ORION C.E.

KAYE
SUBSIDIARY OF AMPHENOL

Computer System Validation

THERMAL VALIDATION SYSTEMS IN SOUTH AMERICA

Author: Emerson Aparecido Miguel-Orcid: https://orcid.org/0000-0003-2582-1182 – 15/11/2021
Key words: Validation, Good Manufacturing Practices, Safety, Computerized systems

Introduction

With the rapid advances of science and technologies within the Life Sciences industries, health agencies throughout South America are continuing to update and define regulations and guidelines around the basic requirements for the development, manufacturing, and distribution of drugs, medicines and devices. The compendium of regulations and guidelines issued in all countries, are intended to ensure that the use of safe practices is observed in the development of activities that attest to the safety and efficacy of medicines for the protection of patients. Through regulatory agencies a more cohesive adopted set of regulations (PIC/S, WHO, ISO etc) around areas such as Validation and Qualifications are continuing to evolve. These regulations provide comprehensive guidelines on the steps and actions required to certify the conformity of processes, equipment, and systems. Computer system validation, CSV, is part of this chain of activities in which we can include the systems used for the practice of thermal validation. Having suppliers who know their role in developing software that can provide accurate, reliable, documented data with integrity while still be able to promote complementary activities based on science, is essential to understand and have total control of these systems throughout their life cycle. This article is intended to provide important information and specific descriptions of the main stages, fundamentals, software and hardware classification related to Computer System Validation, and their impact on thermal validation systems and activities.

CSV Regulations in South America

Several regulatory agencies and their professionals strive to follow paths that guide the regulatory methodology, contributing to the processes to ensure less variability, greater safety, and even better quality of the final product with maximum patient protection. Regulatory agencies in South America are continuing to improve their regulatory methodologies and inspection systems, in order to contribute to these goals and to raise the South American market for globalization in pharmaceutical production. Much of this effort has been influenced by the guidelines of multinationals companies from North American, European and Asian, which has contributed to the migration of best international concepts for inspection and audits. As a result of the changes several new pharmaceutical quality assurance guidelines have been adopted which have helped standardize processes, validation methodology decision making, and risk assessment.

In Brazil, the regulatory agency for good manufacturing practices, ANVISA, emphasizes that these guidelines are widely used to validate a process, a methodology, a cleaning procedure, and even qualify the various equipment used (ANVISA IN47, 2019). Thus, the validation activity has the definition of being the documented proof of any procedure, process, equipment, material, activity, or system operate and function correctly and their execution leads to the expected results (ANVISA RDC 301, 2019).

The present article evaluated and synthesized, some of the requirements of good manufacturing practices in some South American countries, such as Argentina (ANMAT), Chile (ANM), Colombia (INVIMA), Brazil (ANVISA) and Peru (ANM) through the compendium of the regulatory bodies in each of them for the development of the validation methodology in computerized systems regarding the use of systems or instruments for specific thermal validation activity.

Computerized systems, which are defined as all systems that include data input, electronic processing, and output of information to be used for reporting or automatic control, also require special attention, being considered critical support systems and have specific documents for professionals to follow (ANMAT 3602, 2018, ANVISA RDC 301, 2019, ANM 021-2018-AS, 2018 and INVIMA 1160, 2016).

In Brazil, Computerized Systems Validation now has its own focus under the gaze of ANVISA Normative Instruction 43, which "Provides for Good Manufacturing Practices complementary for computerized systems used in the manufacture of Medicines" and aims to adopt the Good Manufacturing Practices guidelines related to computerized systems of the Pharmaceutical Inspection Cooperation Scheme, (PIC/S), as complementary requirements to be followed in the manufacture of medicines in addition to RDC 301 (2019).

Argentina regulations developed by ANMAT, pointing out the procedures to be followed in Annex VI of the national guide of good manufacturing practices. Since January 2008, ANMAT (Argentina) and January 2021, ANVISA (Brazil) integrate the PIC/S, an international initiative for inspection of good pharmaceutical practices having 54 participating members. Among the recommendations described in their compendium, is cited the requirement for confirmation of computerized systems validation provided for use in various processes and with activities included in the stages of qualification of validation processes. Figure 1 shows the representativeness of the PIC/S in the world and its participation in South America, which has Argentina and Brazil as member countries so far.

