ORION C.E.

KAYE
SUBSIDIARY OF AMPHENOL

Computer System Validation

A DEEP DIVE INTO THERMAL VALIDATION SYSTEM

Author: Emerson Aparecido Miguel – Orcid | https://orcid.org/0000-0003-2582-1182 – 29/07/2021
Key words: Validation, Good Manufacturing Practices, Safety, Computerized systems

Summary

The concern of regulatory bodies is recognized worldwide and efforts to ensure that drugs and medicines are produced with the highest safety and quality are expended by all. In Brazil, Anvisa has the support of several national and international guides and technical standards to provide all the necessary requirements for the pharmaceutical industries, which need to prove that their processes are safe and reliable. To contribute for this objective the pharmaceutical quality management system needs to develop validation techniques and qualification of processes and equipment. In recent years, the Computer System Validation has been widely discussed and today has the support of Anvisa's Guide No. 33 for this activity. One of the activities impacted by the Guide was the Thermal Validation activity, regardless of whether it is performed, internally or through third party service providers, it needs to prove the integrity of the data, the security of confidential information, the accuracy of the values measured and even that people without allowed access or appropriate knowledge can interact with the collected data. The information pointed out by these systems is essential for the release of critical equipment in the area of production, quality control, storage and or transportation, therefore, must be correctly validated, meeting national regulatory requirements to promote patient safety. Critical processes such as depyrogenation, sterilization, among others, are monitored by these systems that develop calculations to promote the death of microorganisms and depend directly on the performance compliance of the developed software. Thus, it is also necessary that the company that develops the system is a company that knows the users' needs and that values above all ethics, making the correct use of the technological resources available today.

Introduction

Worldwide the concern and care with the production of drugs and medicines is constant. Several professionals strive to follow paths that ensure less variability in the process, greater safety and even better quality of the final product, in this sense, in Brazil, the National Health Surveillance Agency, ANVISA, has been improving its regulatory methodology and systematic inspection, in order to contribute to these objectives and somehow raise the Brazilian market for globalization also in pharmaceutical production , which, already influenced by the guidelines of multinationals installed in our country, contribute for internalization or migration of the best international concepts of inspection and audits. Faced with these challenges, several tools to guarantee pharmaceutical quality come into play, which help standardize processes, the methodology of proof of efficacy and safety or also develop methods that assist in decision making. These tools are widely used to validate a process, a methodology, a cleaning procedure and also qualify the various equipment used (IN138, 2022).

The definition of validation can be observed in The Collegiate Board Resolution No. 658 of March 30, 2022, RDC 658, and has by definition be the documented proof, according the principles of Good Manufacturing Practices, any procedure, process, equipment, material, activity or system operate and function correctly and its execution leads to the expected results (RDC 658, 2022). The Validation comprises qualification studies, proving any facilities, equipment, utilities and systems work correctly and actually lead to the expected results.

To develop the validation methodology, the companies also have 14 normative instructions, several guides and also with the Brazilian pharmacopoeia, being made available in this way all the requirements standardized in Brazil. Computerized systems, which are any and all systems that include data entry, electronic processing and the output of information to be used for reports or automatic control, also require special attention and have specific documents for professionals to follow (RDC 658, 2022, IN134, 2022 and Guide No. 33 ANVISA , 2020).

The CSV, which is it commonly called Computer System Validation, began to have its own aspects under the perspective of Normative Instruction 134, which "Provides for Good Manufacturing Practices complementary to computerized systems used in the manufacture of Medicines" and has the objective of adopting the Guidelines of Good Manufacturing Practices related to computerized systems of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), as complementary requirements to be followed in the manufacture of medicines in addition to

RDC 658 (2022). Since January 2021, ANVISA has been part of PIC/S, an international initiative to inspect good pharmaceutical practices with 54 participating members. Among the recommendations described in the guide, it mention the mandatory confirmation of the validation of computerized systems provided to be used in the various processes and with activities included in the qualification stages of validation processes (ANVISA, 2020, PIC/S, 2021).

