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# A Review on applications of GAMP -5 in Pharmaceutical Industries

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**Abstract:** The new Good automated manufacturing practices (GAMP)-5 guidelines were released February 2008 at the ISPE(International Society for Pharmaceutical Engineering) Manufacturing Excellence Conference in Tampa, Florida. These guidelines are the latest, up-to-date thinking in the approach to validation of GxP computerized systems. The purpose of the guidelines is to "provide a cost effective framework of good practice to ensure that computerized systems are fit for use and compliant with regulation."
There are five key concepts to GAMP 5:

- Product and Process Understanding.
- Lifecycle approach within QMS.
- Scalable Lifecycle Activities.
- Science Based Quality Risk Management.
- Leveraging Supplier Involvement.

Understanding the product and process is critical in determining system requirements and for making science and risk-based decisions to ensure that the system is "fit for use." In determining "fit for use," attention should be focused on "those aspects that are critical to patient safety, product quality, and data integrity." Defining a lifecycle approach to a computerized system has been expanded from GAMP 4 to include all phases and activities from concept and implementation through operation and retirement. Some applications of GAMP- 5 in Pharmaceutical industries like Monitoring manufacturing, production and storage environments in the pharmaceutical industry, Monitoring the autoclaving process in the pharmaceutical industry, Water purification in the pharmaceutical industry, Freeze drying in the pharmaceutical industry

**Key words**: Computerized systems, Guidelines, Risk- based approach, Validation, Patient safety, Product quality.

## INTRODUCTION:

Good Automated Manufacturing Practice (GAMP) is a technical subcommittee of the International Society for Pharmaceutical Engineering (ISPE), a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry. More specifically, the ISPE's guide Good Automated Manufacturing Practice (GAMP) guide for Validation of Automated Systems in Pharmaceutical Manufacture describes a set of principles and procedures that help ensure that pharmaceutical products have the required quality. One of the interior principles of GAMP is that quality cannot be tested into a batch of product but must be built into each stage of the manufacturing process. As a result, GAMP covers all aspects of production; from the raw materials, facility and equipment to the training and hygiene of staff. Standard operating procedures (SOPs) are essential for processes that can affect the quality of the finished product.[1]

ISPE has published a series of good practice guides for the industry on several topics involved in drug manufacturing. The most well-known is The Good Automated Manufacturing Practice

(GAMP) guide for Validation of Automated Systems in Pharmaceutical Manufacture.

The new GAMP-5 guidelines were released February 2008 at the ISPE Manufacturing Excellence Conference in Tampa, Florida. These guidelines are the latest, up-to-date thinking in the approach to validation of GxP computerized systems. The purpose of the guidelines is to "provide a cost effective framework of good practice to ensure that computerized systems are fit for use and compliant with regulation." [1]

**History:**

GAMP itself was founded in 1991 in the United Kingdom to deal with the evolving U.S. Food and Drug Administration expectations for Good Manufacturing Practice (GMP) compliance of manufacturing and related systems. GAMP published its first guidance in 1994. Soon afterwards the organization entered into a partnership with ISPE, formally becoming part of ISPE in 2000. GAMP has enjoyed the support of numerous regulatory authorities over the years spanning the United States, Europe, and Japan and is now a recognized good practice worldwide. [1]

**Gamp 5 objective:**

GAMP5 guidance aims to achieve computerized systems that are fit for intended use and meet current regulatory requirements, by building upon existing industry good practice in an efficient and effective manner.[1,2]

## Discussion:

***Software categories***

Due to the great variety of medical devices, processes, and manufacturing facilities, it is not possible to state in one document all of the specific validation elements that are applicable. However, a general application of several broad concepts can be used successfully as guidance for validation. These broad concepts provide an acceptable framework for building a comprehensive approach to software validation. [25]

The software categories according to GAMP classes are described in Table- 1

***Hardware Categorization:***

***GAMP recognizes two levels of hardware***

***Hardware Category 1*** - Standard Hardware Components

The majority of the hardware used by regulated companies will fall into this category. Standard hardware components should be documented including manufacturer or supplier details, and version numbers. Correct installation and connection of components should be verified. The model, version number and, where available, serial number, of preassembled hardware should be recorded. [25]

