Presented at the
WBF
European Conference
Barcelona, Spain
November 10-13, 2008

67 Alexander Drive
PO Box 12277
Research Triangle Park, NC 27709
+1.919.314.3970
Fax: +1.919.314.3971
E-mail: info@wbf.org
www.wbf.org

Process Definition Management: Using ISA-88 and BatchML as a basis for Process Definitions and Recipe Normalization

Mike Power
Manager, Life Science Supply Chain
BearingPoint
Gordonsville, VA 22942 – USA
Ph: 540-832-5604
Mike.Power@bearingpoint.com

Paul Wlodarczyk
Managing Director
The Content Guy
Fairport, NY 14450 – USA
Ph: 585-598-6050
paulw@thecontentguy.net

KEY WORDS

Master Recipes, Recipe Normalization, Technology Transfer, Process Definition Management, Recipe Building Blocks, Quality by Design (QbD), ISA 88, BatchML

ABSTRACT

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 and biotech companies are now looking to standard forms of process definition as a means to accelerate time to market, reduce waste, and improve regulatory submissions.

This paper discusses recipe normalization, process definition management (PrDM), the associated industry standards (ISA-88 and BatchML), and supporting technologies, which together will improve product time to market and embed quality into process design from the earliest stages of product R&D.

Process Definition Management: Using ISA-88 and BatchML as a basis for Process Definitions and Recipe Normal

The Life Science Industry Today

The average cost of moving a new pharmaceutical or biotech product through the development process in the United States ranges from $300 million to as high as $1.2 billion. Product 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 product approval, and ultimately reaching the marketplace.[1]

Given this reality, life science companies are moving to aggressively focus on process innovations designed to drive down discovery, development, and commercialization costs and to accelerate time to market. However, a surprising amount of discovery and development lifecycle is still based on manual and disconnected process steps. These manual steps lead to delays, inefficiencies and increased risk product and process technology transfer.

As a result of manual processes and in the face of evolving regulatory requirements, 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 leverage their heavy investments in information technology for maximum value. They suggest that business and IT professionals should search for the intersection of best business practices with the best information technology to drive business value.[2] This search includes systems that don't simply improve one element of the process, but can be used to align all processes from development to regulatory approval; systems that span the product lifecycle while embedding quality into every stage.

The ISA-88 Standard for Recipe Representation

ISA-88 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 ISA-88 formats for creating control recipes.

Three hierarchical universal models are defined by ISA-88:

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.

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 phases of the product lifecycle, using automation and standardization to enforce consistency and control. In other words, build quality into the process design, rather than as a downstream step in manufacturing. QbD principles have been used for decades (with great success) in chemical and high tech manufacturing. Life science companies have been slower to

adopt; however, this is changing as a result of aggressive evangelism from the US (FDA) and European (EMEA) regulatory agencies.

Essentially, QbD requires researchers to define and document the Critical to Quality (CTQ) attributes of the product, and the corresponding critical and key parameters of the manufacturing process. CTQ attributes include 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 CTQs are refined, documented, reported, and monitored throughout the product lifecycle.

Process Definition Management: A foundation for QbD

Process definitions form the foundation for QbD initiatives. Process Definition Management (PrDM) defines detailed process logic as well as parameters for manufacturing phases that include process inputs, process parameters, and process outputs. Process definitions can therefore provide a framework for defining, managing and submitting key and critical parameters for any regulated manufacturing process. The process parameters can include material parameters (ingredients and intermediate products, quantities, scale factors, etc.), equipment parameters (speed, duration, and other equipment control settings), operators instructions, SOPs, resource requirements (e.g. operator qualifications), control / signature strategies, in-process and post-process quality attributes and testing requirements – effectively any aspect of the manufacturing process. Because developers know at design time that certain parameters of the manufacturing process are critical to maintaining the product quality, product developers need a method for capturing and communicating this critical process knowledge throughout the product lifecycle.

Room for Improvement

To create process definitions and recipes, product developers typically use flowcharts or word documents to map or catalog the steps of the manufacturing process. The quality specifications and parameters behind each step are captured in a separate document, often tabular or a spreadsheet. Parameter information can be very complex often resulting in spreadsheets with thousands of rows. The overall size of some of the spreadsheets and tables leads to inefficiencies in recipe management, and presents five distinct areas of opportunity for improvement.