Specific activities of performance qualification in equipment are widely developed using computational and instrumentation resources, used for data collection, statistical calculations and also generation of detailed reports on physical quantities measured inside equipment that have the purpose of transforming, promoting reactions, cleaning, disinfecting, sterilizing, conditioning, incubating or even freezing, etc. The practice of qualifying the performance of this equipment, also known as thermal qualification or even thermal validation, as internationally it is best known, monitor in addition to temperature inside the equipment and/or environments, the pressure, the relative humidity, the light intensity, etc., all of which are mostly associated with thermal equipment. This specific activity in the industry has gained strength for decades and the market currently has highly sophisticated instruments, with great precision, safe and protected against adjustments that would invalidate the results measured (ABNT NBR 16.328, 2014). Thus, instruments equipped with hardware, firmware and software, would fit in the requirements of ANVISA so that also pass through the validation activity, because they have a direct impact on the industries processes, control, storage or transport of products, because when used in the stages of qualification of equipment, confirm or not, whether the process is safe, assisting with vital participation in the decision of the release of the use of the equipment challenged. The choice of instruments from suppliers knowledgeable about the needs of pharmaceutical practice, who have developed their devices taking into account the seriousness in which the processes require is fundamental for a great degree of confidence in all the stages in which the instruments are involved.

The practice of thermal validation, by Brazilian legislation, besides being in large numbers in pharmaceutical processes (table 1 demonstrates examples of thermally validated equipment, process and quantities to be measured), undoubtedly contribute to the purpose initially suggested, lower variability in the process, greater safety and even better quality of the final product, however it is essential that the supplier knows how to develop, with regard to their responsibilities, supporting documents that allow compliance with all the steps required by ANVISA.

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

The ANVISA through Guide no. 33 seeks to facilitate the understanding of all the steps to be developed for a CSV. The document also aims to internalize the contents of the ISPE (International Society for Pharmaceutical Engineering) guide "GAMP5," which is in version 5 published in 2008. The ISPE, founded in 1980 by members of the North American industry, today participants from all over the world including Brazil, use its contributions, being the GAMP 5 the base document for understanding the CSV. The Guide No. 33 of ANVISA, points out that the software categories 3, 4 and 5 of GAMP 5 will be considered in this document, what limits in a certain way what will be covered, but with total completeness with the vital points of Brazilian industries. The RDC 658 also complements this subject with normative instruction no. 134, IN134, in this document ANVISA establishes the interaction of users and the various levels of operation with computerized systems, also affirming the integration with PIC/S, more specifically to the PI 011-3 guide, September 2007. Finally, another very relevant reference to the issue is the 21 CFR part 11 (from FDA (Food and Drug Administration), which states that electronic records and electronic signatures are treated in the same way as paper records and handwritten signatures. Companies regulated with any documents or records in electronic format must comply with the regulation. Table 2 describes the key documents covered for a CSV in addition to RDC 658.

Document	Title	Publication	Who
Guide No 33	Guide for validation of computer systems	14/04/2020	ANVISA
IN134	Provides for Good Manufacturing Practices complementary to the computerized systems used in the manufacture of medicines	30/03/2022	ANVISA
PI 011 3	Good Practices for Computerised Systems in Regulated “GxP” Environments	25/09/2007	PIC/S
21 CFR part 11	Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application	08/2003	FDA
GAMP 5	A Risk-Based Approach to Compliant GxP Computerized Systems	02/2008	ISPE

Table 2 – Main references for the development of validation of computerized systems

The CSV key concepts according to ANVISA's Guide No. 33 for commencing and engaging with the various activities and steps are:

» **Understanding of the Process and the Product:** The guide is concerned that the user has full mastery, based on science, about the process and the product which he is involved, only then will it be possible to prepare the initial documents for decision making when choosing a system for thermal validation practice;
» **Approach of the life cycle within quality management systems:** It is necessary to carry out activities in a systematic way from the design of the system until its retirement, and still hope that as greater knowledge about the system is acquired during its use, the continuous improvement of the process and the system will be allowed. Figure 1 shows the main phases of the life cycle of a computerized system, pointing out all the necessary steps. Ich Q12 can also contribute to better understanding the step-by-step life cycle, in this approach of the pharmaceutical industries, being a valuable reference to increase the understanding of pharmaceutical processes in a high-level view.

