JUST. SYSTEMS

Transforming Technology Transfer and Process Definition Management: From Spreadsheets to Standardized Practices

The ISA-S88 Standard for Recipe Representation

ANSI/ISA-88, or S88, is a standard for addressing batch process control and a design philosophy for software, equipment and procedures in batch manufacturing processes. Many manufacturing execution systems use S88 formats for creating control recipes. Three hierarchical universal models are defined by S88:

1. A **control model** for batch manufacturing, providing a basis for streamlining communications about user requirements, integration among batch automation suppliers and simplifying batch control configuration.
2. A **physical model** that defines "plant-level" equipment in a manufacturing site.
3. A **procedural model** that consists of a hierarchical model for defining recipes in terms of procedures, unit procedures, operations and phases, and defines four types of recipes: general, site, master and control. Procedural models form an excellent representation of all types of recipes from formulation through execution.

Life science organizations have been late to adopt certain best practices that have long been in widespread use in other areas of batch manufacturing. In the face of increasing competition and changing regulatory reporting requirements, pharmaceutical companies are now looking to recipe normalization as a means to accelerate time to market, reduce waste, and improve regulatory compliance. This paper discusses recipe normalization, process definition management (PrDM), the associated industry standards (ISA-S88 and BatchML), and technologies designed to both streamline regulatory submissions and embed quality standards into the process from the earliest developmental stages.

The Pharmaceutical Industry Today

The average cost of moving a new drug through the development process in the United States ranges from $300 million to as high as $1.2 billion. Drug development takes an average of 12 to 15 years, leaving only five to eight years of patent protection; only one in 10,000 candidate compounds will survive the development process, receiving new drug approval, and ultimately reaching the marketplace.[1]

Given this reality, drug companies are forced to aggressively focus on process innovations to drive down discovery, development and commercialization costs and to accelerate time to market. But a surprising amount of discovery and development lifecycle is still based on manual and disconnected process steps, leading to delays, inefficiencies and the potential for risk through breakdowns in technology transfer.

As a result of these issues and evolving enhancements in regulatory submission methodologies, pharmaceutical companies have recognized the critical need for improvements and have been quick to embrace information technologies. In early 2007, Pharmaceutical Commerce encouraged companies to maximize their heavy investments in information technology by leveraging those investments for maximum value. They suggest that business and IT professionals should look for the intersection of best business practices with the best information technology to drive business value.[2] This includes systems that don't simply improve one element of the process, but can be used to align everything from development to regulatory approval—systems that embed quality into every stage.

Quality by Design (QbD)

The concept behind the Quality by Design (QbD) initiative is simple: make quality a fundamental part of the development process from the earliest possible phases of the lifecycle, using automation and standardization to enforce consistency and control. In other words, build quality into the design, rather than attaching it as a downstream step or test in the lifecycle. QbD principles have been used for decades in chemical and high tech manufacturing—and with great success. Life science companies have been slower to adopt, but this is changing as a result of aggressive evangelism from the U.S. Food and Drug Administration (FDA).

1 Pharmaceutical Research and Manufacturers of America (PhRMA). "What Goes Into the Cost of Prescription Drugs?" June 2005.

2 Pharmaceutical Commerce, February 2007 http://www.pharmaceuticalcommerce.com/frontEnd/main.php?idSeccion=450

"The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks."

Janet Woodcock
Deputy Commissioner for Operations, FDA

"The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks," noted Janet Woodcock, Deputy Commissioner for Operations, FDA. This enables the quality reviews to be an integral part of product development, and easily observed by regulatory officials.

Essentially, QbD requires researchers to define and document the Critical to Quality (CTQ) attributes of the manufacturing process. CTQ attributes may include control settings, material purity—and any other variable that is critical to the ultimate quality (effectiveness, stability, toxicity, etc.) of the active pharmaceutical ingredients (API). In QbD, CTQs are identified through rigorous Design of Experiments (DoE) in late phase discovery and early development. Once identified, the CTQ's are refined, documented, reported and monitored throughout the product lifecycle.

Process Definition Management (PrDM): A Key Foundation for QbD

Process definitions form a foundation for QbD initiatives. PrDM defines detailed process logic as well as parameters for manufacturing phases that include inputs, process parameters and outputs, and can therefore provide a framework for defining, managing and submitting CTQs for any regulated batch manufacturing process. The parameters define every aspect of CTQs, including materials, purity, operators, SOPs and instructions.

