Batch S88 Standard Overview

BATCH Standard

Standards exist to facilitate understanding and communication between the people involved. They help optimize revenue and you don't have to start from scratch for every new project. ANSI/ISA S88 is no exception. Although the benefits of S88 may be obvious to some, they are not necessarily as obvious to the decision makers.

S88 defines hierarchical recipe management and process segmentation frameworks, which separate products from the processes that make them. The standard enables re-use and flexibility of equipment and software and provides a structure for coordinating and integrating recipe-related information across the traditional ERP, MES and control domains.

In order to justify the use of S88, it is important to link its technical benefits to the business benefits of such an implementation.

S88 isolates recipes from equipment. When the software (S88-compliant or otherwise) that defines a product (recipe procedure) and the software to run equipment (phase logic) are in the same device (such as a PLC or DCS), the two different sets of code eventually become indistinguishable and, in some cases, inseparable. This makes recipe and equipment control difficult, if not impossible, to maintain. Every additional ingredient and process improvement can lead to lengthy and error-prone software changes. Documenting and validating such a system is also extremely difficult, and doubly so if not S88-compliant.

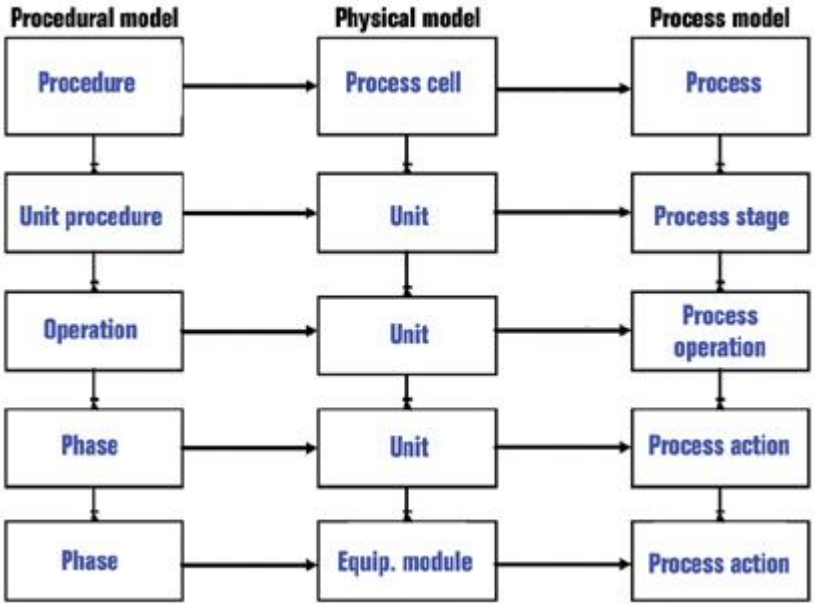
If recipes are kept separate from equipment control, however, the manufacturing process is more flexible and can provide significant advantages: Automation engineers can design control software based on the full capabilities and performance of the equipment rather than on the requirements of the product. Similarly, scientists, process engineers or lead operators who create the recipes can now easily create and edit them.
Separating products from the process that makes them raises the bar on plant flexibility. Equipment that may currently be constrained to one or a limited number of products may be able to accommodate more, improving overall equipment effectiveness (OEE) metric - a metric that has become the crucial link between the financial and operational performance of production assets.

ANSI / ISA S88 Standard

BATCH ANSI / ISA S88

provides standard models and terminology for defining the control requirements for batch manufacturing plants. The models and terminology defined

- emphasize good practices for the design and operation of batch manufacturing plants
- can be used to improve control of batch manufacturing plants and
- can be applied regardless of the degree of automation

