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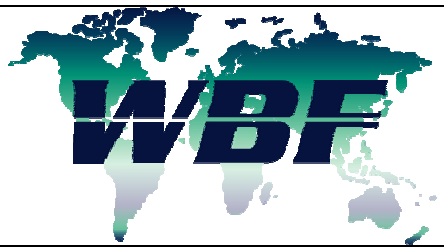

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Using General Recipes for Standardized Multiple Plant Manufacturing Science

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ABSTRACT

Innovation in pharmaceutical manufacturing with faster development, faster new product release, robust process understanding and vastly improved quality by design is a key component of the FDA's 21st century manufacturing initiative.

A pioneering approach using General Recipes as a keystone element is accelerating our understanding of manufacturing science at Pfizer to support standardized multiple plant investigations.

Manufacturing science is the body of scientific knowledge, regulations, and principles involved in the transformation of materials and information into products. Applying manufacturing science across multiple sites has always been daunting. Information which may take months to collect at one site, can not easily be compared against information from other sites due to differences in equipment, unit layouts, and master recipes.

The ISA 88 General and Site Recipe standard provides a method to document standard manufacturing science information. This paper describes an innovative way to extend general recipes to document critical and key process parameters, and a method to convert that information into data collection requirements for plant specific master recipes. This process knowledge thus structured will aid in faster development, release, and improved quality, helping the life science industries achieve their 6-sigma quality goals.

Introduction

Manufacturing science is the terminology used at Pfizer to describe the body of scientific knowledge, laws, and principles involved in the transformation of materials and information into products. One of the key components of manufacturing science is the development of scientifically sound recipe parameters based on investigations and studies.

The application of manufacturing science across multiple sites is challenging as a result of significant variability that exists between sites. For example unit configuration, material handling, master recipes are seldom consistent. Thus the information gained at one site can not easily be compared against information. One method to perform multi-site and multi-process cell investigations is to define a consistent way to describe investigation information independent of the underlying equipment. This information has to address differences may include different unit layouts, different unit sizes, different material transfer methods, and different levels of automation at sites.

This problem is similar to the problem addressed by ISA 88 General and Site recipes, in describing the manufacturing process without reference to the specific target equipment. Not surprisingly, General and Site Recipes are good starting points for documenting the information needed for multi-site manufacturing science. In order to use General Recipes for manufacturing science investigations several elements need to be extended, or customized in the following areas: process parameters, process reports, and observed operational modes.

Process Parameters

General and Site recipes contain process parameters, process inputs and process outputs.

- Process inputs and process outputs are defined as materials.
- Process parameters are defined as "Information that is needed to manufacture a material but does not fall into the classification of process input or process output.
    - *NOTE — Examples of process parameter information are temperature, pressure and time.*"

While these definitions are very open-ended, more rigor is needed for manufacturing science documentation and investigations.

Quality Attributes

We are using the terminology "Quality Attributes" as a specific type of process parameter. Quality attributes define the target qualities of the produced material. Quality attributes are the physical, chemical, or microbiological properties of a material that directly or indirectly impact product specifications. For example a quality attributes for a "Blend" process action may be a measure of the target homogeneity and the appearance of the blend (no visible discolorations or no clumping).

Quality attributes may be further categorized as critical or key. Critical quality attributes are registered with regulatory authorities are a characteristic of the product. Key quality attributes are not registered.

Process parameters

Process parameters define values that must be controlled in the process because they influence quality attributes. Process parameters must be controlled within predefined limits to ensure the product meets its pre-defined quality attributes. Critical process parameters influence critical quality attributes. Key process parameters influence key quality attributes.

Figure 1 illustrates a quality attribute (sterility) and the parameters that must be controlled (time and temperature) to achieve the desired attribute.