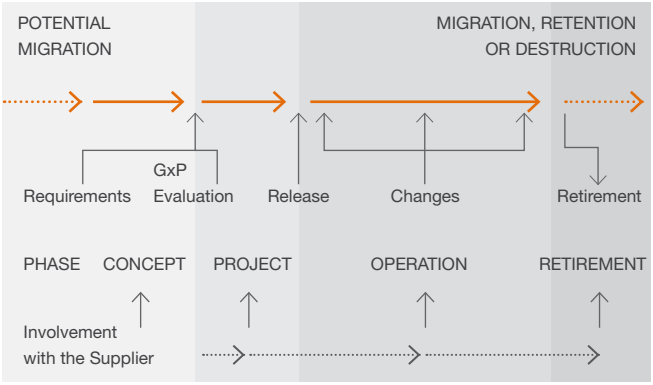

Figure 1 – The life cycle phases of a computerized system
Source: Guide no. 33 ANVISA.

» **Scalable life cycle activities:** should be developed to ensure patient safety, product quality and integrity of the data collected by the thermal validation system, as well as points such as system complexity versus its innovation, supplier evaluation and impact of the system on business are complementary points;
» **Quality risk management based on science:** since this item is widely applied in the industry, it will be addressed in more detail below, thus contextualizing at this time in a systematic process for evaluation, control, communication and review of the risks associated with the processes which the thermal validation system will conduct results for decision making. The GAMP 5, because it is a qualitative management analysis tool, contributes in a unique way as a fundamental point for the development of a risk analysis regarding direct or indirect impact, stored data, understanding of the components of the thermal validation system, but emphasized that the division of tasks with a multidisciplinary team and mutual collaboration in all spheres of the company hierarchy are essential parts to achieve the main objective;
» Take advantage of supplier involvement: Companies should select suppliers of thermal validation systems with special attention, as these suppliers can help in the initial development of the steps, from the user requirements, in the previous stage (risk management), and also according to IN134, competence and trust in the supplier should be considered essential elements during product selection, thereby reinforcing the importance of a good partnership in this activity.

Risk Management Approach

Since this theme contributes to other points of the related process, it should spend more contextualization for the relevance of its use. Thus, risk analysis can be defined as a series of questions to evaluate the probability of an adverse effect happening by an agent, be it physical, chemical, biological, industrial processes, technology, natural process, etc., and what the severity of these effects is, also analyzing that not only loss of production can occur, but also adverse effects related to health, diseases and even death, of the collaborator or client/patient (MOLAK, 1997).

The ICH Q9 structured the necessary risk assessment in all manufacturing activities at each stage. The pharmaceutical industry through quality systems, shows that quality risk management is a valuable component for effective quality management and this does not exclude the systems used for thermal validation activity. It is understood that risk is the combination of the probability of damage occurring, the severity that damage may cause and the ease or not of detection. However, the path to insertion of this analysis is complex, due to having

to achieve a shared understanding between several stakeholders because what may be probable and serious for one, will not necessarily be for the other, and have or not tools to detect it, for this reason it should be well evaluated by a specific and multidisciplinary committee. Throughout the life cycle of facilities, equipment, processes and medicines, risk management should be addressed in reference to the impact that individually and collectively have on the quality of the final product (RDC 658). Risk analysis is commonly used, in Brazil, with the application of the Failure Mode Effects Analysis (FMEA) tool. The FMEA can be understood as a systematic methodology that allows identifying potential failures of a system, project and/or process in order to minimize or eliminate the associated risks before such failures occur (BASTOS, 2006). ICH Q9 features a dozen tools that individual or combined help identify, contain, mitigate and control potential risks that must be applied to evaluate a thermal validation system.

Productive activities have, by nature, some type of risk associated with the process, and can impact on a large or small scale the quality, safety and efficacy of the final product, which, as indicated, has a direct impact through the decisions accepted based on the results of the monitoring performed by the thermal validation instruments. Any risk and/or deviation of quality that may occur at any stage of production must be contained, mitigated and controlled, even if it has never occurred. For any risk that involves product quality, environmental protection, operator and/or patient health, it is essential to identify, evaluate, communicate and control for mitigation.

Within all these perspectives of risk control and management, we assume that it is vital to extend this issue to the approach of thermal validation by associating and merging with the available tools, as we will pull together the threads of this complex, extensive, detailed and interconnected path of production, distribution and dispensing of medicines, all with the goal of saving lives. Thus, it is noticeable that the thermal validation activity, using 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 points addressed by risk analysis, its use will be unfeasible.