***Hardware Category 2*** - Custom Built Hardware Components

These requirements are in addition to those of standard hardware components. Custom items of hardware should have a Design Specification (DS) and be subjected to acceptance testing. The approach to supplier assessment should be risk-based and documented. In most cases a Supplier Audit should be performed for custom hardware development. [25]

***Concepts:***[2]

GAMP wants to make it clear that GAMP 5 is "not a prescriptive method or standard, but rather provides pragmatic guidance, approaches and tools for the practitioner." This means that companies should use these guidelines along with other guidelines and industry best practice to



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determine the best approach for validating GxP computerized systems.

There are five key concepts to GAMP 5 (**Figure 1**)

1. Product and Process Understanding
2. Lifecycle approach within QMS
3. Scalable Lifecycle Activities
4. Science Based Quality Risk Management
5. Leveraging Supplier Involvement

*1) Product and Process Understanding*

Understanding the product and process is critical in determining system requirements and for making science and risk-based decisions to ensure that the system is "fit for use." In determining "fit for use," attention should be focused on "those aspects that are critical to patient safety, product quality, and data integrity."

*2) Lifecycle Approach within a QMS*

Defining a lifecycle approach to a computerized system has been expanded from GAMP 4 to include all phases and activities from concept and implementation through operation and retirement. These activities should be defined within the quality management system (QMS). This allows for a consistent approach across all systems.

There are four major phases defined for any system:

1. Concept
2. Project
3. Operation
4. Retirement

*3) Scalable Lifecycle Activities*

Within the GAMP 5 guidelines GAMP outlines that lifecycle activities should be scaled according to:

- System impact on patient safety, product quality, and data integrity (Risk Assessment)
- System complexity and novelty
- Outcome of supplier assessment

There may be other factors that companies may want to consider when making assessments, but this process should be documented and follow established policies and procedures. By conducting this assessment companies can scale their validation effort and other lifecycle activities to the appropriate levels.[13, 14]

Because of the use of a "scaled" approach, GAMP has reassessed their V-model and has "generalized" the model to account for other possible approaches. (**Figure 2**)

This model can be expanded or even reduced depending on the scale or scope of the system being validated.

*4) Science Based Quality Risk Management*

Science Based Quality Risk Management allows companies to focus on critical aspects of the computerized system and develop controls to mitigate those risks. This is where a clear understanding of the product and process is critical to determine potential risks to patient safety, product quality, and data integrity.[15]

They acknowledge that this is not the only approach and that each company needs to decide what approach best works for its intended use.

Risks that have been identified can be mitigated by:

- Elimination by design
- Reduction to suitable level
- Verification to demonstrate that the risks are managed to an acceptable level

GAMP 5 describes and talks about a five step process for risk management based on ICH Guidelines in **figure 3**.[2]

*5) Leveraging supplier involvement*

Regulated companies regularly involve suppliers throughout the system lifecycle. Suppliers have





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the knowledge, experience, and documentation to assist companies throughout the system's lifecycle.

GAMP 5 suggests regulated companies need to maximize that involvement to "determine how best to use supplier documentation, including existing test documentation, to avoid wasteful effort and duplication.

Documentation should be assessed for suitability, accuracy, and completeness. There should be flexibility regarding acceptable format, structure and documentation practices."

Suppliers can be used to assist companies with:

1. Gathering requirements
2. Creation of functional and other specifications
3. System configuration
4. Testing
5. Support
6. Maintenance
7. System retirement

It is important to remember that the regulated company has the responsibility for the documentation, approval, and compliance of each element of the computerized system lifecycle. With increased involvement of the supplier in the lifecycle, regulated companies need to assess that the supplier has processes in place to ensure quality of the product. GAMP has included a section in GAMP 5 dedicated to supplier activities to assist suppliers in understanding the needs of their customers. [26, 27]

***GAMP 5 sets the main requirements for the use of computerized systems in pharmaceutical applications:*** [31]

- Patient safety, product quality and data integrity.
- Effective governance to achieve and maintain GxP compliance.
- Quality by design (QBD).
- Continuous improvement with in Quality management system (QMS).
- Critical quality attributes (CQA).
- Improving GxP compliance efficiency.
- Configurable systems and development models.
- Use of existing documentation and knowledge.
- Effective supplier relationships.
- Scalable approach to GxP compliance
- Science based quality risk management system.
- Life cycle approach within QMS.