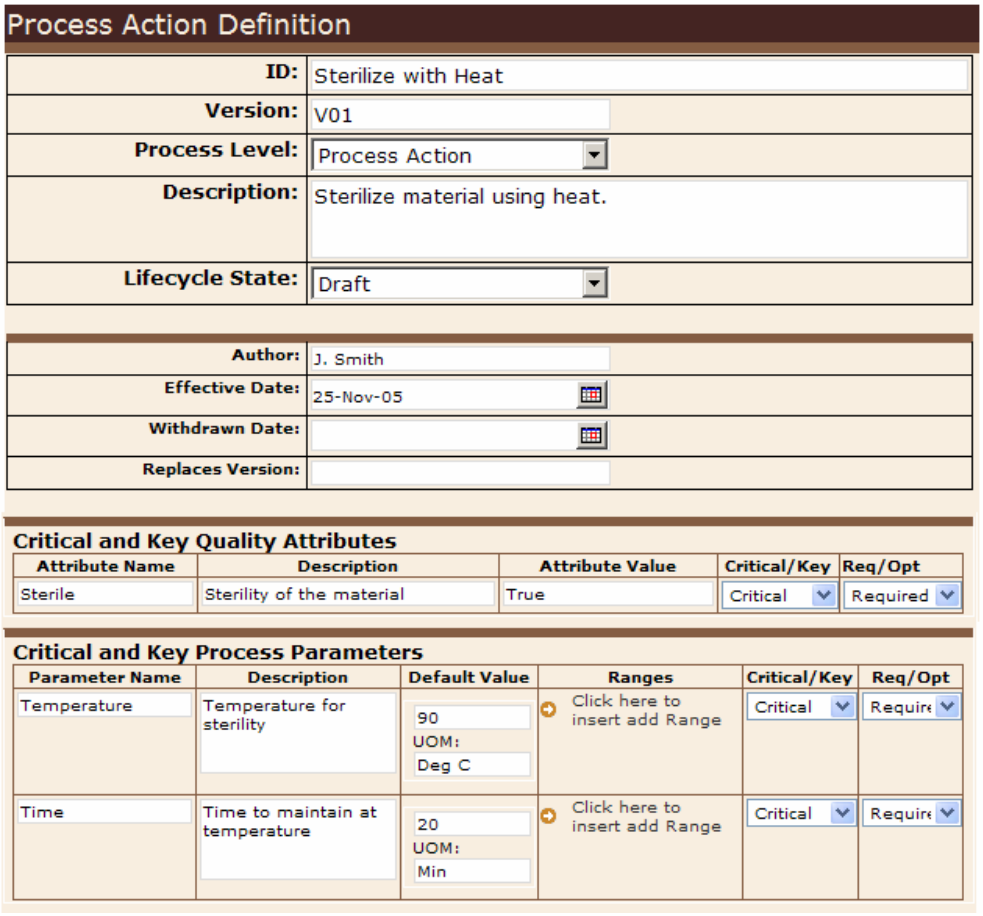


Figure 1 - Quality Attributes and Process Parameters

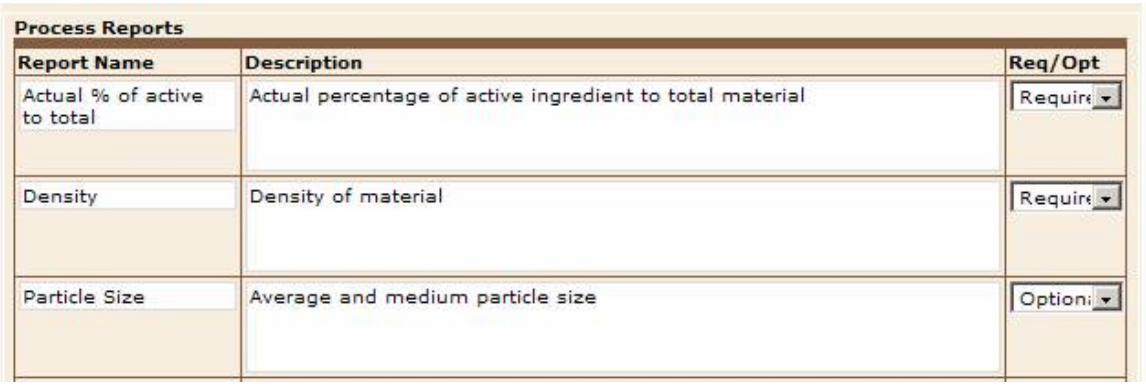
Process parameters and quality attributes become some of the primary inputs used in converting a general recipe to a master recipe.

Process Reports

In addition to defining attributes and parameters, investigations also need a place to document information which needs to be reported as a result of the execution of the process action. These are called “Process Reports”. They define the information that must be collected and reported on during execution of the process. Figure 2 illustrates some typical process reports.

