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COPADATA

The Validation Monster

How to tame it using zenon Pharma Edition

Whether you are involved with the pharmaceutical industry or not, you can appreciate the strictly regulated operations that characterize the production of drugs. After all, these are very toxic substances and it is critical that each tablet contains the exact recipe. How do we ensure production operates within the strict regulatory policies? The answer is validation of the processes, procedures and equipment. zenon has a successful history in pharmaceutical production. In operation, it goes beyond the direct needs of the FDA regulations and helps users to identify opportunities to better the process. In this article, I would like to look at the validation process: the path from design concept to the turning of the key which begins production.

WHY DO WE NEED TO VALIDATE?

Just because somebody says they can do something, it doesn't mean they can do it to a satisfactory standard. The validation process balances the user requirements of the equipment or process with the appropriate testing and proof. At the heart of validation is the requirement to prove that a process fulfils its intended purpose – and to demonstrate that the product is produced each time within the limits of variation stated.

WHAT IS THE DIFFERENCE BETWEEN QUALIFICATION AND VALIDATION?

We qualify equipment and validate processes. This means equipment operation is compared against requirement specifications: does it work as intended? Does it fulfil the required purpose? Validation looks at the whole process: SOPs (Standard Operating Procedures), cleaning, calibration, maintenance, and training. Qualification is, therefore, part of validation. Of course, HMI/SCADA applications control the machine, so they are involved in the machine qualification. But user interfaces are at the heart of validation: SOPs run via the operator through the visualization system so the validation of a process also directly involves the HMI/SCADA.

WHAT DOES VALIDATION COST?

We are very familiar with the design aspect of a project. The decisions and detail attacked at this stage determine the success at the commissioning stage. This is no different with validation: having a clear focus on qualification at each stage of the project significantly improves validation results and reduces its cost by reducing the time required.

Project design needs at least one person. Validation needs at least two people: one person carrying out the qualification and the other checking this work. Now we start to see where the costs escalate; we have a situation where the cost of validation is at least twice that of the design stage.

This fact makes the validation effort a key factor in decision-making concerning change in the pharmaceutical industry. Business risk is assessed with each change to an element on the concept drawing board: what does it cost? What are its benefits? What cause and effect prognosis can be determined? Didn't life just get difficult!

As difficult as it may be, validation is not going away. Nor should it; as well as underwriting consumer safety, as a result of it better philosophies, mechanisms and processes have been developed over the years which have shaped the industry. Every process has its life-cycle and in the early 1990s the current approach to learning and the implementation of validation in an automated world started to unfold. Back then, the need to apply qualification to automated equipment that fulfils the FDA paper-based processes on pharmaceutical production regulation increased. This has developed into a "validate all" culture, which has made innovation difficult and halted progress. But the world keeps turning, and now we are witnessing a new phase in this life-cycle.

Validation to achieve regulatory compliance is not the only element of the equation which has halted innovation in pharmaceutical production. The drug patent has generated substantial revenue to support significant growth in the industry. The patent guarantees sole proprietary of revenue from each patented drug for its originator, which means increased profits to recover Research and Development expenditure. This patent protection has given the pharmaceutical industry security to produce at a high cost and funded a $700 billion distribution market.

"By the early 2000s, automation projects were being implemented with only 10% of the effort on design and coding, but 90% of the effort on testing and producing documentation*," says Dave Adler, Process Control Engineer and Certified Automation Professional at Brillig Systems Inc.

From Adler's observation, we can see that the money involved in the industry has itself