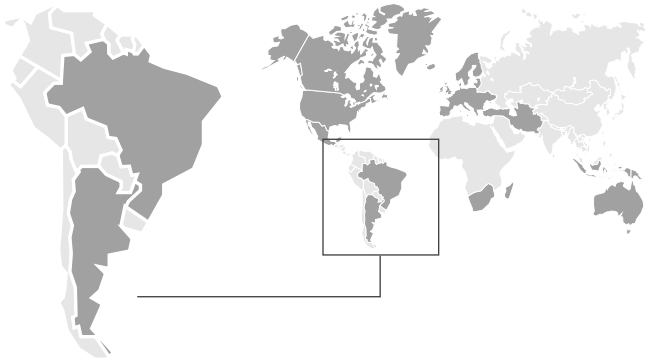

Figure 1 – PIC/S member countries around the world with a focus on South America | Source: Kaye

Specific activities of equipment performance qualification are largely developed with the use of computer and instrumentation equipment, used for data collection, statistical calculations and even the generation of detailed reports of critical process measurands and sensors used to validate that the equipment is fit for its purpose. e practice of qualifying the performance of this equipment, also known as Thermal Validation, includes the monitoring of critical process parameters such as temperature pressure, relative humidity, light intensity, etc., to validate the performance of the process t as shown in figure 2. According to the Brazilian Association of Technical Standards, ABNT, this specific activity in the industry gained strength decades ago and the market currently has highly sophisticated instruments, with great precision, safe and protected against adjustments that would invalidate the measured results (ABNT NBR 16.328, 2014).

Figure 2 – Example of thermal equipment to be qualified
Source: Kaye, istockphoto

The choice of instruments from suppliers who know the needs of the pharmaceutical industry and have, developed their devices taking into account the important of data accuracy, repeatability, reporting and protection is critical to all your validation efforts.

The thermal validation practice, in general, besides being obligatorily in large number in pharmaceutical processes (table 1 shows examples of thermally validated equipment, process and quantities to be measured), undoubtedly contribute to less variability in the process, greater safety, and even better quality of the final product.

Equipment	Process	Involvement stage	Measured quantity
Cold chain (cold chambers, refrigerators, freezers)	Packaging of raw materials, reagents, finished products	Production (formulation), quality control, distribution	Temperature
Stability / photostability chambers	Packaging of finished or partially produced product without the final packaging	Quality control	Temperature, relative humidity, light intensity
Tanks and reactors	Mixing, reactions	Production (formulation), sterilization	Temperature
Sterilizers (autoclaves)	Sterilization, decontamination, heat treatment	Production (formulation), quality control and final stage (finished product)	Temperature, pressure
Incubator	Incubation, growth	Quality control	Temperature
Freeze dryers	Freeze-dried, sterilization	Production (formulation)	Temperature, pressure
Kilns and dry sterilization tunnels / depyrogenization	Sterilization, depyrogenization	Production, quality control	Temperature
Water bath	Incubation, heat treatment	Quality control	Temperature

Table 1 – Example of thermal validation application in pharmaceutical industry equipment

CSV fundamentals and steps of a thermal validation system

ANMAT (Argentina) through the provision 3602/2018 in its annex VI, provides about the basic requirements that evaluate the risks, the personnel involved, suppliers of the systems and services, as well as each step to be proven when using computerized systems as part of the activities regulated by the Good Manufacturing Practices. ANVISA (Brazil) through the Guide n°33 seeks to contribute with the understanding of all the steps to be developed for a CSV. In both documents, these two countries aim to internalize the content of the ISPE (International Society for Pharmaceutical Engineering) guide "GAMP5", which is in version 5 published in 2008. The ISPE was founded in 1980 by members of the North American industry, and today has participants from all over the world, and the South American countries can benefit from its contributions, with the GAMP 5 being the base document for understanding the CSV. The interaction of users and the various levels of operation with computerized systems, is further affirmed by the integration with the PIC/S, more specifically through the PI 011-3 guide, from September 2007. Finally, another reference that is very relevant to the issue, is the FDA (Food and Drug Administration) 21 CFR part 11, which states that electronic records and electronic signatures are treated the same as paper records and handwritten signatures. Regulated companies with any documents or records in electronic format must comply with the regulation, and this point is described in the documents of resolution 1160 of INVIMA (Colombia) and in item 5.66,

section V (critical support systems) of ANM Supreme Decree 021-2018-AS (Peru) as highlighted points due to concerns about access, manipulation, traceability of confidential data and electronic signatures when making use of computerized systems. Table 2 describes the main documents addressed for a CSV evaluated in this article, however it is highlighted the fact that it was not possible to investigate if in the South American continent there are other documents of impact in this process and that could contribute to the improvement of the practice pointed out in CSV.