Process reports are to be collected regardless of the equipment layout or level of automation. They provide the raw material used in multi-site investigations. The most time consuming part of an investigation is the collection of the process data. By formalizing the minimum amount of data that

should be collected and made available the time to perform multi-site investigations should drop by a substantial amount.



Process Reports

Report Name	Description	Req/Opt
Actual % of active to total	Actual percentage of active ingredient to total material	Require
Density	Density of material	Require
Particle Size	Average and medium particle size	Option

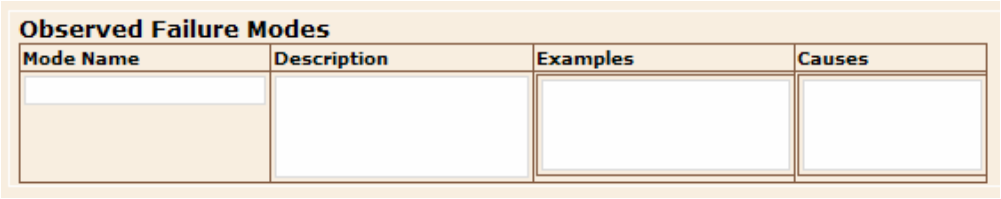
Figure 2 - A Process Report Definition

Observed Modes

Other manufacturing science information can also be added to a general recipe. The general recipe can be used as a form of process knowledge repository. "Other Information" in the ISA 88 standard is used to contain information that is not captured in other recipe elements. Additional structure can be added to "other information to record information that includes, but is not limited to:

- Observed failure modes – Any failure modes that have been observed in actual operation.
- Observed alarm modes – Any modes that have resulted in alarm conditions that have been observed in typical operations.
- Observed exception modes – Any modes that have resulted in exception conditions that have been observed in typical operations.

Figure 3 illustrates some of the information associated with different modes, including know examples and discovered causes.



Observed Failure Modes

Mode Name	Description	Examples	Causes

Figure 3 - Documenting Observed Modes

Parameter/Attribute Relationships

Once causal relationships have been established between parameters that can be controlled, and attributes that can be measured, these relationships must be captured and maintained. This information is obtained from validation batches, process capability studies and investigations. This critical information also provides a good framework for risk management. Again, the general recipe can be used as a repository for this information. Many of the relationships are product or material specific, such as

the relationships between blending speed, blending time, and output material homogeneity. Even though much of this information may be unit or equipment specific, it is a valuable resource for investigations. While this information is often maintained at a site level, keeping this at the corporate general recipe level supports multi-site investigations.

Multiple-Site Manufacturing Science

The previous extensions capture corporate process knowledge in general recipes. This knowledge must be combined with site knowledge, production knowledge, and manufacturing science investigations for a more complete manufacturing science environment.

- General recipe information can be expanded to become a repository of manufacturing science.
- The extensions defined for general recipes can also be applied to site recipes for the capture of site knowledge.
- Production history can be recorded in ISA 88 Part 4 Batch Production Records.

The relationships between these are shown in Figure 4. The relationships allow a cycle of continuous improvement in manufacturing.

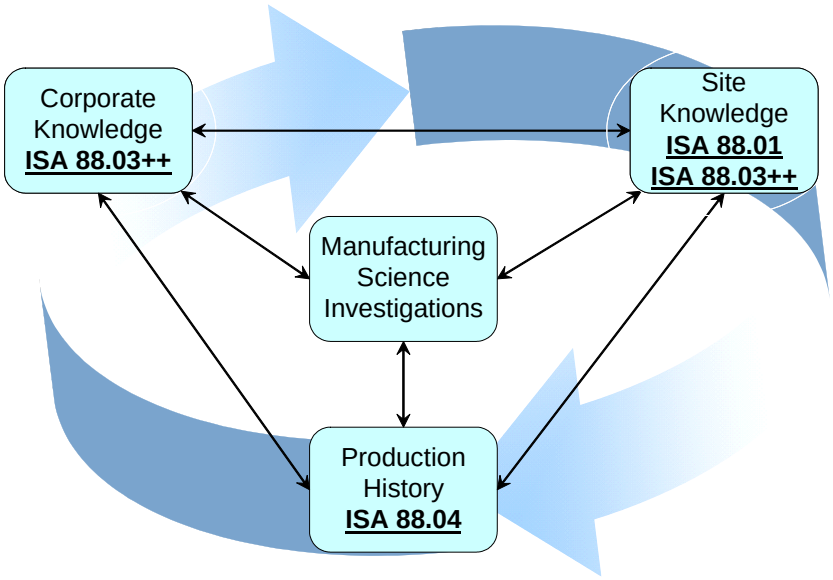


Figure 4 - Elements of Multi-Site Manufacturing Science

The elements of the extended general recipe and site recipes are shown in Figure 5. Master recipes can also be extended to include different observed modes, as aids to operations and as aids to process engineering.