Key steps for CSV of a thermal validation system

The main steps pointed out in Guide No. 33, which will contribute to obtaining safety regarding the operation of a thermal validation system can be, but not limited only to:

- **Specification of user requirements:** Document intended to contain the specification for equipment, installations, utilities, systems (in general) and obviously thermal validation systems. This document can be supplemented, called or included in a "functional specification" of the system;
- **Master Validation Plan (MVP):** Document designed to contain the entire strategy for the CSV activity and contains at least the objective points, responsibilities, system description and interfaces, validation strategy and scope, procedure and premises, acceptance criteria, change control program, program for handling deviations, maintenance of validated status and documentation management. The thermal validation system must be contemplated in this document;
- **Risk analysis:** as previously addressed, it plays a fundamental role, being considered by some professionals as one of the most important phases of the CSV process;
- **Functional technical specification:** Contains the specific data of system operation, in this step is pointed out in more detail the components parts of the target system and necessary for thermal validation practice;
- **Installation Qualification (IQ):** Consists of the documented verification that the system as installed, complies with the approved project and the manufacturer recommendations. This document is commonly developed by the thermal validation system vendor;
- **Operation qualification (OQ):** Consists of the documented verification that the system performs its functions as planned within the pre-established operating intervals. Like IQ 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 reproductively 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 monitor its use in routine processes, for a short period predetermined, without any addition to the tests already performed in the OQ, which can confuse the purpose or even be disregarded from the CSV steps;

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

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

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

As demonstrated, several areas and professionals join in the CSV development, the responsibility can be shared or exclusive of the user within the industry, but the involvement of the supplier is essential for testing and proofing that the company that is acquiring the thermal validation system does not have access. Thus, it is suggested through Figure 2 that a flowchart synthesizing the steps, sequences and responsibilities be created to better visualize the involvement of all members.

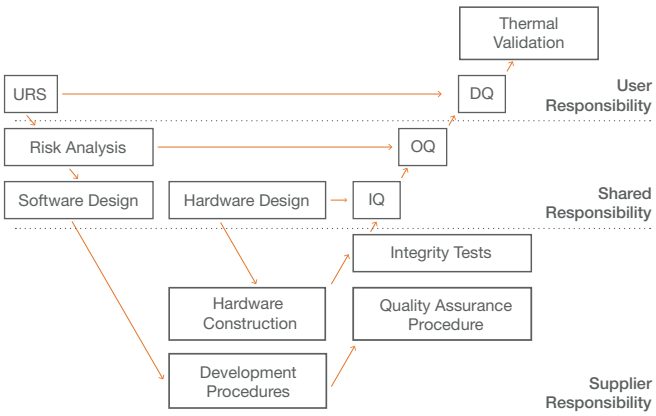

Figure 2 – Suggested flowchart of CSV development and control steps for thermal validation systems for the pharmaceutical industry

Classification of computerized systems

Anvisa guide no. 33 points at the document beginning, which will cover software categories 3, 4 and 5 of computerized systems extracted from GAMP 5, which are simplified below:

» **Software category 3** – non-configured products: Considered by many the category of thermal validation systems, this category is pointed out by the Guide as software with shelf functions used in general. In this modality the software cannot be configured for a possible user customization, but in a thermal validation system may have a function that can be considered configurable, what is related to lethality calculations for disinfection, sterilization and despirogenization cycles. It is because thermal validation systems are developed to meet a range of processes like that and the user should receive specific training for the development of this activity that is widely applied in the hospital, food and pharmaceutical areas. The dealing with this category boils down to a simplified approach to the lifecycle, the supplier evaluation must be based on risk management, the user requirements are developed with a focus on the fundamental aspects of use. It is not necessary the 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), who has great expertise in the development of thermal validation systems and who add important contributions in Brazil with software development according to international technical standards of big impact, presents next, attributes of documentary proof which makes this system a strong candidate to also set into category 4, where the levels of requirement for the system are higher.

» **Software category 4** – configured products: As its name suggests, in this category the pharmaceutical industry can configure the system for a specific business process, so functional and design specifications are necessary, but may come from the manufacturer, but the regulated company must have complete documentation that ensures the traceability of functional specifications and their respective tests. The

lifecycle approach and supplier evaluation with risk-based assessment, as well as the demonstration of its quality management system is necessary, explaining why the Kaye line systems would meet these requirements, since there are documents that support this framework. Tests to demonstrate your application as designed in a risk-based testing and production environment are developed, even as a procedure for maintaining attendance and adequacy for data usage and management.