***GAMP 5 illustrates the specification, design, and verification process ( Figure 4)*** [31]

**SOME APPLICATIONS OF GAMP-5**

1. Monitoring manufacturing, production and storage environments in the pharmaceutical industry.
2. Monitoring the autoclaving process in the pharmaceutical industry.
3. Water purification in the pharmaceutical industry.
4. Freeze drying in the pharmaceutical industry

*1) Monitoring manufacturing, production and storage environments in the pharmaceutical industry.* [3]

- Provides independent verification and validation of the manufacture, production and storage processes

The conditions under which pharmaceutical products are manufactured and stored can have a major impact on their quality. Factors such as temperature, humidity, air quality, time and production process characteristics can all have a

significant impact on the final quality of a product or batch of products.

For the purposes of traceability, it is necessary to adhere to GAMP 5 guidelines to accurately record every stage in the production lifecycle of a product, encompassing not just the manufacturing process but also the storage and distribution stages. In doing so, manufacturers can prove to have acted in accordance with best practice by building in quality from the outset and designing failure out of the process.[10]

*Manufacture, storage and distribution*

GAMP guidelines advise that the manufacture, storage and distribution stages of pharmaceutical products are monitored to ensure that any facilities involved meet the required standards. Of the various parameters that need to be carefully controlled, temperature and humidity are perhaps the two most critical.

All parties involved in the manufacture, storage and distribution of pharmaceutical products are required to record and keep details of temperatures during these processes. Efficient handling and processing of sensitive materials is critical to the profitable manufacture of pharmaceutical products. GAMP encourages manufacturers to use measurement techniques that allow a better understanding of the interaction between material properties, equipment design and operating conditions, in processes such as capsule forming and drying, pan coating, parenteral manufacturing, sterile filling, spray and powder drying, and tablet compression.

For many products requiring storage in cool conditions, refrigeration plant is widely used, which needs to be carefully monitored to ensure that the correct temperatures are maintained. Exactly how this is achieved varies according to the type and size of refrigerator being used and the type of product in question. High-risk products, for example, must be maintained between 2°C and 8°C and stored in precisely controlled refrigerators. For operators of a storage plant, it is necessary not only to ensure that products are stored at the right temperature, but also that the refrigeration plant is capable of accurately maintaining that temperature.

Adopted by many countries worldwide, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) regulations stipulate that the performance of refrigeration plant used to store pharmaceutical products needs to be regularly checked. To achieve this, operators need to map their refrigeration equipment using one or more thermometers and /or temperature probes to ensure that temperature is uniformly maintained. The resulting temperatures need to be recorded as proof of compliance with the required standards. The requirement to accurately map the storage temperatures also extends beyond refrigeration equipment to include warehouses and controlled temperature rooms.

*2) Monitoring the autoclaving process in the pharmaceutical industry.*[7]

- Provides independent verification and validation monitoring of the autoclaving process

Sterilization permits the re-use of pharmaceutical equipment such as instruments, utensils, lab equipment and media preparation, and is necessary to eliminate transmissible agents such as spores, bacteria and viruses. It is possible to kill some microorganisms with chemicals, irradiation, and dry heat but the most effective and inexpensive method is with saturated steam.

The most popular piece of equipment for use in steam sterilization processes is the autoclave. An autoclave is a pressurized vessel that that uses steam to apply pressure and heat to a load placed inside. The advantage of using an autoclave is that it can reach temperatures higher than boiling water alone, so it can kill not only bacteria but also bacterial spores, which tend to be resistant. Autoclaves commonly use steam heated to 115–134°C (250–273°F). To achieve sterility, a holding time of at least 30 minutes at 115°C, 15 minutes at 121°C (250°F) or 3 minutes at 134°C (273°F) is required. Verification of the process is usually recorded on chartor paperless recorders, though the latter is becoming more widespread. These recorders will need to be validated to GAMP guidelines, according to the FDA and other authorizing bodies.