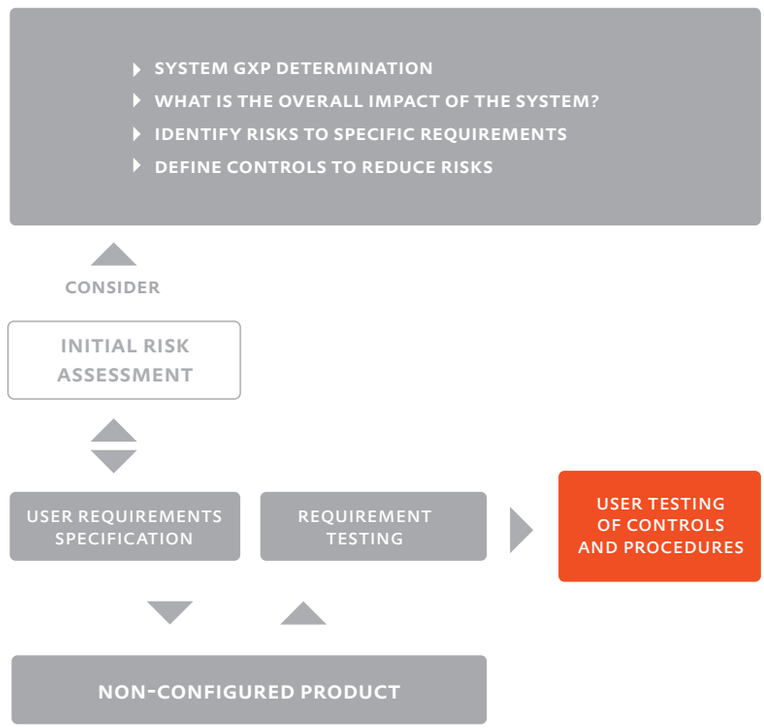

Figure 1

* Source: http://www.isa.org/InTechTemplate.cfm?template=/ContentManagement/ContentDisplay.cfm&ContentID=81660