Version control

Flow charts representing process logic and spreadsheets/tables containing process parameters are often managed as separate documents, and easily become out of synch. Version control and synchronization of the spreadsheets/tables are critical to improving process definition management.

Content Reuse

Creating and managing process definitions within unstructured documents like flowcharts and spreadsheets provides no mechanism for reusing process elements. However recent studies and pilot projects have shown that reuse of pre-defined libraries of process segments offers the primary means of codifying knowledge of products and knowledge of manufacturing best practices.

In practice, product development projects proceed independently without sharing insights from other project teams. Process definitions for similar compounds are authored at different times by different process engineers, in separate unstructured documents. As a result, there is no means of sharing common knowledge of product science or manufacturing. Recently an FDA CRADA study demonstrated that product developers should be able to share best practices—essentially by sharing "chunks" of recipes or product definitions. By capturing product knowledge – knowledge of chemistry, biology, physics – within reusable recipe building blocks, product developers have a method for capturing, sharing, discovering best methods and of incorporating them seamlessly into new product designs.

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

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

Median Application Time for New Products, 2001: 14 months

Median Application Time for NME, 2001: 20 months

In most cases, manufacturing process innovations occur in plant systems (such as a DCS or MES), in which case the knowledge is represented in master recipes or master batch records. Technologies and business processes do not exist to feed back innovations from manufacturing to earlier process designs and process definitions in development. By capturing best practices in the form of process definitions and codifying them into a library of reusable manufacturing actions, these innovations in manufacturing are available to be fed back into new product development.

Knowledge Management

Process definitions collectively represent the intellectual property of a life science firm, combining knowledge of product science (chemistry / biology / physics) and knowledge of manufacturing capability (current and future). Yet because this knowledge is represented in unstructured documents there are limited effective tools for searching process definitions or recipes to enable discovery of product or process innovations.

To make matters more difficult, each organization—and often, each individual within an organization—uses methods 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. This inconsistency creates additional challenges, making knowledge sharing difficult when attempting to reuse content or transfer technology.

Technology Transfer

The manual nature of technology transfer is perhaps the most significant weakness in the product lifecycle. When a process definition (in the form of a document) passes from development to pilot manufacturing, the information from flowcharts and spreadsheets needs to be transferred to the batch control systems. Today, this process is manual. Re-keying 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 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 biological blockbuster products, the revenue benefit associated with faster time to market may be as high as US $1 million per day.

Technology transfer is not just limited to initial scale-up from pilot to commercial. It is repeated every time the product definition needs to be transferred to a new manufacturing site – when the product enters short-run production for clinical trials; when adding a facility to scale-up; when scaling-down and

changing to a smaller plant; and when products go off-patent and are moved to lower-cost contract manufacturers (CMOs).

Given the addressable impact on time to market, improving technology transfer is likely to be the most significant area of opportunity for most firms implementing PrDM.

Regulatory Submissions

The fifth area of opportunity is regulatory submissions. QbD — as it becomes a regulatory framework — will require reporting on all CTQ attributes and the controls in place to manage them. CTQ attributes and the corresponding critical / key parameters 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 critical attributes and parameters throughout the product lifecycle.

Barriers to effective process definition management

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

One barrier to process definition management has been the absence of a standard tool for process specification during development. Another barrier is converting a process definition into an executable recipe. Many batch control systems have recipe editors, and use standards-based formats, such as ISA-88, to represent process flows. In batch control, the recipe is authored in a manner that promotes process control and execution rather than process definition – and the master recipes are very equipment-specific. Because these master recipes are equipment-centric and because they are not created until the product goes into commercial-scale manufacturing, these recipes cannot provide the same benefits as a process definition generated upstream in the product and process lifecycle.

Another barrier is the wide array of standards for representing the process definition itself during development. While this is addressed by ISA-88, even industries that have widely adopted ISA-88 typically use it for master and control recipes during manufacturing, but not a means to represent standard process definitions during development.