More recently significant focus has been placed around "Data Integrity" guidelines around the protection, and storage of data.

Document	Título	Publication	Agency/Country
3602/2018 (DI-2018-3827-APN-ANMAT)	Good Manufacturing Practices Guide for Manufacturers, Importers/Exporters of Medicines for Human Use	19/04/2018	ANMAT/Argentina
Exento 159	Updates technical standard n°127, named, "technical standard of good manufacturing practices", approved by decree n°28 exempt, from 2012	11/04/2013	MS-ANM/Chile
1160	Resolution 1160 from 2016. Good Manufacturing Practices for Medicines: Fundamental Principles	10/04/2016	INVIMA/Colombia
021-2018-AS	Manual of Good Manufacturing Practices for Pharmaceutical Products	20/08/2018	ANS-ANM/Peru
Guide No 33	Guide for validation of computer systems	14/04/2020	ANVISA/Brazil
IN43	Provides for Good Manufacturing Practices complementary to the computerized systems used in the manufacture of medicines	21/08/2019	ANVISA/Brazil
PI 011 3	Good Practices for Computerised Systems in Regulated "GxP" Environments	25/09/2007	PIC'S/Switzerland
21 CFR part 11	Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application	08/2003	FDA/EUA
GAMP 5	A Risk-Based Approach to Compliant GxP Computerized Systems	02/2008	ISPE/EUA

Table 2 – References evaluated for the development of CSV in South American countries

The key concepts of a CSV for starting and engaging with the various activities and steps can be:

» **Process and Product Understanding:** The references are concerned that the users have detail, science-based, knowledge of the process and product to which they are involved. Only then will it be possible to prepare the initial documents for decision making when choosing a system for thermal validation practice;
» **Life cycle approach within quality management systems:** It is necessary to perform activities in a systematic way from the conception of the system until its retirement, and it is expected that as more knowledge is gained about the system during its use, continuous improvement of the process and of the system will be allowed. Figure 3 demonstrates the main phases of the life cycle of a computerized system, pointing out the main stages. The ICH (International Council for Harmonization), an entity globally recognized for contributions to harmonization in pharmaceutical processes in more than 25 years of existence, can also contribute to understanding the step-by-step of a life cycle through the Q12 guide (ICH Q12), being a valuable reference to broaden the field of vision in a macro way to the processes.

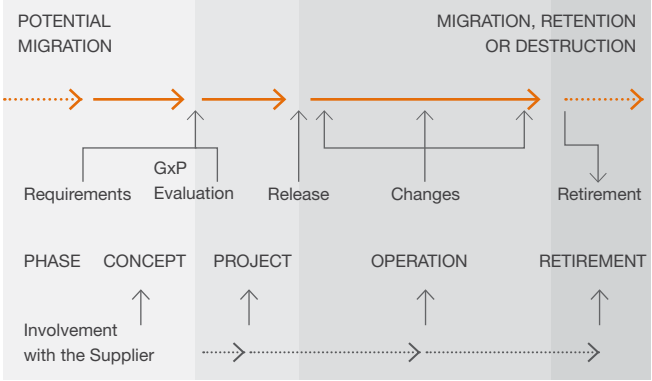

Figure 3 – The life cycle phases of a computerized system
Source: Guide no. 33 ANVISA.

» **Scalable life cycle activities:** Should be developed in a way that ensures patient safety, product quality, and integrity of the data collected by the thermal validation system. It also points to issues such as system complexity versus innovation, vendor evaluation, and business impact of the system.
» **Leveraging Supplier Involvement:** Companies should select the suppliers of thermal validation systems with special attention, as these suppliers can assist in the initial development of steps, since the user requirements in the risk management stage. Competence and trust under the supplier should be considered essential elements during product selection, thus reinforcing the importance of a good partnership throughout the activity.
» **Quality risk management (science-based):** Since this item is currently widely applied in the industry according to the provision 3602/2018 of ANMAT (Argentina) and the RDC 301/2019 of ANVISA (Brazil), it will be addressed in more detail below, thus contextualizing at this point a systematic process for evaluation, control, communication, and review of risks associated with the processes to which the thermal validation system will lead results for decision making. The GAMP 5 is a qualitative tool for management analysis that contributes in a unique way as a fundamental point for the development of a risk analysis regarding the direct or indirect impact, stored data, understanding regarding the components of the thermal validation system. However, it should be emphasized that the division of tasks with a multidisciplinary team and mutual collaboration at all levels of the company hierarchy are essential to achieve the main objective.