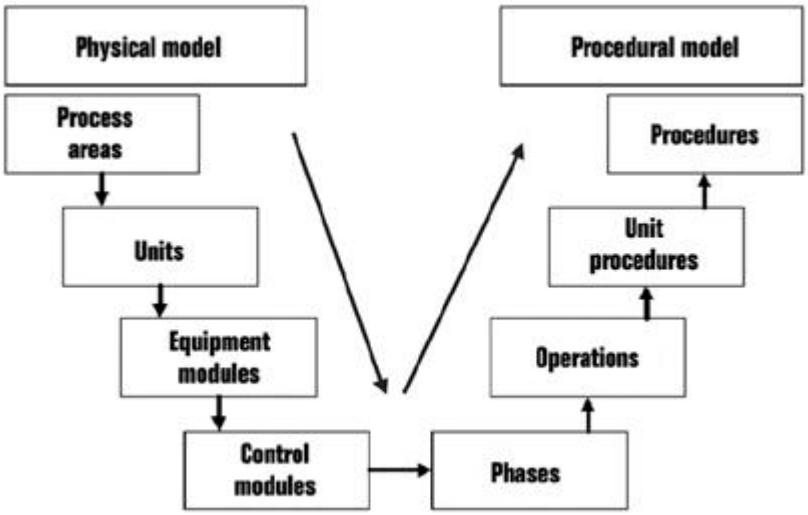


S88 Overview

Process, Physical, and Procedural models are interrelated to form a complete system

ANSI/ISA Batch S88 provides a standard terminology and a consistent set of concepts and models for batch manufacturing plants and batch control that will improve communications between all parties involved and that will

- reduce the user's time to reach full production levels for new products
- enable vendors to supply appropriate tools for implementing batch control
- enable users to better identify their needs
- make recipe development straightforward enough to be accomplished without the services of a control systems engineer
- reduce the cost of automating batch processes and
- reduce life-cycle engineering efforts.



S88 Modularization

The Physical Model is constructed from the top down and the Procedural Model is built from the bottom up.

Pharmaceutical Validation

Pharmaceutical Validation is the implementation of a quality system approved by the FDA.

It is designed to ensure that every part of a pharmaceutical installation meets the standards during every stage of its lifecycle (design, construction, startup, production, maintenance and decomissioning). Keywords are "Good practices" and "Traceability". It is a very large field and some parts of it may not require much technical knowledge. However, if you have to prove that a certain program in a controller will act in certain ways, it may be useful to at least know how these things work in order to design a testing procedure to prove (validate) that this is true.

Pharmaceutical Validation is always teamwork. Mechanical, electrical, automation, control, process and software engineers each have to assist the validation officer with all the necessary documentation and testing. The only person that is not really a technical specialist is the validation officer. However to be successful, he must have a broad knowledge of technical stuff without real specialized knowledge in a specific field. His main job task is the interfacing between the technical staff and the FDA and therefore he is responsible for the final FDA approval of the entire project.

Check out the 21-CFR-Part 11 regulations (Electronic Records, Electronic Signatures), which has become the standard for the pharmaceutical industry.

ANSI/ISA S88 design concepts make validation easier. A modular S88 design will allow one to validate (and revalidate) procedures and equipment separately. With well-written equipment phases, for example, once Phase A is validated, modifying other phases will not upset Phase A's validated state.
Also, validating a recipe procedure is easier once the phases are validated. Since recipe procedure code is decoupled from equipment phase code, the need to revalidate a recipe procedure does not necessarily require that all phases be revalidated. Theoretically, one can validate new additions to a process or revalidate changes to a process faster. Moreover, the S88 modular design approach helps minimize the risk that a change to one part of the process will affect another. Validating new additions to a process or revalidating changes to a process faster, results in the product making it to the market quicker.

IQ / OQ / PQ

Installation Qualification, Operational Qualification, and Performance Verification of equipment and instruments is a vital link in the quality chain. One of the major areas of focus for both FDA (or any other regulatory body) and client audits. All equipment and instruments must meet manufacturer's or preset standards for operation and performance.

Installation Qualification does not just apply to a brand new piece of equipment or instrument. A used instrument or piece of equipment that is new to the site must also undergo installation qualification. Movement of equipment or instruments requires re-Installation Qualification to ensure proper operation. Many new pieces of equipment and instruments include either instructions for IQ or options for the manufacturer to perform IQ for you.

Operation Qualification and Performance Verification must be perform at least annually for every piece of equipment or instrument. Most manufacturers have provisions for performing these services, at a cost. This can be confusing, time consuming and costly to allow the manufacturer to perform.

Performance Verification is also necessary for movement of equipment and instruments to prove the operation prior to and after the movement of said equipment and instruments.

What is Biotechnology?