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 ISA-88 procedure models within a single operational language (e.g. an XML format such as BatchML) 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. XML-based systems can help to track, define, and streamline information throughout the product lifecycle, from late phase discovery through to commercial manufacturing.

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.

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 critical and key parameters through the product lifecycle.

The current management of process definitions 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 critical and key process parameters from a recipe for reporting purposes. Finally, there is no method for importing process definition documents into execution systems, so the process of converting process definitions into executable master recipes for batch control 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) — is an emerging best method for representing data for ISA-88 recipes, and enabling that information to flow between systems for submissions, recipe and formula management, execution, asset management, and quality control.

BatchML implements the ISA-88 standard, and is an excellent tool to use when exchanging ISA-88-based data, providing a set of XML element definitions that may be used in part or in whole for batch control, master and general recipes, and equipment data.

A Start-to-Finish Solution 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 parameters (spreadsheets) cannot continue as separate systems. A single solution is needed to create process definitions that combine parameters and process logic, that enable reuse of predefined recipe building blocks, and that can be transformed into executable Master Recipes based on re-useable steps and actions.

It is recommended that such a solution would use class-based ISA-88 Master Recipes as the format for a process definition, with the data stored as BatchML.

ISA-88 compliant sequential function charts may form the basis for capturing procedure, unit procedure, and operation process logic. Parameters may be associated with phases through property sheets and user dialogs. In this way, users may easily navigate the process flow and easily associate parameters with specific recipe elements. Likewise, audit trail ("header") information must be associated with any recipe element.

Recipe building blocks may be represented as reusable fragments of ISA-88 recipes (visible to users as parts of sequential function charts). BatchML provides a mechanism for specifying recipe building blocks in the form of reusable XML objects at the data layer. Together this enables content reuse of process logic and standardized parameters through reusable templates. The templates can be stored in libraries using content management technologies.

The authors have developed a working prototype of a process definition editor. Screen captures of the user interface of this system are included herein.

A process definition editor as described above would enable process manufacturers to:

- Improve information transfer between development and manufacturing, including contract manufacturing organizations (CMOs), through BatchML
- Improve product quality and overall manufacturing processes through better management of critical and key 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 and faster time to scale from pilot to commercial scale
- Reduce scale-up cycle time and waste from failed batches through improved technology transfer and better communication of critical and key process parameters
- Improve submissions to FDA by using class-based ISA-88 Master Recipes as the basis for capturing and reporting both process logic and critical and key process parameters within the Description of Manufacturing Process and Process Controls (section 3.2.S.2.2) of the Common Technical Document.

The cycle time benefits from improved technology transfer through process definition management are significant. Forrester Research reports that a single day of delay on a US $1 billion product can cost a life science 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. This level of ROI is achievable from a single PrDM pilot project on one product by reducing recipe authoring cycle time, and through improved time to scale through more effective technology transfer.