Risk Management Approach

Risk analysis can be defined as a set of questions to assess the probability of an adverse effect happening by an agent, whether physical, chemical, biological, industrial processes, technology, natural process, etc., and what is the severity of these effects, also analyzing that may occur not only loss of production, but also adverse effects related to health, disease and even death, of the employee or customer / patient (MOLAK, 1997).

The ICH Q9, indicated in the provision 3602/2018 of ANMAT (Argentina), structured the risk assessment required in all manufacturing activities, at each step. The pharmaceutical industry through quality systems, makes it evident that quality risk management is a critical component to having an effective quality management system and this does not exclude the systems used for thermal validation activity. It is understood that risk is the combination of the probability of a damage occurring, the severity that this damage may cause, and the ease or not of detection. However, the way to insert this analysis is complex because it must reach a shared understanding

among several stakeholders because what may be probable and serious for one, will not necessarily be for the other, and having or not tools to detect it, for this reason it must be well evaluated by a specific and multidisciplinary committee.

Throughout the life cycle of facilities, equipment, processes, and medications, risk management should be addressed in reference to the impact they individually and collectively have on the quality of the final product (ANVISA RDC 301). Commonly, risk analysis is used, with the application of the FMEA tool (Failure Mode Effects Analysis). FMEA can be understood as a systematic methodology that allows the identification of potential failures of a system, project and/or process with the objective of minimizing or eliminating the associated risks before such failures occur (BASTOS, 2006). ICH Q9 presents several tools that individually or in combination help identify, contain, mitigate, and control potential risks and that should be applied to evaluate a thermal validation system.

Production activities have, by nature, some type of risk associated with the process, which may impact to a greater or lesser extent the quality, safety, and efficacy of the final product, which as indicated have a direct impact through the decisions accepted based on the results of the monitoring performed by the thermal validation instruments. Any risk and/or quality deviation that may occur at any stage of production must be contained, mitigated, and controlled, even if it has never occurred. For any risk involving product quality, environmental protection, operator and/or patient health, its identification, assessment, communication, and control for mitigation becomes essential.

Within all these perspectives of risk control and management, we assume that it is vital to extend this issue to the thermal validation approach, associating and merging it with the available tools, because we will join all the ends of this complex, extensive, detailed, and interconnected path of medicine production, distribution, and dispensing, all with the major objective of saving lives. Therefore, it is clear that the thermal validation activity, with the use of computerized systems available in the market, begins its validation process even before the visualization of its operational tools, because if it is not possible to ensure that the system complies with all the points addressed by the risk analysis, its use will be unfeasible.

Key Steps for CSV of a Thermal Validation System

The main steps pointed out in the evaluated compendium, which will contribute to obtain assurance about the operation of a thermal validation system, which are exemplified in figure 4, can be, but are not limited to:

» **Qualification of design or project (QbD or QP):** Document intended to prove that new or refurbished facilities, systems and equipment have been developed and designed in correspondence with good manufacturing practices and that they are suitable for their designed purpose. It applies when facilities, systems and equipment have not been built at the time of its evaluation, so that it can be prevented at the documentary level and not at the physical level.
» **User Requirements Specification:** This document is intended to contain the entire strategy for the CSV activity and contains at least the points objective, responsibilities, description of the system and interfaces, validation strategy and scope, procedure and assumptions, acceptance criteria, change control program, deviation handling program, maintenance of the validated status, and documentation management. The thermal validation system should be covered in this document.

Figure 4 – Thermal Validation System | Source: Kaye

» **Master Validation Plan (MVP):** This document is intended to contain the entire strategy for the CSV activity and contains at least the points objective, responsibilities, description of the system and interfaces, validation strategy and scope, procedure and assumptions, acceptance criteria, change control program, deviation handling program, maintenance of the validated status, and documentation management.

The thermal validation system should be covered in this document.

» **Risk analysis (RA):** as previously discussed, it has a fundamental role, being considered by some professionals as one of the most important phases of the CSV process.

» **Functional technical specification (FTS):** Contains the specific data of the system operation, in this stage it is pointed out in more detail the components of the target system and necessary for thermal validation practice.