The control functions of an autoclave are normally performed using an integrated control system from the manufacturer. However, it is usual that key parameters are independently recorded against time, including temperature and pressure. The number of temperature and pressure points that are independently recorded varies by the size of the autoclave to ensure that a representative record is retained. Typically three temperature and one pressure signals are used. These are totally independent sensors from the control system. One temperature sensor is typically located in the 'drain' or the coolest location; one in the load of the product being sterilized; and one in the 'free space' (typically the hottest location). The pressure signal is there to cross correlate the temperature, as pressure is directly proportional to temperature for saturated steam.

Some installations look to have the mathematical calculation for $F_0$. This takes the temperature and uses an exponential calculation to give 'killing points' for any temperature below the required sterilization temperature. The higher the temperature the faster the 'killing points' accrue. The result is an equivalent time at the sterilization temperature. This can shorten total autoclave cycle times by taking into account the killing temperatures prior to the required sterilization temperature being reached. It is important to perform a regular calibration check and to be able to perform full calibration adjustment for the system inputs as it is important to verify that the measurements made are reliable.

The system that records the data also independently triggers warning and active alarms should the accepted process parameters be exceeded. In this instance it is usual for a 134°C sterilizing temperature to have a high alarm at 137°C. The use of independent recorders for monitoring the autoclave gives confidence that the process has performed as required and is usually part of the product release documentation.

*3) Water purification in the pharmaceutical industry:*[4]

- Provides independent verification and validation of the water purification process.

Water is a major commodity used by the pharmaceutical industry. Different grades of water quality are required according to the pharmaceutical process. The United States Pharmacopoeia (USP) and the European Pharmacopoeia (EP) are the governing bodies that issue guidelines for the manufacture of drugs to their respective markets. Amongst these guidelines are regulations, legally enforceable by the FDA and European equivalents (such as the MHRA), for the purification of different grades of water used in the pharmaceutical processes:

- ✓ Purified water – is used in preparation of medicinal products other than those that require the use of water to be sterile.
- ✓ Highly purified water - intended for use in the preparation of products where water of high biological quality is needed, except where water for injection is required.
- ✓ Water for injection – the purest grade of bulk water monographed by the USP and EP and is found in the manufacture of parenteral, ophthalmic and inhalation products.

The validation and qualification of water purification systems are a fundamental part of Good Automated Manufacturing Practice (GAMP) and form an integral part of the GAMP inspection. Different grades of water are produced according to USP and EP requirements, usually by: distillation; reverse osmosis; deionisation; or ultrafiltration. All of these processes need to be validated and recorded according to specific standards.

Each set of guidelines outline legal requirements for the chemical content of each grade of water, including a three stage conductivity test for inorganic compounds that will determine pH and total organic oxygen (TOC) levels. The FDA states that implicit in the term "Purified Water" is that it has some reasonable, objective level of purity. TOC testing allows for evaluating impurities in water besides those which are inorganic anions and cations. Although there are no absolute microbial standards for water, GAMP regulations require that appropriate specifications be established and monitored. Action or alert limits must be based upon validation data and must be set low enough to signal significant changes from normal operating conditions. In all these instances a range of instrumentation is required to meet GAMP guidelines, including conductivity meters, pH meters, and temperature sensors and recording equipment. An independent monitoring and recording system should therefore be put in place to provide sufficient and secure data to ensure these processes meet the various specific standards. As there are a number of methods for producing purified water of different grades there are also a variety of different parameters that need to be monitored and controlled, including conductivity, pH, temperature and pressure, amongst others. It is important to perform a regular calibration check and to be able to perform full calibration adjustment for the system inputs, as it is important to verify that the measurements made are reliable.

The system that records the data should also independently trigger warning and active alarms, should the accepted process parameters be exceeded. These often incorporate a time delay and / or a hysteresis. This only triggers the alarm once the parameter has exceeded acceptable levels by a certain amount of time, which helps prevent nuisance alarms.

The use of independent recorders for production of purified water allows specific, independent and easily validated processes to be monitored without the requirement of validating an entire complex Distributed Control System (DCS). It shows exactly what has happened, together with details of any alarms in real-time.