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

» **Hardware category 1** – Standard hardware components: Most hardware used by the pharmaceutical industries is into this category, as do thermal validation systems. According to ANVISA Guide the standard hardware components should be documented including details about the supplier, who, for the thermal validation activity is directly responsible for maintenance and technical assistance during the life of the product. In this category, configuration management and change control must be developed by the user.

» **Hardware category 2** – Embedded custom hardware components: The Systems for Software category 5 typically have hardware into this category and in this activity is applicable in addition to category 1 controls, a design specification (DS) being subject to acceptance testing, a vendor audit for custom hardware development, configuration management and change control.

CSV Importance and Impact of a Thermal Validation System

When evaluating the documents involved in the CSV activity, we observe whether thermal validation systems require the development of all the points discussed throughout this work or still if these points have been met, and when studying the activities developed by companies like Kaye we find all the paths that support what is necessary to raise the importance of these systems with robust documentation and sufficiently detailed to demonstrate the security of the processes involved, leaving behind a time when spreadsheets, question about traceability data, no control of use by users and still doubts about the integrity of the data collected probed the routine of all professionals and regulatory authorities. Thus, in addition to the demonstration of accuracy, repeatability and instrumental adequacy for measurements in the various environments and equipment mentioned above in the practice of thermal validation, the systems need to assure regulatory authorities that they are able to control and protect valuable information about the evaluated processes and also have a documentary basis, according to table 3, which support that all vital points in this practice were correctly developed and tested before the release of the system.

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 – Kaye CSV development documents

Another point to be discussed in this process is that there is a very important need also in the measurement accuracy of these instruments, which may or may not favor, 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, in his document NBR 16.328 from 2014, points out the maximum error of all components involved in thermal validation systems when using temperature sensors and also the maximum error obtained during pressure and humidity calibration. This specification must be respected according to table 4.

For critical processes such as sterilization and depyrogenation, the failure to meet these items may result in an immeasurable catastrophe due to their impact on the approval of partial or terminal injection stages, which have among the 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). These values, if they are wrong due to error or inaccuracy in their reading, mislead in decision making, because the conversion performed by reading temperature to F0 or FH are strongly impacted by calibration errors or even lack of technical specification for this purpose. Table 5 shows the impact on the calculation of F0 and FH taking into account reading errors of up to 1°C for steam or dry heat sterilization processes.

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 thermal validation system sensors

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 national and international regulatory and guiding documents that thermal validation systems need to adapt to CSV practices due to the impact on decision making when participating in the monitoring and release of equipment used in the various spheres in the production of drugs and medicines. Critical decisions are established through the results of these instruments that are governed by complex software. The CSV steps should be known by those responsible for this activity as well as system users, who contribute in certain stages of this activity. CSV's fundamentals, even as the mastery of process automation, software categories and current regulatory requirements are essential.

As a complement, risk management should evaluate items such as life cycle according to ANVISA Guide No. 33, traceability, master validation plan, computerized systems inventory, user requirements, supplier selection and functional and design specifications.
An important role in this process is pointed out in IN134 also regarding the supplier, who must be efficient, effective and demonstrate a high degree of partnership and trust offering a product with data integrity, with full reliability in the collection and records, so that patient safety, based on science is established. The supplier's documentary base can provide the company with the equivalent support of an audit at the supplier's facilities, what becomes difficult in most situations, but which can be proven by this properly developed supplement.

There are processes in the thermal validation activity that have a big complexity, such as sterilization and depyrogenation among others, and are highly impacted by the accuracy or inaccuracy of the measuring instruments, so these systems can influence the results of conclusive analyses and negatively achieve the quality of the final product, if they do not have the correct specification, harming business and endangering patients' health.

References

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

ABNT NBR ISO 17.665-1:2010. Esterilização de Produtos para Saúde – Vapor – Parte 1: Requisitos para o desenvolvimento, validação e controle de rotina nos processos de esterilização de produtos para saúde.

ABNT NBR ISO 20.857:2019. Esterilização de Produtos para Saúde – Calor seco – Requisitos para o desenvolvimento, validação e controle de rotina de um processo de esterilização para dispositivos médicos.

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 658 Nº 658, de 30 de março de 2022. Dispõe sobre as Boas Práticas de Fabricação de Medicamentos.

BRASIL. ANVISA. Agência Nacional de Vigilância Sanitária. Instrução Normativa – IN Nº134, de 30 de março de 2022. 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 Nº138, de 30 de março de 2022. 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.

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 e 2005.

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

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.

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