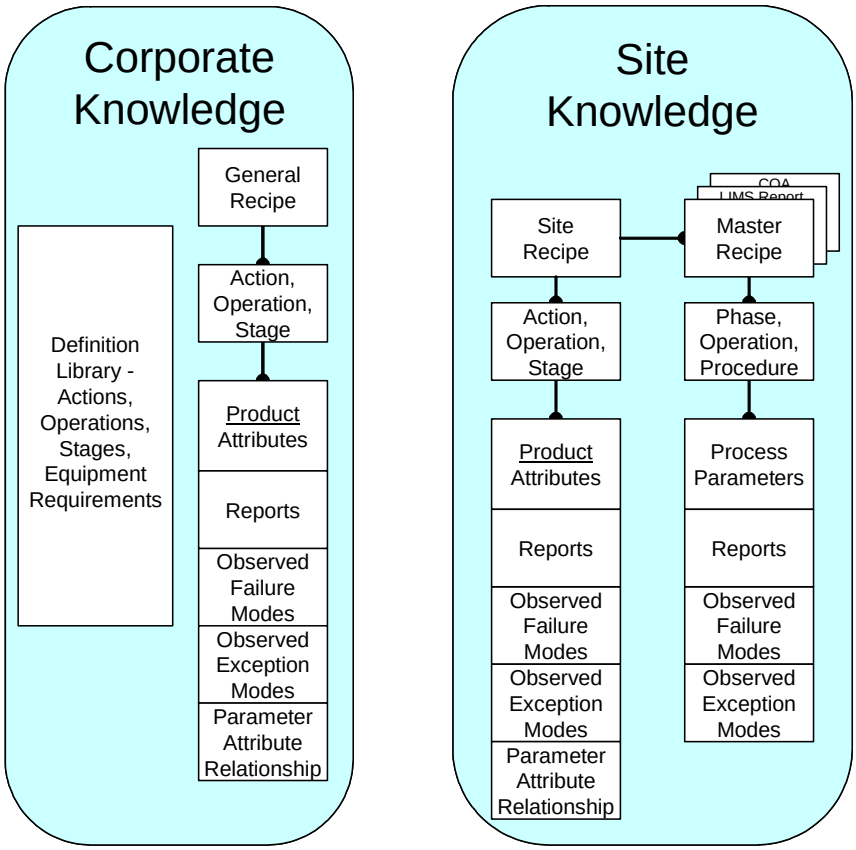


Figure 5 - Corporate and Site Knowledge

Production History and Manufacturing Science Investigations are comprised of the elements illustrated in Figure 6.

Production history involves more than just the batch history recorded in a Batch Production Record, it may also include information from other sources, such as Laboratory Information Management Systems (LIMS) and Certificate of Analysis (CoA) systems. Often the important information needed for manufacturing science is not in the batch records, but is in systems that support production. This includes information about the storage history of raw, intermediate, and final products, lab tests on intermediates, information about the environmental conditions of production (what material was produced before the investigated batch).