*4) Freeze drying in the pharmaceutical industry:* [5]

➢ Provides independent verification and validation monitoring of the freeze drying process.

Freeze drying is a technique used by pharmaceutical manufacturers to derive dry product from aqueous solutions. Originally developed during the 1940s, the technique





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produces a dry product which can be readily reconstituted to its original form by adding water when required. As such it is as an ideal way of prolonging the life of pharmaceutical products, particularly where this may involve long periods of storage and transit prior to use.

The freeze drying process itself entails first freezing the aqueous form of the product on shelves in a vacuum chamber, after which the chamber is evacuated. At the next stage, the Primary drying process, the product is slowly warmed up over a number of hours to boil off the liquid, with any moisture being evacuated throughout the process through a cold condenser.

This is then followed by a Secondary drying process, during which the temperature in the chamber is raised to help remove any residual water. As a final check that the product is dry, a pressure rise test is carried out, with any more than a fractional rise in pressure indicating that there is still some residual liquid present .Any control system used for a freeze drying application should ideally be capable of automatically adjusting the process to maintain the ideal conditions. Traditionally, open loop control systems have been used, with the freezing and heating temperatures and the chamber pressure being controlled according to a specific profile. However, this approach has several drawbacks, including the inability to cope with temperature variations outside of the set profile. With no way of accelerating the process if conditions change, the overall freeze drying period is also prolonged.

For optimum control of the freeze drying process, a closed loop control system should instead be used. Data from the pressure and temperature sensors is fed back to the controller where it is compared against a reference value. The controller takes the difference between the output and the reference value and uses it to change the inputs to the system to help compensate for the difference. The result is a more dynamic and precise control of the freeze drying process, with the ability to address any unexpected fluctuations in process conditions.

The control functions of a freeze dryer are normally performed using an integrated control system from the manufacturer. However, it is usual that key parameters are independently recorded against time, including humidity, temperature and pressure (or vacuum). The system that records the data also independently triggers warning and active alarms should the accepted process parameters be exceeded. These often incorporate a time delay. This then triggers the alarm once the parameter has exceeded acceptable levels by a certain amount of time, which helps prevent nuisance. It is important to perform a regular calibration check and to be able to perform full calibration adjustment for the system inputs as it is important to verify that the measurements made are reliable.

To satisfy FDA requirements, all data from the freeze drying process should be recorded. Where data recorders are used, the requirements of the International Society of Pharmaceutical Engineers (ISPE)'s Good Automated Manufacturing Practice (GAMP) will also apply, including the stipulation that any recording equipment has to be validated for use in pharmaceutical processes. A recorder with Ethernet connectivity allows historical recorded data and alarm and audit trail information to be retrieved automatically to a central database where archive and analysis, if required, can take place.

Any electronic recording equipment also has to be compliant with the FDA's 21 CFR Part 11 rule. A key aspect of 21 CFR Part 11 is its focus on security, particularly relating to the prevention of data tampering and the ability to identify specific individuals and events involved in the production and / or data management processes. [21]

The use of independent recorders for monitoring the freeze dryer allows specific, independent and easily validated processes to be monitored without the requirement of validating an entire complex Distributed Control System (DCS). It shows exactly what has happened and alarms, in real-time.

## Conclusion

While there are new revolutionary concepts in GAMP 5, it does bring together the latest industry and regulatory thinking in GxP computerized system validation into one concise guidance. By using the basic concepts that the GAMP, FDA, PIC/S, and other groups have been touting, such as -Using a scientific risked based approach to validation and leveraging vendor documentation, regulated companies can reduce the time and cost necessary for validation and maintain their systems in a compliant state.