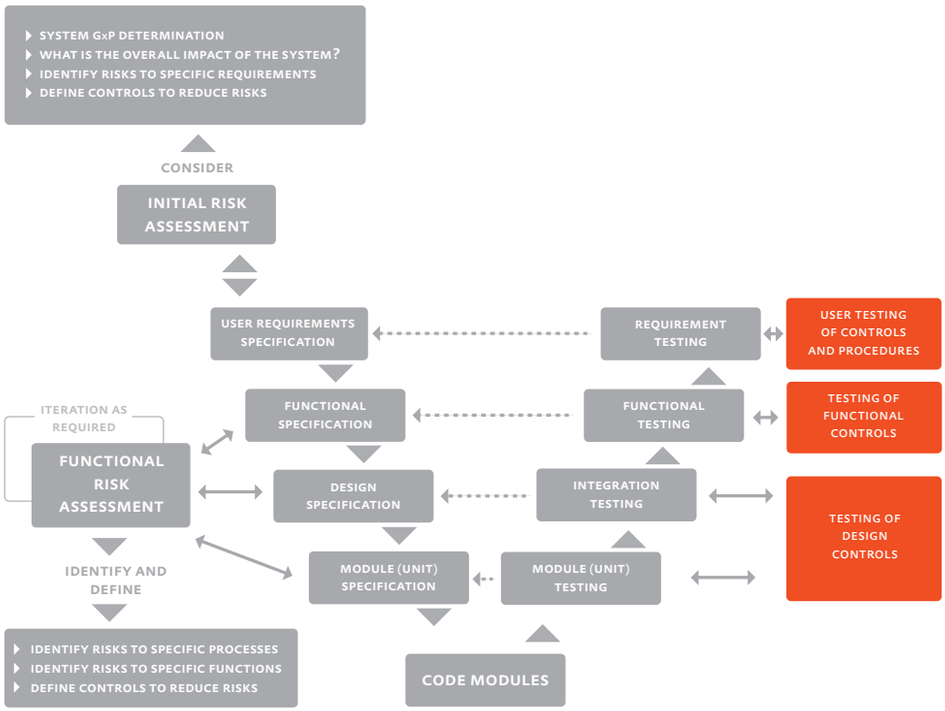

Figure 2

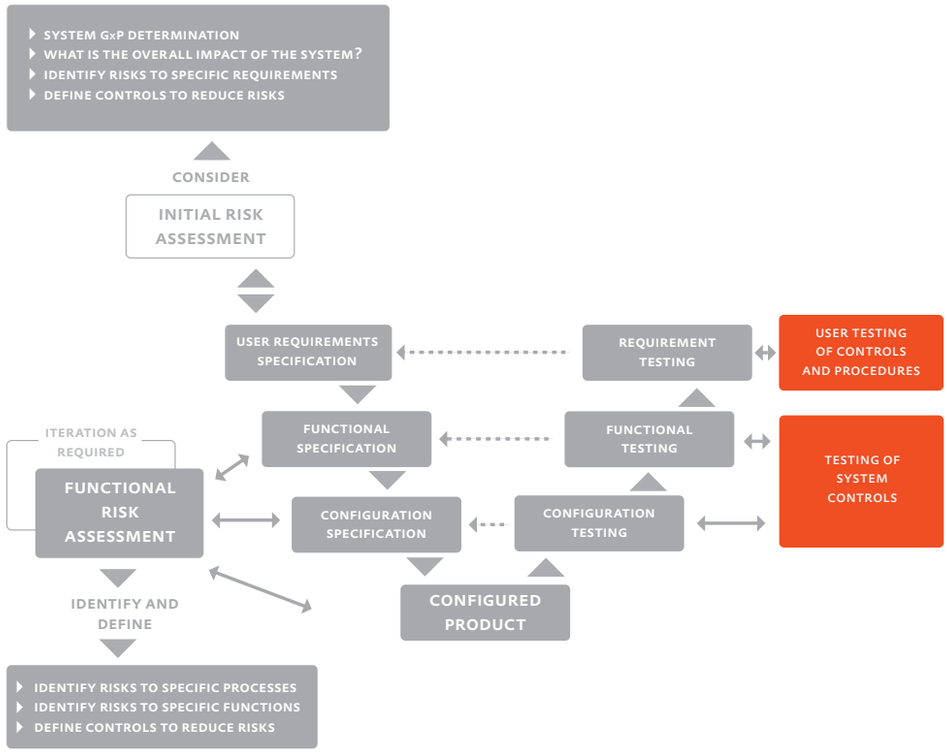

Figure 3

funded the FDA, which in turn has helped to increase quality and safety to patients, which is good. The validation path is a long one, and many lessons have been learnt along the way, with positive outcomes to regulation. With elapsing patents, the potential cost recuperation is not guaranteed and the cost of manufacturing and manufacturing efficiencies become important parameters in the equation. The FMCG industry has excelled in innovation, with very enviable OEE figures; in contrast, pharmaceuticals see diminished OEE figures due to a lack of innovation. Now, the focus for pharmaceutical production is changing from new drug introduction with patent protection, to greater efficiencies. The industry is learning how to adapt and the validation process will play a big part in this picture.

THE VALIDATION PROCESS

COPA-DATA addresses these issues in zenon: parameterization instead of programming, with integral functionality makes any project a GMP project. Creating automation simply by enabling parameters goes beyond merely applying the FDA Part 11 – zenon removes the additional effort required when using other systems.

Let us take a look at the types of control processes and the effect on validation. The ISPE (International Society for Pharmaceutical Engineers) is a global organization for professionals focusing on automation and innovation in the pharmaceutical industry. ISPE documents industry best practices. It publishes the GAMP (Good Automated Manufacturing Practice) guidelines on approaching compliance using automation: The following describes how different levels of software are validated.

GAMP SOFTWARE CATEGORY 3

Our first example looks at a software category 3 application – a non-configured system, such as a standalone PID controller.

Our scenario involves a temperature controller which reads from a certain temperature probe, the output of which is connected to a heating element or valve. The output is controlled around a specified temperature point. The controller only has one function and cannot be used for another task. Its function can be well-defined, with ranges and behaviour tested.

The risk to a process with this type of control is low, because only one control path can be taken. The complexity is low and the novelty is low; it is well-defined and testing produces documentary evidence.

Figure 1: This validation model shows the stages of design and the type of validated evidence they require to prove their operation meets the intended purpose. Here, only the user requirement level is tested within its defined limits.

GAMP SOFTWARE CATEGORY 5

The opposite end of the scale to the standalone PID controller example is programmed code. There are a thousand and one ways to code a certain function. Each programmer has his or her style and the range of operation and width of output can be very large. The outcome of each line of code has effects on the operation and variation. Couple this with the complexity and unpredictability of unique and novel programmed code functionality and the risk to the process is high.

Figure 2: This validation model illustrates how much greater effort is required for the achievement of validation when programmed code is involved.

GAMP SOFTWARE CATEGORY 4

Modern facilities cannot be a collection of PID controllers. We appreciate better intelligence and communication is needed to facilitate leading-edge solutions in pharmaceutical production. COPA-DATA has long since advocated parameterization in zenon's automation functionality. Parameterization eases the design burden in a project. By creating a library of functions which cover most of the engineering challenges in the automation business, we reduce the complicated protocol of these functions to simple parameter-setting. Whole projects can be administered without a single line of code. Configuration has one unique benefit in terms of validation: it sets a well-defined path with limitations on risks. The designer builds these pre-defined blocks together to produce the desired result, each block is proven, and the individual parameters

are clearly visible and can be verified easily.

Figure 3: This validation model shows the reduced number of levels needed to create the same level of control that the programmed code achieved. The complexity and novelty is reduced and less bespoke documentation is needed so the effort required for validation is far less.

PROVEN FUNCTIONALITY HELPS PREDICT RISK

Figure 4 shows how the risk of a certain function is determined. The severity is balanced against the probability of occurrence. Therefore, if the chance of this event happening is very low, the effect on the system can be great before this needs attention. On the other hand, when an occurrence is very likely, only a slight effect can have significant consequences. This eventuality is then balanced against whether an event can be detected and the affected product removed or quarantined.

Figure 4: All of this process needs to be proven and documented. This is where proven functionality, which has been tested and verified, significantly reduces the total project costs.

