Validation Effects and Issues from the Perspective of the Pharmaceutical Industry

Vothia Surian Subramaniam and Shahrul Kamaruddin

***Abstract*—Quality is an imperative for customers whenever they consider a product or service. It is also important as it relates to life-saving products such as pharmaceuticals. In this regard, the Food and Drug Administration introduced good manufacturing practice (GMP) to maintain and improve the quality of pharmaceutical products. GMP ensures that products are consistently produced and controlled according to the quality standards appropriate to the intended use and as required by the marketing authorization. One of the major GMP requirements is that all of the critical manufacturing equipment, utilities, and facilities in the pharmaceutical industries must be properly validated prior to production. Currently, this practice forms the core of the regulations that are strictly followed by pharmaceutical companies worldwide. This study aims to identify and classify the issues and needs that must be resolved towards a better understanding of the validation process practiced in the pharmaceutical industry.**

***Index Terms*—Good manufacturing practice, pharmaceuticals, validation.**

I. Introduction

The concept of validation was first proposed by Ted Byers and Bud Loftus in the mid-1970s to improve the quality of pharmaceutical products [1]. Currently, in the pharmaceutical manufacturing industry, validation plays a vital role in producing high-quality pharmaceutical products that meet good manufacturing practice (GMP) guidelines. Validation is an important requirement imposed by authorities worldwide to regulate the production of pharmaceutical and medical devices. An equipment, utility, or facility that is not validated may produce inferior outputs [2]. Thus, the Food and Drug Administration (FDA) requires validation, which is defined as the process of collecting and evaluating data to draw scientific evidence that an equipment, utility, or facility is capable of consistently delivering quality products. On the one hand, validation involves confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use are fulfilled [3]. In the pharmaceutical concept, validation refers to the establishment of documented evidence that an equipment, utility, or system, when operated within established parameters, can perform effectively in producing a medicinal product that meets the predetermined specifications. On the other hand, qualification is a process of ensuring that a specific equipment or system is capable of achieving the predetermined acceptance criteria, in order to confirm that it can perform its defined purpose [4]. FDA classified qualification as activities to prove that utilities, facilities and equipments in pharmaceutical companies perform properly and according to their intended use.

There are four stages of qualification actions that need to be executed to have a proper and complete validation. This includes design, installation operational, and performance qualifications. The design and functional requirements are defined in design qualification. It will also ensure that the facilities, utilities and equipments have all the required design, function and performance criteria that meet the user requirements. Installation qualification is a documented evidence that a facility, system or equipment has been properly installed according to the requirements stipulated in protocol. It provides surety that all equipments, facilities and utilities used in the manufacturing process achieve specified requirements and are designed, constructed, placed, and installed accordingly. At this stage, verification on necessary documentation, design features, product contact material, equipment features, safety features and instrumentation will be carried out before it moves to the following stage which is operational qualification. This stage is to test if the equipments or utility systems are capable of consistently functioning within established limits and tolerances. It can also be used to verify that the systems and equipment can operate as intended throughout the anticipated operating ranges. Functionality of all the components, safety devices, alarm and interlock system will be tested during operational qualification. Also, calibrated instruments will be used to verify critical operational parameters which decide the performance level of an equipment or utility system such as temperature, motor speed or pressure at this qualification. Performance qualification will be executed after the completion of installation and operational qualification. Performance qualification is a process to demonstrate that the system or equipment is able to fulfill all predetermined requirements outlined in the design qualification. The main objective of this stage is to carry out tests which determine if an equipment or utility system is capable of consistently producing final products which meet the requirements. It should be executed under actual operating conditions using actual process materials throughout the anticipated working range

II. Effect of Validation on the Pharmaceutical Industry

Validation aims to achieve success in the first production of a new product, and aims to fulfill the regulatory requirements of respective government authorities in each

Manuscript received November 12, 2013; revised March 10, 2014.

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country. Companies which have undergone proper audits or inspections will always produce high quality products. Proper validation ensures the ideal condition of a piece of equipment, utility system or facility, thus minimizing machine downtime, maintenance work, and the amount of defective products. This process reduces the cost for re-inspection, rework, and maintenance work. Validation ensures the safety and quality of the medicines that so many people depend on everyday [5]. This assurance is due to the safety procedures that are used to validate the equipment, utilities, and facilities in the pharmaceutical industry. For example, if a certain product comes into contact with parts of a machine during production, then the machine must be made of316L-grade stainless steel that is free from corrosion. Proper validation ensures that a machine or system can consistently perform at the optimum level. It also increases the capability of a piece of equipment or system, thus maximizing production yield and eventually increasing company profit. This positive result is due to the reduced machine downtime, maintenance work, rejects, and rework of the products. Aside from ensuring quality, validation also ensures the timely delivery of products to customers.