Biotechnology is technology based on biology, especially when used in agriculture, food science, and medicine. The UN Convention on Biological Diversity has come up with one of many definitions of biotechnology: "Biotechnology means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."

Traditional pharmaceutical drugs are small chemicals molecules that treat the symptoms of a disease or illness - one molecule directed at a single target. Biopharmaceuticals are large biological molecules known as proteins and these target the underlying mechanisms and pathways of a malady; it is a relatively young industry. They can deal with targets in humans that are not accessible with traditional medicines. A patient typically is dosed with a small molecule via a tablet while a large molecule is typically injected.
Small molecules are manufactured by chemistry but large molecules are created by living cells: for example, - bacteria cells, yeast cell,animal cells.

Modern biotechnology is often associated with the use of genetically altered microorganisms such as E. coli or yeast for the production of substances like insulin or antibiotics. It can also refer to transgenic animals or transgenic plants, such as Bt corn. Genetically altered mammalian cells, such as Chinese Hamster Ovary (CHO) cells, are also widely used to manufacture pharmaceuticals. Another promising new biotechnology application is the development of plant-made pharmaceuticals.

Biotechnology is also commonly associated with landmark breakthroughs in new medical therapies to treat diabetes, Hepatitis B, Hepatitis C, Cancers, Arthritis, Haemophilia, Bone Fractures, Multiple Sclerosis, Cardiovascular as well as molecular diagnostic devices than can be used to define the patient population. Herceptin, is the first drug approved for use with a matching diagnostic test and is used to treat breast cancer in women whose cancer cells express the protein HER2.

What is a Bioreactor?

A bioreactor may refer to any device or system that supports a biologically active environment. In one case, a bioreactor is a vessel in which is carried out a chemical process which involves organisms or biochemically active substances derived from such organisms. This process can either be aerobic or anaerobic. These bioreactors are commonly cylindrical, ranging in size from some liter to cube meters, and are often made of stainless steel.

A bioreactor may also refer to a device or system meant to grow cells or tissues in the context of cell culture. These devices are being developed for use in tissue engineering.

On the basis of mode of operation, a bioreactor may be classified as batch, fed batch or continuous (e.g. Continuous stirred-tank reactor model). An example of a bioreactor is the chemostat.

Organism growing in bioreactor may be suspended or immobilized . The simplest, where cells are immobilized, is a Petri dish with agar gel. Large scale immobilized cell bioreactors are:

- packed bed
- fibrous bed
- membrane

Bioreactor design is quite a complex engineering task. Under optimum conditions the microorganisms or cells are able to perform their desired function with great efficiency. The bioreactor's environmental conditions like gas (i.e., air, oxygen, nitrogen, carbon dioxide) flowrates, temperature, pH and dissolved oxygen levels, and agitation speed/circulation rate need to be closely monitored and controlled.

Fouling can harm the overall sterility and efficiency of the bioreactor, especially the heat exchangers. To avoid it the bioreactor must be easily cleanable and must be as smooth as possible (therefore the round shape).

A heat exchanger is needed to maintain the bioprocess at a constant temperature. Biological fermentation is a major source of heat, therefore in most cases bioreactors need water refrigeration. They can be refrigerated with an external jacket or, for very large vessels, with internal coils.

In an aerobic process, optimal oxygen transfer is perhaps the most difficult task to accomplish. Oxygen is poorly soluble in water -and even less in fermentation broths- and is relatively scarce in air (20.8%). Oxygen transfer is usually helped by agitation, that is also needed to mix nutrients and to keep the fermentation homogeneous. There are however limits to the speed of agitation, due both to high power consumption (which is proportional to the cube of the speed of the electric motor) and the damage to organisms due to excessive tip speed.

Industrial bioreactors usually employ bacteria or other simple organisms that can withstand the forces of agitation. They are also simple to sustain, requiring only simple nutrient solutions and can grow at astounding rates.

In bioreactors where the goal is grow cells or tissues for experimental or therapeutic purposes, the design is significantly different from industrial bioreactors. Many cells and tissues, especially mammalian, must have a surface or other structural support in order to grow, and agitated environments are often destructive to these cell types and tissues. Higher organisms also need more complex growth medium.