ZENON PHARMA EDITION

zenon is perfectly placed in pharmaceutical production automation. The zenon Pharma Edition builds on this expertise and provides a framework for regulation. The software specifically addresses the regulatory aspects of a project, creates a central placement of regulation parameters, and provides proof of how and where security is enabled. This design knowledge is stored in a configuration file, which can then be validated once and transferred across all and any projects. The backend of the project is also addressed with automated project documentation and project comparison. These two features create and record information on project content and evolution, which focus on specific elements under the validation inspection. These can be used to prove the content of a project, to accurately display changes and additions in a project, and compare it against a benchmark. This helps users to manage the regulatory aspects of projects from conceptualization to implementation.

Each configuration file holds the parameter knowledge for user administration, alarm and audit trail activity, network and redundancy. The profile combines these parameters with proven templates for screens, data types, reaction matrix, colour schemes, symbols and reports. An entire project behaviour is defined, where only the specific automation control needs to be added. Each project can begin with this profile installed, or it can be applied during project development, or during machine use. Thus, the zenon Pharma Edition helps users maintain a secure compliance culture across a production facility, across third party machine builders and system integrators, thereby covering the entire corporation. Regulated customers have the ability to use the same process model, created and stabilized in

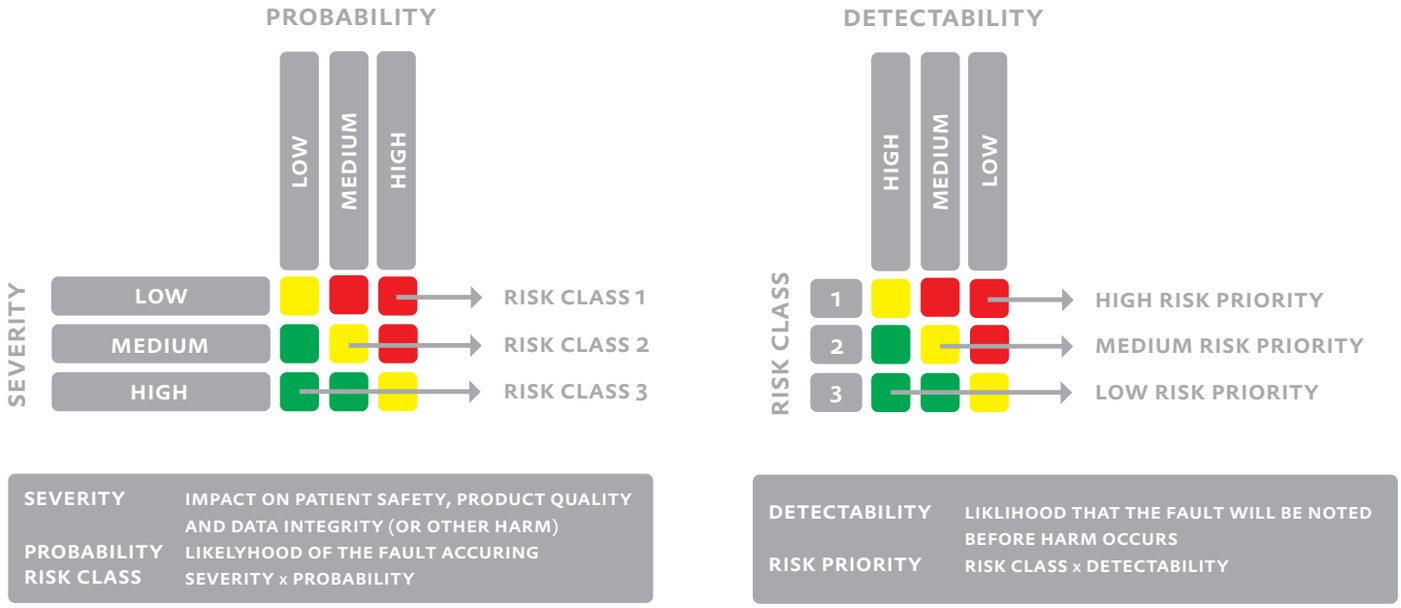

Figure 4

the laboratory, then applied directly into the commercial operation under the same basis for regulation, security and validation control. As a result, zenon users retain the regulatory knowledge, to be applied time and time again – not reinvented each time.

CONCLUSION

In the pharmaceutical industry it is necessary to define and fix your requirements before development: it is significantly more difficult to iron out bugs and errors during start-up than at the conceptualization.

In light of the validation process each project element must complete successfully, using a proven profile to form the foundation and backbone of a project and documenting the detailed contents and behaviour of the project and its evolution aids the project at all stages of its life-cycle.

Let the technology be the facilitator of the work and detail, so you can direct your energies into improving efficiency and innovation in your project design. With the zenon Pharma Edition you can easily deliver GMP projects and, step-by-step, remove the hoops you need to jump through before you achieve project sign off. *Robert Harrison*