III. Types of Validation

Validation activities practiced in the pharmaceutical industry comprise many types as illustrated in Fig. 1.

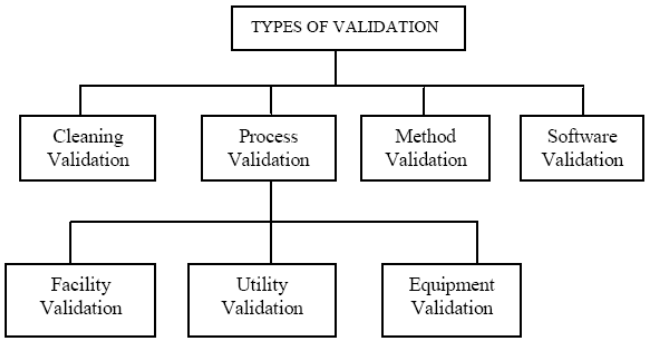

Fig. 1. Type of validation.

Process validation establishes documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality characteristics. The capability of a process in consistently producing quality products can be evaluated and documented. It is also described as a collection and evaluation of data, from the process design stage throughout production. Process validation can be performed in design stage, qualification stage and verification stage. Facility validation, utility validation and equipment validation are executed under process validation.

Meanwhile, software validation ensures that a computerized system performs its exact purpose consistently and reproducibly. It is a process to assure that system specifications are able to meet the requirements of the user and intended uses consistently. It is highly necessary that software or programs applied by pharmaceutical companies in manufacturing of pharmaceutical products must work properly without any error. Cleaning validation is conducted to ensure that equipment cleaning procedures are effectively removing residues in accordance with the predetermined level of acceptability. Adequate cleaning procedures are essential in removing the residues of earlier products, thus preventing cross contamination. Method validation assures if an analytical method is capable to meet the minimum requirement by FDA as guidance for accuracy, precision, selectivity, sensitivity, reproducibility and stability. It proves if an analytical method is acceptable for its intended purpose. Method validation becomes highly important crucial during a development of new method, revision of established methods and method change by quality control department. Method validation increases the value of test results as well as justifying customer's trust

The suitability of facilities in the pharmaceutical manufacturing area is inspected and confirmed through facility validation. The physical requirements of walls, floors, and ceilings in the production rooms are verified in order to confirm if these structures are made of appropriate materials and have proper finishing in order ensuring sufficient and adequate cleaning. Additionally, the availability of the proper drainage system, adequate room size, and light illumination level are also validated under facility validation. Facility validation will also ensure the supply points of compressed air, purified water and electrical power are available. All the related documents such as layout diagram, electrical diagram, compressed air supply diagram and purified water system diagram must be verified under facility validation.

Utility validation covers the validation of utilities such as heating, ventilation, and air conditioning (HVAC), purified water, and compressed air systems which must also be validated before they are released for manufacturing of pharmaceutical products. Installation qualification of HVAC system mainly focus on the proper installation of air handling units, blower fans, filters, ducting system and all the HVAC related components. Besides, the verification of related drawings, material certificate of contact parts, calibration certificate for instruments and training records are carried out during this stage of qualification. The functionality of the HVAC system is verified by testing the control panel which controls the whole HVAC system. This includes the testing of alarm and interlock system. Meanwhile, the performance qualification of HVAC system is to ensure the delivery of environmental parameters which fulfill the requirements, such as temperature, relative humidity, air change per hour, non viable particle count and microbial counts of production rooms and pressure difference between the production rooms against corridor. However, the performance qualification for the warehouse HVAC system requires temperature mapping which uses data loggers to identify critical points for temperature and relative humidity to ensure both reading are within the validated state. The performance qualification of compressed air system requires the air quality tests in which the percentage of component gases i.e. carbon dioxide, carbon monoxide and also oil content in the compressed air will be detected to confirm if the compressed air is suitable for production use. Similarly, purified water system must undergo sanitization, total organic carbon (TOC), conductivity and microbial tests before declared suitable for manufacturing use. All the test results must be documented

properly and must be available for regulatory audit purposes.