» **Installation Qualification (IQ):** Consists in the documented verification that the system as installed, complies with the approved project and the recommendations of its manufacturer. This document is usually developed by the supplier of the thermal validation system.

» **Operation qualification (OQ):** Consists of the documented verification that the system performs its functions as planned within the pre-established operating ranges. As with IQ it is commonly developed by the manufacturer of the thermal validation system.

» **Performance Qualification (PQ):** Consists of the documented verification that the system performs its functions effectively and reproducibly according to the approved specifications, but for a thermal validation system, which does not have the role of participating in a transformation process in the production chain, its development is considered by many professionals as being necessary only to follow its use in routine processes, for a short predetermined period, without any addition to the tests already performed in the QO, which may confuse as to its purpose or even be disregarded from the CSV steps. The manufacturer of the thermal validation system may contribute to defining the tests and evaluation period for the development of this item, but usually the end user is the one who defines the strategy to be used based on its validation routine and available equipment.

» **Traceability matrix:** Document developed so that requirements are addressed and traceable to the respective design/functional specifications and their verifications. This activity focuses on critical aspects for patient safety, product quality, and data integrity. Like the MVP, it must also include the thermal validation system.

» **Inventory:** Spreadsheet type document that integrates all the systems used in the industry with information about the responsible area, version, CSV status, among other available points.

» **Final Report:** As with all quality activities in a pharmaceutical industry, a conclusive report on the CSV must be issued and controlled by the pharmaceutical quality system. The items in the report can be risk analysis, test protocols, deviations, evaluation of the results found, change control, traceability matrix, annexes, or addendums for demonstration of supporting data of the tests used as evidence of execution, references used, such as manufacturer's manuals, guidelines, technical documents in general.

In other compendia such as Exento 159 of ANM (Chile) from April 2013, we find in Appendix 5 of Annex 1 the following steps for CSV and that should also be applied for thermal validation systems:

» System specification
» Operation specification
» Security
» Backups
» Validation (hardware and software)

In this document, the Institute of Public Health of the Chilean Ministry of Health develops some of the main items pointed out in this work with a wealth of useful details for compliance with good practices for CSV.
As shown, several areas and professionals come together in the development of the CSV, the responsibility can be shared or exclusive of the user within the industry, but the involvement of the supplier is essential for testing and verification which the company that is acquiring the thermal validation system does not have access. Thus, it is suggested through figure 5, that a flowchart summarizing the steps, sequences and responsibilities is created for better visualization of the involvement of all members.

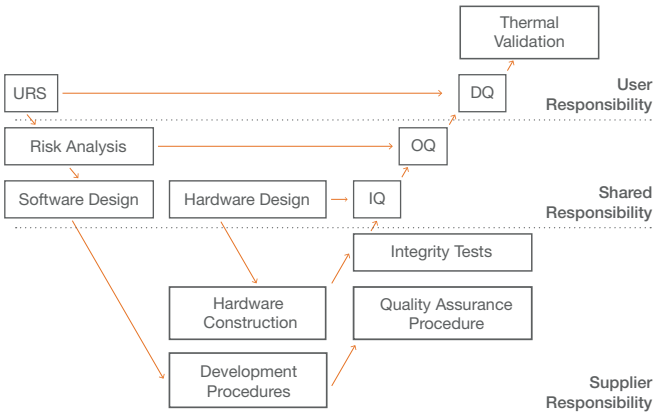

Figure 5 – Suggested flowchart of CSV development and control steps for thermal validation systems for the pharmaceutical industry

Classification of computerized systems

For this paper we will address the software categories 3, 4 and 5, "non-configured products", "configured product" and "custom applications", and hardware categories 1 and 2, "standard hardware components" and "custom embedded hardware components", of the computer systems extracted from GAMP 5, which have been simplified as follows:

» **Software category 3 – non-configured products:** Considered by many to be the category of thermal validation systems, this category is noted as software with off-the-shelf functions used generally. In this category the software cannot be configured for possible customization by the user, but in a thermal validation system there may be a function that can be considered configurable, which is related to lethality calculations for disinfection, sterilization, and depyrogenization cycles. This is because thermal validation systems are designed to address a range of processes of this nature and the user must receive specific training to develop this activity that is widely applied in the hospital, food, and pharmaceutical areas. The treatment of this category is summarized in a simplified life cycle approach, the supplier evaluation should be based on risk management, the user requirements are developed focusing on the fundamental aspects of use. There is no need for functional and design specifications, and verification consists of a single phase of testing, however standard operating procedures and training must be developed, as well as risk analysis, installation qualification, operation, and performance. A supplier / manufacturer such as "Kaye" (an Amphenol Advanced Sensors company), which has great expertise in the development of thermal validation systems and which makes important contributions worldwide with software development according to international technical standards of great impact, presents further below, attributes of documentary evidence such that, makes this system a strong candidate to also fall into category 4, where the levels of requirements for the system are higher.