Room for Improvement

Engineers have historically used flowcharts to create process definitions and recipes to map out the steps of the manufacturing process. The quality specifications and parameters behind each step—control points, tolerances, inputs, etc.—are meticulously documented in a separate document, often a spreadsheet. Each time a parameter changes, the spreadsheet is updated accordingly. This information can be very complex and may constitute thousands of rows of information. This creates several inefficiencies in recipe management, and presents five distinct areas of opportunity for improvement.

Average Cost of New Drug Development: more than $800 million

Average Time to Market for New Drugs: 12-15 years

Median Application Time for New Drugs, 2001: 14 months

Median Application Time for NME, 2001: 20 months

Version control

Flow charts representing process logic and spreadsheets containing process parameters are often managed as separate and independent artifacts, which means they can easily become out of sync. Version control and synchronization of these artifacts is critical to improving recipe management.

Content Reuse

Creating and managing process definition elements within unstructured documents provides no mechanism for reusing the elements, which codify documented best practices. Process definitions for similar compounds, authored at different times by different process engineers, should be able to share process innovations and best practices—essentially "chunks" of recipes. Projects proceed independently without the insight of other project teams that may be working in parallel within the same building. Often it's the case that the process innovations happen at commercial scale, and are only represented in master recipes that exist within manufacturing execution systems (MES). Physical or process mechanisms do not exist to feed back innovations from commercial or early clinical manufacturing to earlier process design activities in late phase discovery.

Knowledge Management

Process definitions collectively represent the intellectual property of a life sciences firm, yet there is no simple way of searching the content and structure of recipes to enable researchers in one product line to discover relevant process innovations in another.

Yet each organization—and often, each individual within an organization—utilizes standards and formats that have evolved out of personal habits, or "the way things have always been done." From annotations in lab notebooks to operating instructions, rarely are the documentation formats consistent. These additional challenges make knowledge sharing difficult when attempting to reuse content or transfer technology.

Technology Transfer

The manual process of technology transfer is a significant weakness in the development process. When a process definition (usually in a spreadsheet or document) passes from R&D to pilot manufacturing to become a recipe, the information from the flowcharts and spreadsheets needs to be transferred to the manufacturing execution systems. Today, this process is manual. Rekeying of process logic and parameters is time consuming and introduces errors in technology transfer, putting quality at risk, reducing yield by increasing waste from bad batches, and adding to cycle time. A typical manual based technology transfer occurs in four to eight weeks. With the right tools and approach for technology transfer, the process may be completed in days rather than months. For certain biologic based blockbuster drugs, the revenue benefit associated with technology transfer may be US $1 million per day.

Technology transfer is not just limited to the handoff from late phase clinical to commercial. It is repeated as the product definition moves from pilot to short-run production through a contract manufacturer for clinical trials; for full-scale manufacturing at yet another facility; and yet again when products go off-patent and are moved to lower cost contract manufacturers.

Regulatory Submissions

The fifth and probably most significant area of opportunity is regulatory submissions. QbD—as it becomes a regulatory framework—will require reporting on all CTQs and the controls in place to manage them. CTQs will need to be reported from the earliest pre-clinical submissions through to large-scale manufacturing. Rather than being part of an entirely separate process, the process definitions themselves can provide a framework for organizing, managing, and reporting on CTQs throughout the product lifecycle.

Barriers to Effective Recipe Management

If process management can provide such broad benefits to life sciences, why hasn't it been more widely adopted, and what innovations have occurred to make it possible today?

Extensible Markup Language (XML) is a key enabler of a QbD initiative, providing a dramatically more efficient way to create, access, manage and reuse information across the pharmaceutical lifecycle. XML helps to unlock the value of unstructured content previously trapped in documents and repositories, and better utilize the structured data in databases, manufacturing execution systems, asset management systems and quality management systems.

One barrier to process management has been the absence of a standard tool for process specification during formulation. Another barrier is converting a process definition into an executable recipe. Many manufacturing execution systems (MES) have recipe editors, and use standards-based formats, such as S88, to represent process flows. In MES, the recipe is authored in a manner that promotes execution rather than process definition. However, because recipes are not created in these systems until manufacturing, their use does not provide benefits upstream in the product and process lifecycle.

Another barrier is the wide array of standards for representing the process definition itself during formulation. While this is addressed by S88, even industries that have widely adopted S88 typically use it for execution of master and control recipes, but not a means to represent standard process definitions.

