities of input materials of a formulation (e.g., excipients, APIs,
process aids) to an ordered set of processing activities over a finite period of time using one or more pieces of equipment. Reference S88 3.7 “Batch Process” Includes the strategy for carrying out a process that is a defined order of one or more Unit Operations. Reference S88 3.37 “Procedure”

• Unit operation: A major processing activity that usually results in chemical or physical change in the material being processed. Reference S88 3.44 “Process Operation”

• Batch: Unique material that is being produced or that has been produced by a single execution of a manufacturing process. An entity that represents the production of material at any manufacturing process stage. Reference S88 3.5 “Batch”

Taking it a step further beyond ELN, the application of these standards enables the creation of data warehouses for a further level of data analysis. Lab-based characterization data on batches of material can be combined with on-line measurements and process parameters. Process optimization is then possible to provide more predictable manufacturing outcomes.

The benefits of the application of S88/S95 are many:

• It is a modular approach enabling ease of changing formulations, manufacturing processes and unit operations.

• Formulations and processes can be templated for consistency across formulators, projects and departments.

• Recipes and modules can be shared for re-use of institutional knowledge.

• Enables ease of technology transfer from formulations into clinical manufacturing or out to a contract manufacturer; designs can flow into electronic batch records.

• Allows for a common terminology across researchers, enhancing communication.

• Ease of access of characterization data for material science analyses

• Supports principles of quality by design

Formulations is a challenging blend of science and art. Traditional methods of individual design and data management will not work in the new era of team science, externalization and pressures on cycle time and efficiency. A structured approach balancing flexibility is offered by current generation ELN, but terminologies and process standardization is needed to move information in a consistent manner. S88 and S95 are excellent foundations for building an integrated ELN platform.

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