» **Software category 4 – Configured Products:** As the name suggests, in this category the pharmaceutical industry can configure the system for a specific business process, so functional and design specifications are required, but they can come from the manufacturer, but the regulated company must have complete documentation that ensures the traceability of functional specifications and their respective tests. A life cycle approach and risk-based supplier evaluation and demonstration of the supplier's quality management system is required, explaining why the Kaye systems would meet these requirements, because there are documents to support this framework. Tests to demonstrate your application as designed in a risk-based test and production environment are developed, as well as procedures for maintaining compliance and suitability for use and data management.

» **Software category 5 – Customized applications:** These are products developed specifically for the pharmaceutical industry; therefore, all levels of documentation and testing are applicable, which makes this activity more complex than the other categories.

» **Hardware Category 1 – Standard Hardware Components:** Most hardware used in the pharmaceutical industry falls into this category, as do thermal validation systems. The standard hardware components should be documented including details about the vendor, who for thermal validation activity is directly responsible for maintenance and service during the lifetime of the product. In this category, configuration management and change control must be developed by the user.

» **Hardware category 2 – Customized embedded hardware components:** Category 5 systems for software typically have hardware which falls into this category and in this activity a design specification (DS) is applicable in addition to the category 1 controls and is subject to acceptance testing, an audit at the supplier for custom hardware development, and configuration management and change control.

Importance and Impact of CSV of a Thermal Validation System

Thus, in addition to demonstrating the accuracy, repeatability and instrumental suitability for measurements in the various environments and equipment mentioned above in the practice of thermal validation, the systems need to ensure the regulatory authorities that they are amenable to control and protection of valuable information on the processes evaluated and also that they have documentary basis, as shown in Table 3, to support that all points vital in this practice were properly developed and tested before releasing the system for use.

Item	Document	Document approach
1	Quality control document	Control of quality documents, policies and implementation, quality certification
2	Development procedures	Design control and project management and functional specification
3	Quality Assurance Procedures	Test plan procedure and quality assurance test case
4	Release documents	Release documents, product quality assurance certification and other product information
5	Quality Assurance Test Documentation	Functional testing documents of all system components (software / hardware / firmware)
6	Installation Qualification Protocol	Installation test plan indicated to the end user
7	Operation Qualification Protocol	Operational test plan indicated to the end user
8	Validation reference documents	Compiled from all documents listed above

Table 3 – Document's part of Kaye's CSV development

The various steps to be completed can and must have the participation of the supplier of the thermal validation system, thus, figure 6 illustrates in which documents and activities, more specifically, the involvement of the supplier of the thermal validation system is necessary, either in partnership with the industry or individually by the supplier or the industry, which based on science, has fundamental participation in this process of developing documents that support each of the activities pointed out:

» MVP – Master Validation Plan
» User Requirements Specification
» RA – Risk analysis
» FT / FS – Functional technical and Functional specification
» QbD – Qualification by design
» IQ – Installation Qualification

Another point to be discussed in this process is the measurement accuracy of these instruments, it is a very important point, also it can be favor or not, processes with serious deviations if they do not have the correct level of assertiveness in their readings. To this requirement the technical standard of the Brazilian Association of Technical Standards, ABNT (Brazil), in its document NBR 16.328 of 2014, points out the maximum error of all components involved in thermal validation systems when using temperature sensors and the maximum error obtained during the calibration of pressure and humidity. This specification must be respected according to table 4.