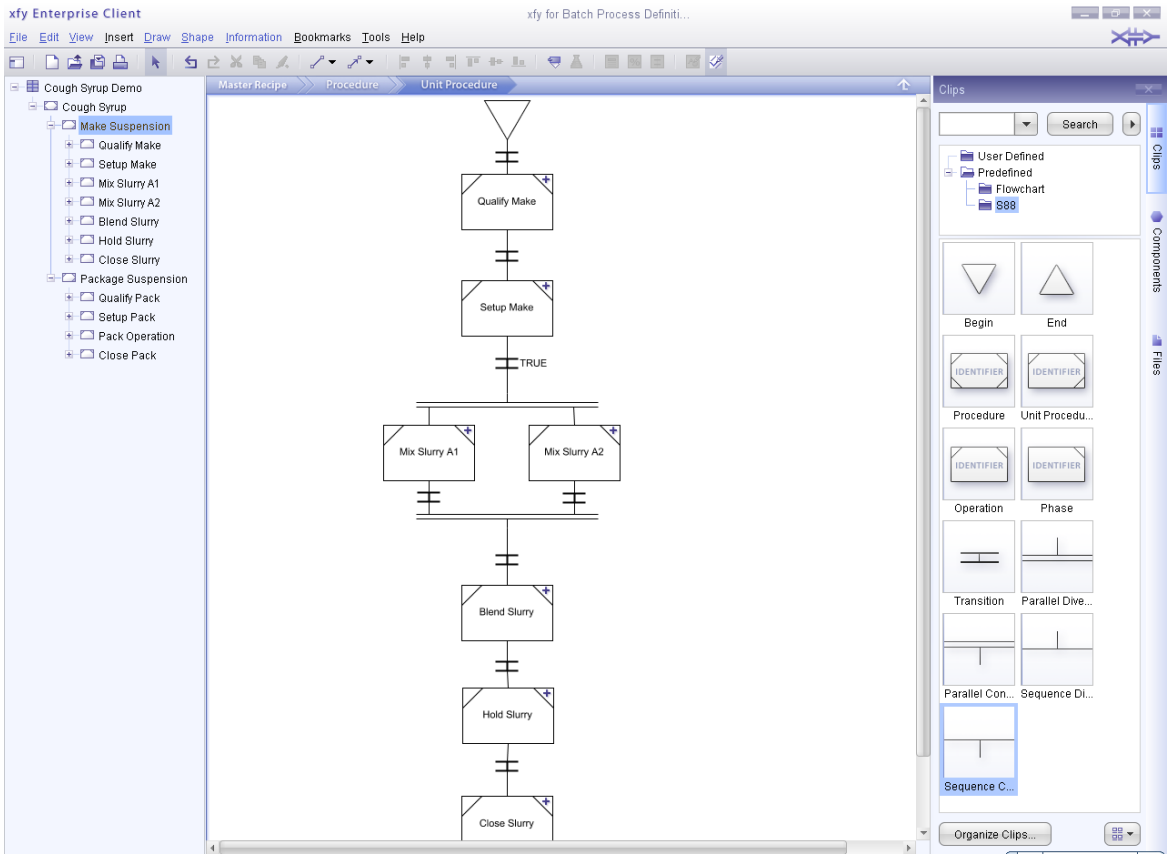

Figure 1: ISA-88 Sequential Function Chart View of several Operations within a Unit Procedure in a prototype Process Definition Editor (Courtesy JustSystems)

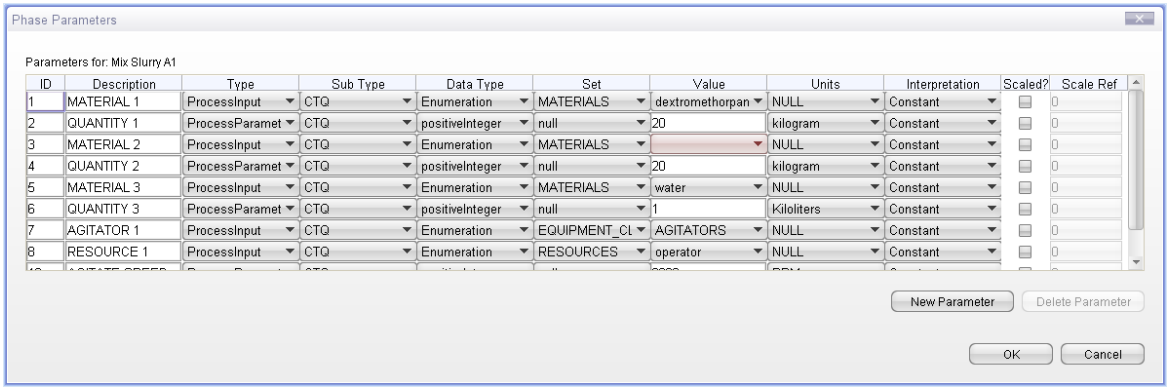

Figure 2: Sample dialog for specifying Phase Parameters (accessed by double-clicking a Phase object in the SFC view) (Courtesy JustSystems)

Conclusion

Pharmaceutical companies are investing heavily in R&D focus on new products, 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 greatly reduce time to market, embed quality into their processes, improve productivity, reduce costs, mitigate risks, and simplify regulatory submissions by implementing ISA-88-based process definitions and by representing this information as BatchML. A process definition editor that combines ISA-88 and BatchML can help integrate disconnected business processes formerly locked in static documents, not only to streamline internal processes, but external interactions with contract manufacturers, other supply chain partners, and regulators.

References

[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

[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