**Table 1:** Describes the software categories according to GAMP classes [2]

| GAMP CLASS | CATEGORY | VALIDATION ACTION |
|---|---|---|
| 1 | Operating systems | Record version |
| 2 | Instruments and controllers. | Record configuration and calibration |
| 3 | Configurable packages. | Audit supplier, validate any bespoke code. Apply full life cycle requirements. |
| 4 | System that the code or part of the code are configurable. | Audit supplier and code, validate any bespoke code. Configurations apply full life cycle requirements. |
| 5 | System utilizing custom or bespoke code which develop predicate rules information | Audit supplier, validate all code, apply full life cycle requirements. |

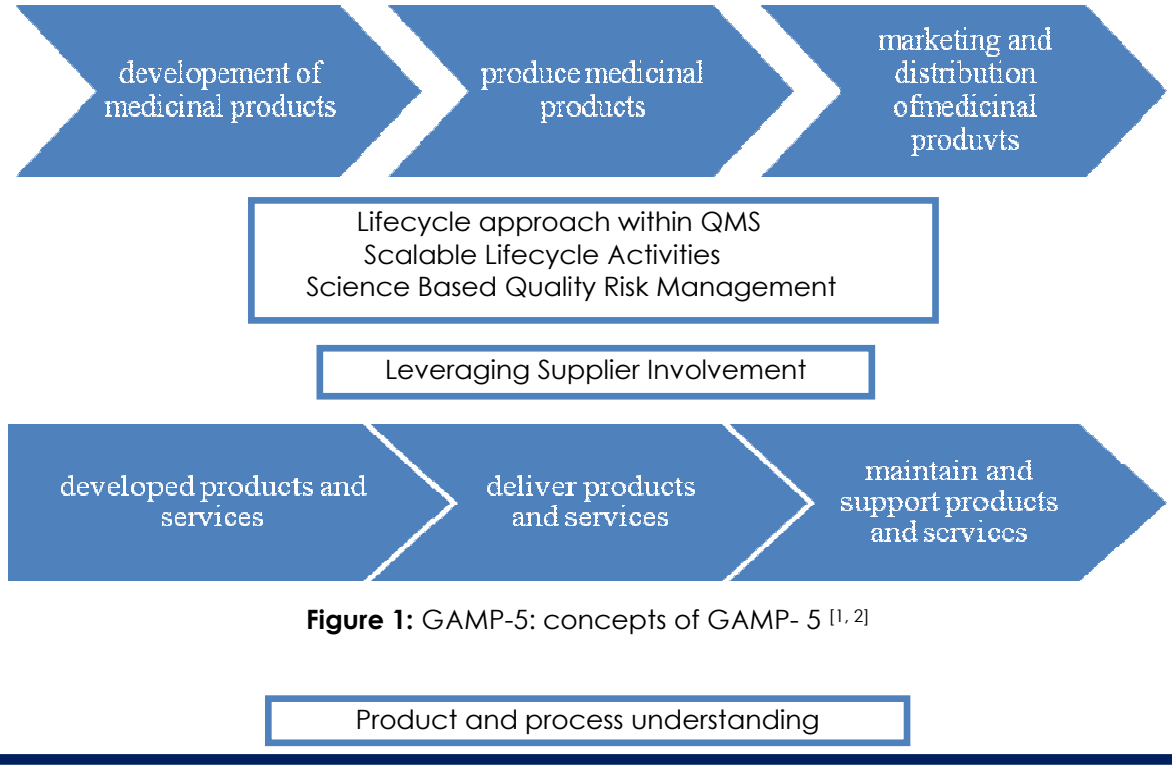


**Figure 1:** GAMP-5: concepts of GAMP- 5 [1, 2]

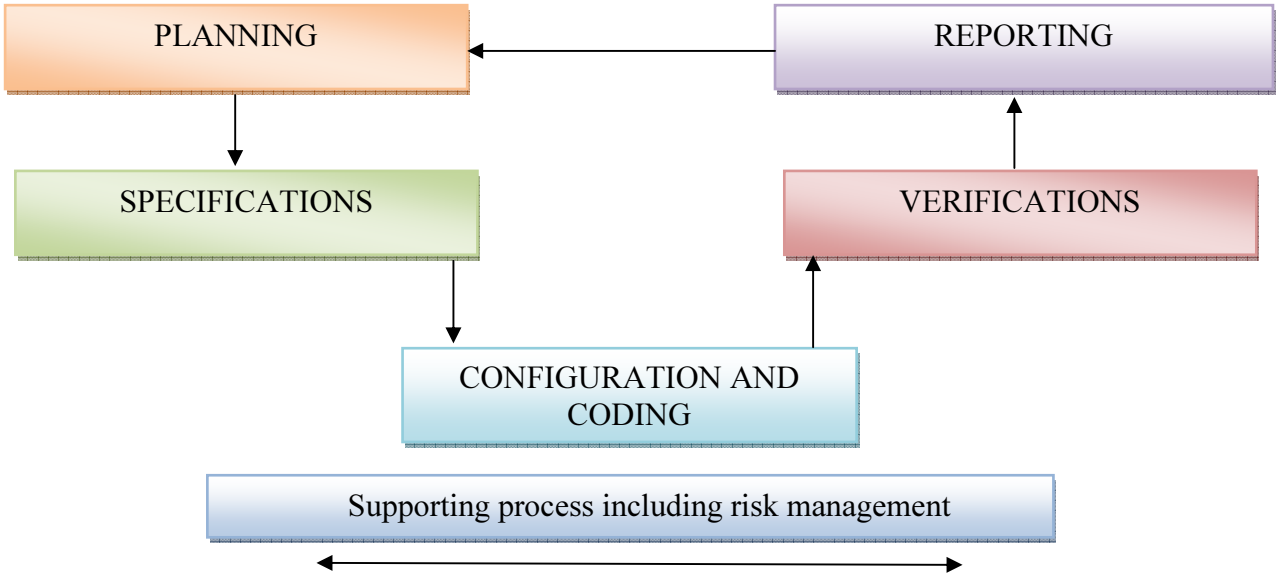