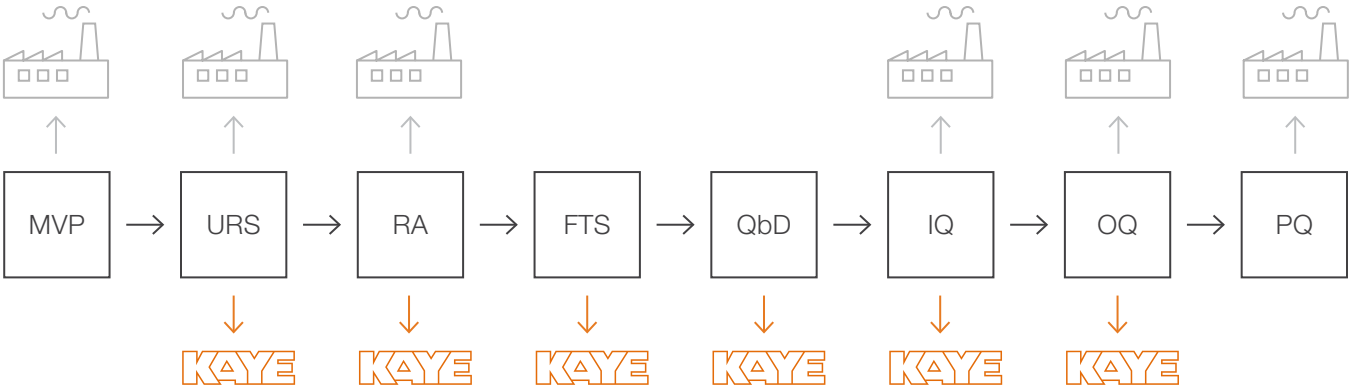

Figure 6 – Activities for CSV of the thermal validation system and the participation of the document developers together or individually

Measured quantity	Device Type	Allowable error by NBR 16.328	Comments
Temperature	Thermocouple type T	0,3°C	Total error (cold joint, analog to digital converter, linearity, medium thermal and working temperature measurement standard)
Humidity	Capacitive-type moisture transmitters	3% RH	Transmitter must be loop calibrated
Pressure	Signal transmitters in volts or milliamps	0.8% of the full scale in the range of 4kPa to 100kPa	Transmitter must be loop calibrated

Table 4 – Technical specification for sensors in thermal validation systems

For critical processes such as sterilization and depyrogenization, failure to meet these items may result in an immeasurable catastrophe due to its impact on the approval of stages of partial or terminal production of injectables, which have among their acceptance criteria, the results of lethality calculations, F0 and/or FH (mathematical calculations to stipulate the level of death of microorganisms - F0, or level of destruction of endotoxins – FH) noted in technical standards such as ISO 17. 665-1:2006 and ISO 20.857:2010. These values, if wrong due to error or inaccuracy in their reading, negatively influence decision making, because the conversion performed through the temperature reading for the F0 or FH are strongly impacted by calibration errors or lack of technical specification for this purpose. Table 5 shows the impact on the calculation of F0 and FH considering reading errors up to 1°C for steam or dry heat sterilization processes based on the guidelines of the technical standards cited.

Reference temperature for steam sterilization	Lethality, F0 accumulated (minutes)	Reading with 1°C error	Error in calculation of lethality, F0 accumulated (minutes)	Reference temperature for dry heat sterilization	Lethality, FH accumulated (minutes)	Reading with 1°C error	Error in calculation of lethality, FH accumulated (minutes)
121,1°C	1,00	122,1°C	1,26	160°C	1,00	161°C	1,12
121,1°C	2,00	122,1°C	2,52	160°C	2,00	161°C	2,24
121,1°C	3,00	122,1°C	3,78	160°C	3,00	161°C	3,37
121,1°C	4,00	122,1°C	5,04	160°C	4,00	161°C	4,49
121,1°C	5,00	122,1°C	6,29	160°C	5,00	161°C	5,61
121,1°C	6,00	122,1°C	7,55	160°C	6,00	161°C	6,73
121,1°C	7,00	122,1°C	8,81	160°C	7,00	161°C	7,85
121,1°C	8,00	122,1°C	10,07	160°C	8,00	161°C	8,98
121,1°C	9,00	122,1°C	11,33	160°C	9,00	161°C	10,1
121,1°C	10,00	122,1°C	12,59	160°C	10,00	161°C	11,22
Percentage total error in lethality			**25,90%**	**Percentage total error in lethality**			**10,87%**

Table 5 – Simulation of 1°C reading error in thermal validation systems for F0 calculations in 10-minute exposure processes

Conclusion

It becomes clear when evaluating guidance and regulatory documents around the world, especially in South American countries, that thermal validation systems need to conform to CSV practices because of their support of critical processes and their impact on decision making when participating in the monitoring and release of equipment used in various spheres of drug and pharmaceutical production.