Equipment validation ensures that a piece of equipment is properly installed and is functioning in accordance with guidelines, thus ensuring the consistent production of high-quality products. Equipment validation comprises Installation Qualification, Operational Qualification and Performance Qualification. Installation qualification focuses mainly on the verification of documentation such as standard operating procedure, layout drawing and training records for the machine, design features, equipments features, instrument verification, safety features, material calibration certificates and utilities supply. Operational Qualification is carried out to ensure that the functional and the alarm and interlock system of the machine are functioning properly according to the requirements. This can be executed by testing each button and switch on the machine control panel and check the functionality of the machine. The proper function of safety features must be given top consideration during this stage. The functionality of the safety alarm and emergency stop button must be tested to ensure both systems are in proper condition. At this stage, several tests also will be carried out to confirm that the critical parameters of the equipment are within the acceptable range. This includes temperature, pressure, machine speed and other parameters of the equipment which determine the performance level of the machine. On the other hand, performance qualification is to check the capability of the equipment to perform at maximum level, i.e. produce maximum output when the machine runs at maximum speed. The performance qualification varies with the type of the equipments. For tabletting machines, the performance qualification will be carried out by measuring the weight, hardness and thickness of the tablets manufactured. The tablet weight will be used to calculate the machine capability which must be 1.33 and above to prove the capability of the machine. Similarly, the content weight of the capsules will determine the capability of the capsuling machine. On the other hand, fluid bed dryer requires temperature mapping at various points in the machine to verify the consistency of the temperature at those selected points. In addition, samples need to be taken from fluid bed dryer to carry out the Loss of Drying (LOD) test which confirms the drying capability of the dryer. Likewise, homogeneity test results will determine the capability of a dry mixer

IV. Types of Validation Approaches

The validation approaches that are normally practiced in pharmaceutical industries can be classified into three types. Prospective validation is conducted on newly installed equipment, utility systems, and facilities before they are allowed for use in product manufacturing. This approach can also be applied to validate modified and relocated equipment or system that is yet to be used for actual production. Concurrent validation is conducted during routine production. This approach is used to validate old equipment or systems that have been used for many years but have not been validated. When a prospective validation cannot be completed before routine production or when the product to be produced is either of different strength and different shape but the process is well understood, then retrospective validation is performed. Retrospective validation is based on the accumulated historical data and information about a piece of equipment, which can be collected from batch records, production log books, control charts, inspection results, and audit reports.

V. Common Validation Problems

Validation plays a key role in helping pharmaceutical companies increase their profit and strengthen their competitiveness against their rapidly-growing counterparts. Similar to all other professionals in regulated industries, validation experts in pharmaceutical industries have difficult jobs and face various problems on a daily basis [6]. Moreover, several validation personnel commit common mistakes that often result in the failure of their validation projects. In turn, these lead to higher costs, prolonged production time, and so on. A few of the major problems in validation are shown in Fig. 2 and discussed below.

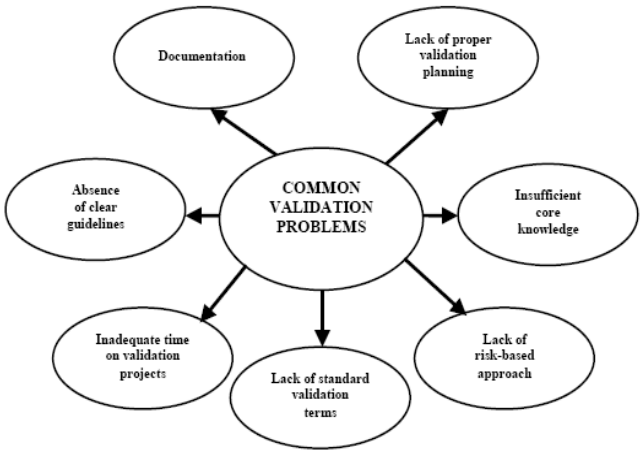

Fig. 2. Common validation problems.

Documentation, this is considered the backbone of validation projects in pharmaceutical companies. Every validation activity must be documented properly. It is a permanent record of the validation effort and represents the specific validation work as well as associated systems, procedures, and performance. However, at present, the low quality of validation documentation has been identified as a crucial ongoing problem in pharmaceutical industries. Inadequate content, the presence of spelling and grammatical errors, as well as substandard, incomprehensible explanations are some of the most significant validation documentation errors reported [7]. Omission of fundamental information, inconsistency among the statements about the same topic in the same document, and details that are below the requirement of the validation document because of incorrect or insufficient information provided by the validation team also result in validation documentation problems. Additionally, lack of acceptance criteria for verifying the actual results, the absence of proper training records, and violation of GMP also lead to low-quality validation documentation. The drawbacks of the validation

documentation system are depicted in Fig. 3.