A third barrier to effective PrDM is interoperability. At execution, master recipes must be able to be imported by a variety of enterprise systems in the manufacturing process. They often need to share master data from manufacturing, such as references to equipment and materials. Normalization of recipes as S88 procedure models within a single operational language is a best practice for enabling QbD.

The Rise of XML for Regulatory Submissions

Since the FDA mandated the transition from PDF submissions to XML-based submissions through the electronic Common Technical Document (eCTD) and Structured Product Labeling (SPL) standards, XML tools have changed the way that pharmaceutical companies do business. Corporate adoption of XML continues to accelerate, not only to meet these regulatory mandates; companies are also starting to realize the efficiency that XML-based systems bring to many elements of the lifecycle, above and beyond submissions.

But using XML for regulatory submissions is only part of the equation. XML-based systems have far greater applications and can help to track, define, and streamline information throughout the product lifecycle, from late phase discovery through to commercial manufacturing.

XML as a Process Definition Enabler

While QbD brings life science companies the benefits of improved yield and quality, the regulatory costs include increased reporting on CTQ parameters through the product lifecycle.

The current management of formulations in pharma and biotech relies heavily on the use of unstructured documents—flowcharts and spreadsheets—to capture manufacturing process logic and parameters. Spreadsheets can typically grow to be thousands of rows in length; there is no simple way of abstracting only the CTQs from a formulation for reporting purposes. Finally, there is no method for importing these documents into execution systems, so technology transfer—the process of converting formulations and process definitions into executable master recipes for process connected devices—is unnecessarily time consuming, iterative and error-prone. XML-based tools and standards can alleviate many of the challenges that life science companies have faced with traditional documentation.

BatchML can address a host of technology transfer and interoperability requirements of recipe management. BatchML—an industry standard that consists of a set of XML schemas written using the World Wide Web Consortium's XML Schema language (XSD)— has high potential as a method for representing data for S88-based formulations, and enabling that information to flow between systems for submissions, recipe and formula management, execution, asset management and quality control.

BatchML implements the models and terminology in the s88 standard, and is an excellent tool to use when exchanging S88-based data, providing a set of XML type and element definitions that may be used in part or in whole for batch, master recipe and equipment data.

A Start-to-Finish Solution: The JustSystems xfy for Batch Process Definition

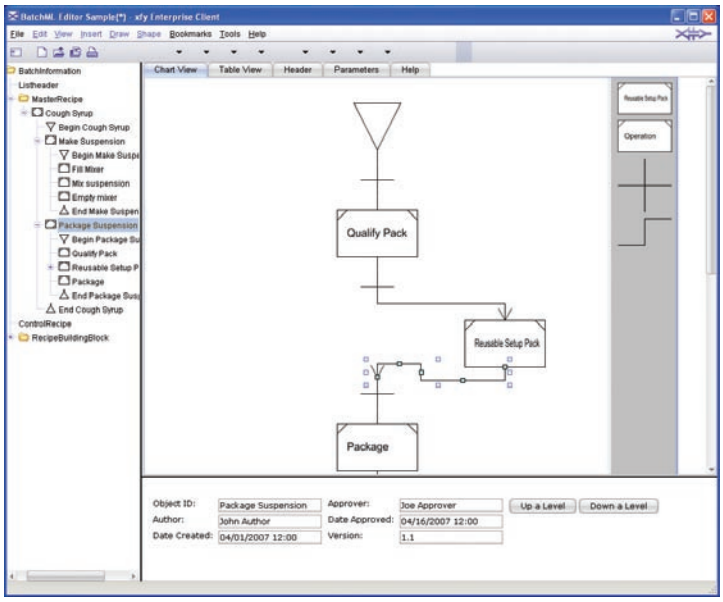
With all of the places for the process to break down in the flowchart-and-spreadsheet scenario, documentation of process (flowcharts) and quality (spreadsheets) cannot continue as separate systems. A single solution is needed to take authored process definition to executable recipes based on reusable steps and actions.

JustSystems has developed a powerful and unique solution for normalizing the creation, management and transfer of S88 process definitions using BatchML. The JustSystems xfy for Batch Process Definition enables life science and other process manufacturers to follow the QbD approach by standardizing and normalizing recipe development and transfer, and reusing processes across products.

JustSystems xfy for Batch Process Definition is the only solution available today that supports both the s88 graphical standard for procedural models and BatchML, the XML standard for batch processing. This makes this solution compatible with other BatchML applications, such as manufacturing execution systems (MES), product lifecycle management (PLM) and compliance solutions.