The stages of CSV must be known by those responsible for this activity as well as the users of the systems, who contribute to certain stages of this activity. The fundamentals of CSV, as well as mastery of process automation, software categories, and current regulatory requirements are indispensable. In addition, risk management must evaluate such items as life cycle, traceability, master validation plan, computer system inventory, user requirements, vendor selection, and functional and design specifications.

Equally important is the selection of the supplier of the thermal validation system, which must be efficient, effective, and demonstrate a high degree of partnership and trust by offering a product that meets the data integrity, collection and record reliability requirements for meeting 21 CFR Part 11 and Data Integrity requirements. The ability of the supplier to themselves be aware of the current guidelines as well as based their development, testing and documentation to support those requirements can provide the company the equivalent support of an on-site audit at the supplier's premises, which is difficult in most situations, but can be proven by this properly developed supplement. There are processes in the thermal validation activity that have a high degree of complexity, such as sterilization, freeze drying and depyrogenation among others, that can be highly impacted by the accuracy, reliability, calculations / and analysis tools of the measuring instruments. These systems can influence the results of the conclusive analysis and negatively affect the quality of the final product if they do not have the correct specification, thus damaging the business and putting at risk the health of patients.

References

ABNT NBR 16.328:2014. Esterilização de Produtos para Saúde – Procedimento de ensaios para medição de temperatura, pressão e umidade em equipamentos.

ARGENTINA. ANMAT. Administración Nacional de Medicamentos, Alimentos y Tecnologia Médica. Guía de Buenas Prácticas de Fabricación para Elaboradores, Importadores/Exportadores de Medicamentos de Uso Humano de 19 de abril de 2018 – 3602/2018.

BASTOS, A. L. A. FMEA (Failure Mode and Effect Analysis) como ferramenta de prevenção da qualidade em produtos e processos – uma avaliação da aplicação em um processo produtivo de usinagem de engrenagem. Fortaleza, 2006.

BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada - RDC 301 N° 301, de 21 de agosto de 2019. Dispõe sobre as Boas Práticas de Fabricação de Medicamentos.

BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Instrução Normativa - IN Nº43, de 21 de agosto de 2019. Dispõe sobre as Boas práticas de Fabricação complementares aos sistemas computadorizados utilizados na fabricação de medicamentos.

BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Instrução Normativa - IN Nº47, de 21 de agosto de 2019. Dispõe sobre as Boas práticas de Fabricação complementares às atividades de qualificação e validação.

BRASIL. Ministério da Saúde, Agência Nacional de Vigilância Sanitária. Anvisa é aprovada para Cooperação em Inspeção Farmacêutica – PIC/S. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2020/anvisa-e-aprovada-para-cooperacao-em-inspecao-farmaceutica-2013-pic-s. Acesso em: 06/06/2021

BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Guia para Validação de Sistemas Computadorizados. Guia n° 33/2020 – Versão 1.

CHILE. ANM. Instituto de Salud Pública de Chile. Agencia Nacional de Medicamentos. Norma Técnica Buenas Prácticas de Manufactura (BPM) para la Industria de Productos Farmacéuticos. Exento 159 de 11 de abril de 2013.

COLOMBIA. INVIMA. Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Resolución 1160 de 2016. Buenas Prácticas de Manufactura para Medicamentos: Principios Fundamentales.

FDA. Guidance for Industry Part 11, Electronic Records/ Electronic Signatures – Scope and Application. August 2003.

ISPE. GAMP 5 – A Risk-Based Approach to Compliant GxP Computerized Systems. 2008.

ICH Q9. Quality Risk Management. 09 de November de 2005.

ICH Q12. Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle management. 20 de November de 2019.

ISO 17.665-1:2006. Sterilization of health care products - Moist heat Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.

ISO 20.857:2010. Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices.

Kaye Instruments. https://www.kayeinstruments.com/en/about-us/information/kaye-amphenol. Acesso em: 12 de julho de 2021.

MOLAK, V. Fundamentals of Risk Analysis and Risk Management. Boca Raton: Lewis Publishers, 1997.

PERU. ANM. Autoridad Nacional de Productos Farmacéuticos, Dispositivos Médicos y Productos Sanitarios. Manual de Buenas Prácticas de Manufactura de Productos Farmacéuticos. Decreto Supremo 021-2018-AS de 20 de agosto 2018.

PIC/S. Guidance on Good Practices for Computerized Systems in Regulated "GxP" Environments (PI 011-3). September 2007. (disponível em http://www.picscheme.org)