Lack of proper validation planning, the pressure of commercial manufacturing can prompt many pharmaceutical product manufacturers to spend little time in planning for validation projects. They focus more on releasing the equipment or system for quick production in order to meet the customers' demand and generate profits in the shortest period. However, insufficient planning is inefficient and may cause failure of validation tasks.

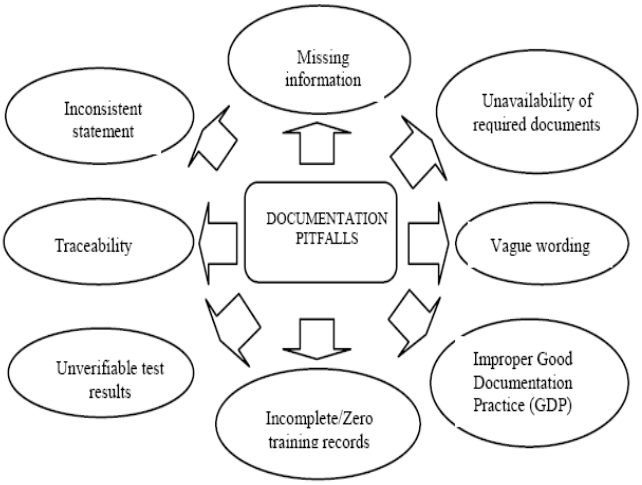

Fig. 3. Validation documentation pitfalls.

Lack of risk-based approach, one way to perform validation is by conducting an effect assessment to determine the extent of validation that should be performed without the unnecessary documentation and planning [8]. Validation should address the critical and non-critical areas so as to identify the factors that exert a direct effect on product quality. Effect assessment can also reduce the number of equipment and systems that require validation. However, unfortunately, many manufacturers ignore this important approach.

Insufficient core knowledge, prior to initiating a validation planning process, pharmaceutical product manufacturers sometimes do not consult all of their employees responsible for validating, using, and maintaining the equipment or system. These employees' inadequate knowledge on the equipment or system delays the completion of the validation projects and can even lead to a failure to meet the requirements. Proper training is usually not given to the validation and maintenance personnel.

Lack of proper monitoring, pharmaceutical companies fail to assign a special team to monitor the ongoing validation projects. Management should be notified of successful test completions as well as delays or problems encountered by the testing team. Such notification allows a faster and more efficient resolution of any failure and avoids project schedule delays that could result if the problems are not discovered immediately [9].

Lack of standard validation terms, regulators and manufactures use different terms to discuss validation activities. This lack of uniformity can cause confusion among the validation practitioners. For example, "acceptance criteria" is also called "acceptable limits" by other pharmaceutical manufacturers to refer to the design and functional requirements of the validation tests. Similarly, "Yes" is also written as "Pass" by different manufacturers to indicate the outcome of the executed test.

Inadequate time on validation projects, the most realistic reason for skipping validation in pharmaceutical industries is time constraint [10]. In this rapidly progressing industry, manufacturers are often forced to reduce time-to-market and cost. Consequently, companies fail to devote as much time as necessary to fully understand the equipment or system before the validation projects begin.

Absence of clear guidelines, the absence of clear guidelines that specify exactly how validation should be performed is an important contributor to the complex nature of the validation process. When the content of the validation protocols is inaccurate or unclear, it may lead to difficulties in understanding the requirements during a validation process. Moreover, incomprehensible and limited explanations are problems commonly encountered during validation [11].

VI. Conclusion

The findings regarding the effect and issues identified in this paper can serve as guidelines that should be considered by future implementers of validation projects. Pharmaceutical manufacturers can definitely improve their validation projects by performing several measures to minimize or eliminate the deficiencies in the validation problems discussed above. Collaboration, prioritization, planning, oversight, and clarity of purpose can also substantially promote the success of validation projects. Research study on the existing validation frameworks should be carried out to identify possible positive elements which may help to eliminate most of the pitfalls discussed in this paper. These elements can be incorporated in a framework which fulfills the basic framework design requirements. It must be simple, systematic, can easily be understood by the future implementers and flexible enough to adapt itself to different contexts. This framework must be validated by applying it in case studies which must be carried out in pharmaceutical companies to confirm its flexibility, robustness and validity. In order to achieve it, it is suggested that these case studies should be conducted in three different backgrounds in a pharmaceutical company to validate facilities, utility systems and equipments. The possible application of this new validation framework into the existing validation procedure can help future implementers to achieve remarkable improvements in validation scope, thus significantly saving manufacturers' time, effort, and money invested in validation projects.

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