Using xfy for Batch Process Definition, master recipes are created as S88 procedure models, stored as BatchML, and centrally managed within a system of record. Using the S88 model as a graphical user interface, the process flows are drawn, and then parameters can be attached to each node of the S88 hierarchy through property sheets. The parameters and the drawing are bound and synchronized. All of the underlying CTQ parameters are up to date, because they're centrally managed in the process definition, which becomes the one authoritative version of the truth.

Utilizing a drag-and-drop visual flowchart interface—a format already familiar to scientists and manufacturers—scientists can create and edit sequential processes in a process definition.



Using xfy for Batch Process Definition, R&D engineers can visually manipulate and edit an S88-based flow chart to assemble master recipes based on normalized recipe and procedural definitions. The result is a consistent recipe definition, enabling error-free technology transfer and eliminating the need for re-keying information between phases. This accelerates time to market, reduces operational costs and dramatically reduces the risk, waste and poor quality associated with inaccurate recipes.

Process elements can be stored, templatized and re-used at any level, such as Procedure, Unit Procedure, Operation and Phase.

xfy for Batch Process Definition enables process manufacturers to:

- Improve information transfer between engineering and manufacturing, including third-party contractors and partners, through BatchML
- Improve product quality and overall manufacturing processes through better management of CTQ parameters
- Increase efficiencies through process reuse across products using recipe building blocks and through recipe normalization
- Accelerate product time-to-market through improved technology transfer
- Reduce waste from failed batches through improved technology transfer and better management of CTQs
- Comply with regulatory submissions of master recipes and speed up the approval process with the FDA by using S88 recipes as the basis for capturing and reporting CTQs

xfy for Batch Process Definition makes process definition a seamless, end-to-end process, utilizing the same tools throughout. These integrated elements facilitate technology transfer and submission, saving time and money.

The Benefits of a Flexible XML Solution

Automating regulatory submissions of master recipes and batch can streamline and accelerate the approval process, reducing the time-to-market for new products or revisions to existing products.

A highly flexible system like the xfy for Batch Recipe Definition will enable scientists to more rapidly author and execute experiments, define quality processes and provide a key component to the electronic development record.

In manufacturing, the old adage that time is money couldn't be more appropriate. How much time is lost with each new recipe by starting from scratch? With each re-key of the process as the technology is transferred from R&D to manufacturing? With regulatory submission delays? With QbD initiatives in place, how much time and money could be saved?

Forrester Research reports that a single day of delay on a US $1 billion drug can cost a manufacturer US $2.74 million in lost sales.[3] An acceleration and cost savings of just 2% could mean 58-73 days in acceleration, a revenue difference of US $158-200 million.

Conclusion

Pharmaceutical companies are spending vast sums of money to bring drugs to market, and even incremental improvements can make a huge difference to the bottom line. Yet cost-cutting measures can't come at the expense of quality. Fortunately, companies can embed quality into their processes, improve productivity, reduce costs, mitigate risks and ease regulatory review by implementing xfy for Batch Process Definition. One tool can help integrate disconnected business processes formerly locked in static flowcharts and spreadsheets, not only to improve internal operations, but external operations with contract manufacturers, partners and regulatory officials.

JUSTSYSTEMS.
http://na.justsystems.com
Email: sales@justsystems.com

North America: (tf) +1.866.793.1542
+1.866.JSI.4.XML
Europe: +44.0.1753.607.650
International: +1.604.697.8705

About JustSystems

JustSystems is a leading global software provider with a 27-year history of successful innovation in office productivity, information management, and consumer and enterprise software. With over 2,500 customers worldwide and annual revenues over $110M, the company is continuing a global expansion strategy that includes the launch of its new enterprise software offering called xfy (pronounced 'x-fie'), and XMetaL content lifecycle solutions. JustSystems has worldwide office locations including global headquarters in Tokyo, and regional offices in New York, Palo Alto, Vancouver, and London. The company currently employs over 1,000 people. Major strategic partnerships include IBM, Oracle and EMC.

Customers include Cisco, DaimlerChrysler, HP, Kodak, Microsoft, Philips, RIM, Southwest Airlines, Sybase, Symantec, Texas Instruments and USA Today.

3 UPS Supply Chain Solutions cites Forrester Research with the following quote: "each day delay for a $1 billion drug costs the manufacturer $2.74 million in lost sales." http://www.ups-scs.com/solutions/white_papers/wp_pharma1.pdf