**Figure 2:** Flow chart of V-model. [1, 2]

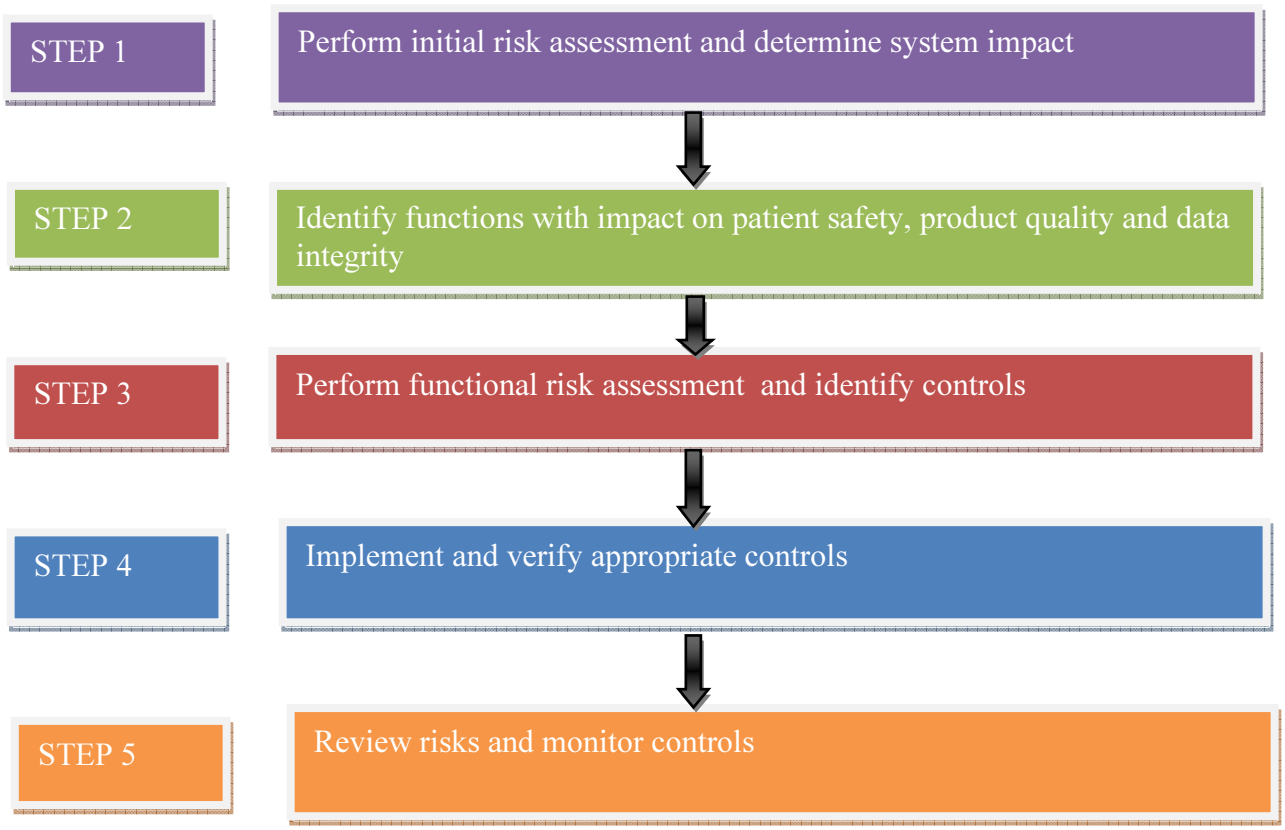


**Figure 3:** Five step process for risk management based on ICH Guidelines [1,2]

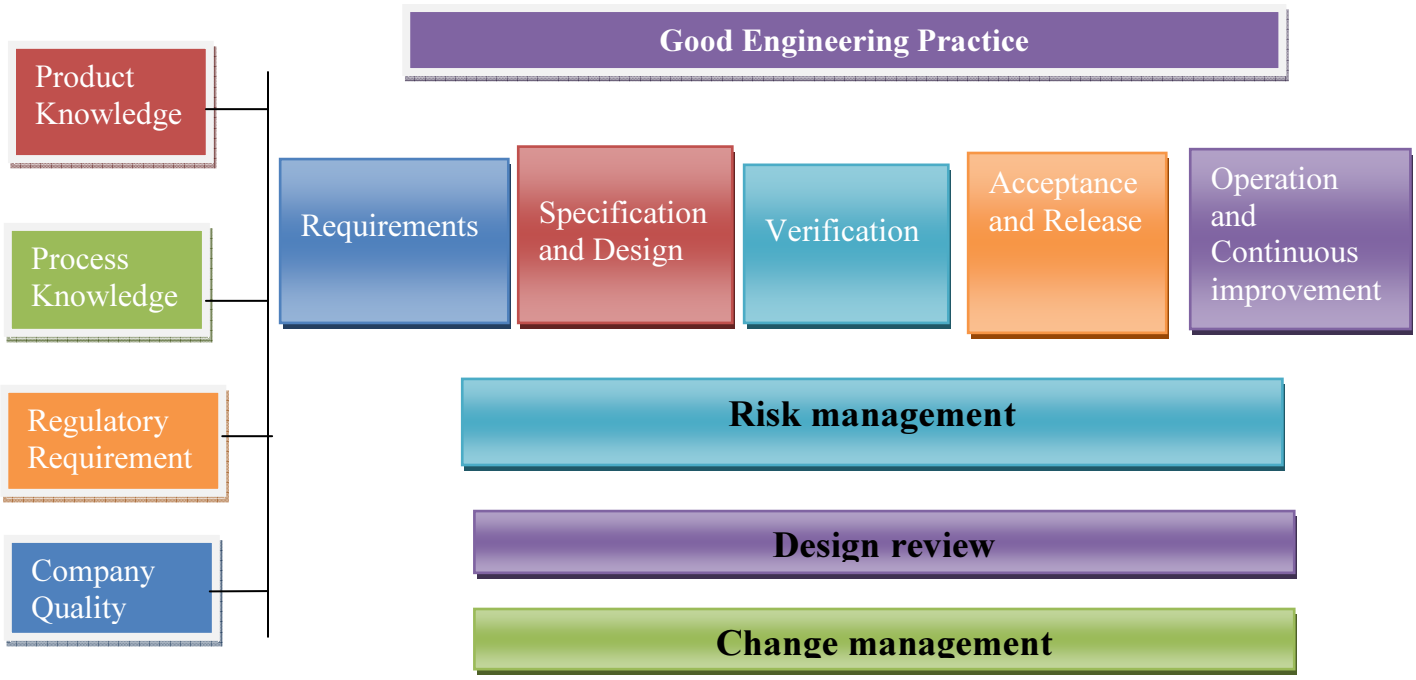


**Figure 4:** The Specification, Design, and Verification Process – Diagram from ASTM E2500 [31]

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