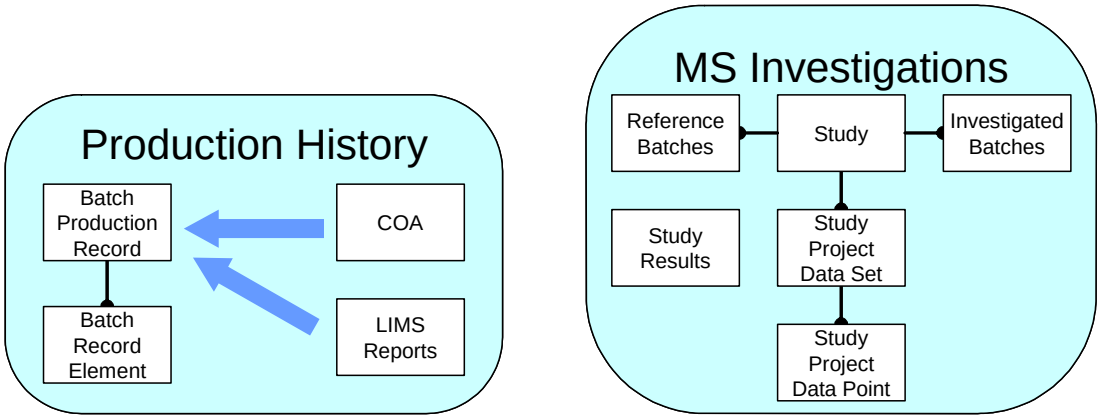


Figure 6 - Production History and Manufacturing Science Investigations

Manufacturing Science Investigations often start with a study. Studies may be performed to optimize processes, investigate incidents, discover improvement opportunities, or any number of reasons. Each study often is related to a set of investigated batches and may also use reference batches. Most studies try to encompass at least 30 batches in order to discover statistically significant relationships.

A study project contains a study data set; a multi-dimensional data set comprised of different batches and different data elements. The study data set is derived from the "Process Reports' that were initially defined in the general recipe. The complete set of relationships is shown in Figure 7.

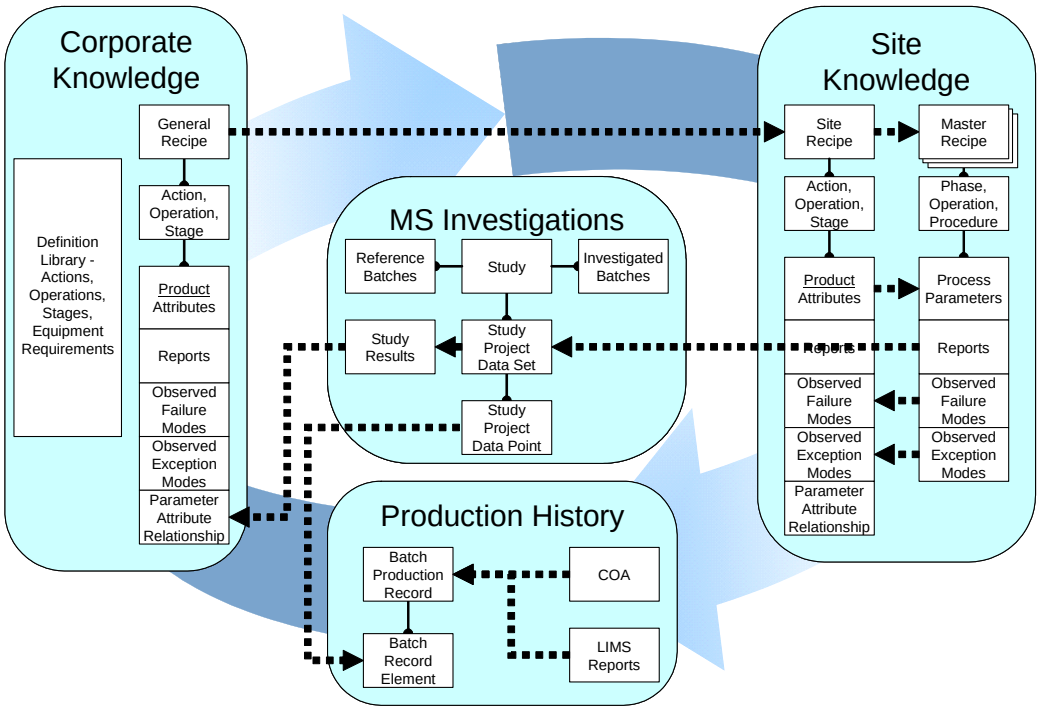


Figure 7 - Elements of Manufacturing Science

The structure shown in Figure 7 is conceptual, and not related to any specific software product or database repository, but it does illustrate how extended general and site recipes, used with batch production records can be used to support multi-site investigations.

Conclusion

Multi-site investigations need process data that is specific to individual site equipment peculiarities. By defining process reports in the general recipe, and letting each site determine how to collect the data, the information can be made available for multi-site investigations, without knowing the details of the specific master recipes. Even if the same operation is performed in different process cell layouts in different sites, with different numbers of units, the information across sites can be compared. However, applying this to real-world multi-site problems requires rigor in defining the process and product specific information reports that must be collected. This rigor should pay off in much faster multi-site investigations, with reduced effort for site personnel and corporate investigators.