Review Article

Overview of the validation procedures for a vaccine production: from R&D level to the pre-qualification stage

Kaghazian H, Doroud D*

Production and Research Complex, Pasteur Institute of Iran, Karaj, Iran.

ABSTRACT

Just like any other process, vaccine manufacturing procedures are defined as a series of interrelated functions and activities using a variety of specified actions and equipment designed to produce a defined product. To assure the reproducibility and consistency of such processes, they must be carried out using validated equipment and under the established procedures that meet all the acceptance criteria, at least 3 times. In many cases, "worst case" conditions are used for the validation purposes to ensure that the process would be acceptable in extreme cases. Therefore, the validation concept in vaccine production facilities is a key element of the quality assurance goals which may reduce the dependence upon intensive in-process and finished products testing. Nevertheless, the concept of validation has expanded through the years to embrace a wide range of activities such as analytical methods used for quality control of drugs, the computerized systems for the clinical trials, the labeling and the process control. To perform such validation activities properly, the updated knowledge of the current regulations are needed. Therefore, the present article focuses on the recommendations in the related guidelines addressing different aspects of validation procedures related to the vaccine production facilities as a part of the product's life-cycle.

KEYWORDS: Validation, GMP, Process, Analytical Method, Regulation.

INTRODUCTION

The term "validation" has been defined in the literature in many ways. Although the terminology could be diverse, the sense of the meaning is always the same: specify and implement, test whether the specifications are met and document the findings. In any validation effort, the main questions are: "where is the optimum?", "how to find the optimum?" or "how much validation is enough?" and hopefully with the help of this article and the information in related references introduced here on the risk-based validation, the reader will have an appropriate guide to find this optimum for a specific process. However, this task also depends on the complexity of the process or the system and the involved risks of the system on the product quality and finally, on the consumer safety. The definition and the involved steps of a validation process are briefly illustrated in the Fig.1.

Vaccine manufacturers like other pharmaceutical companies must validate their manufacturing processes as well as their analytical methods by attaining adequate understanding about the characteristics of the product to be manufactured. These approaches assure the consistency of the production processes and express the aptitude of the industrial scale manufacturing processes, in order to give a high degree of assurance for obtaining pharmaceuticals that meet the required quality attributes of safety, purity and efficacy on a continued basis. Process validation (PV) is a collection and assessment of data from process-design step using three commercial batches of the product that provides a scientific proof that a manufacturing process is capable of consistently producing products with the desired quality and can meet its predetermined specifications and quality attributes. This is an important concept by current Good Manufacturing Practice (cGMP) regulation and is also known as a crucial aspect of the drug quality assurance [1]. As it has been known that the quality cannot be effectively assured just by in-process and finished-product inspection and tests, validation offers assurances that a process is practically protected against the variability sources which could affect the product and the public health, negatively. Also in the cases of any changes in operational parameters through the necessary scale-ups of the production process, such as new facilities and equipment, PV will verify that the product characteristics will not vary [2].

This article will mainly focus on the different aspects of validation procedures related to the vaccine production facilities as a part of the product's life-cycle, recommended by the International Conference on Harmonization (ICH) in Q8 Pharmaceutical Development and Q10 Pharmaceutical Quality

***Corresponding Author:** Delaram Doroud, Ph.D Research and Production Complex, Pasteur Institute of Iran, 25th kilometers of Tehran -Karaj highway, Iran.
Email: d_doroud@yahoo.com, d_doroud@pasteur.ac.ir
Tel/Fax: (+98) 26 36100967

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System of World Health Organization (WHO) and in line with the requirements of both FDA (Food and Drug Administration) and the EU (European Union). It also summarizes all the practical aspects of validation and qualification in analytical laboratories where the most important applied regulations are the Good Manufacturing Practices (GMPs), Good Clinical Practices (GCPs) and Good Laboratory Practices (GLPs). The best-known quality standards are the ISO 9000 series which provide generic standards for development, manufacturing and services. The most frequently used quality and accreditation standard in chemical testing laboratories is known to be the ISO 17025 standards.

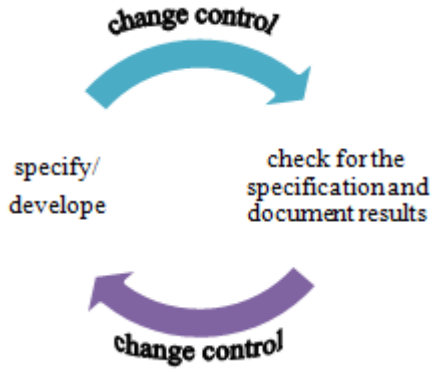


Fig. 1. Definition and steps of validation for launching documented evidence, assuring that a specific process will consistently produce a product with predetermined specifications (FDA 1987b).

Validation versus verification and qualification: Do they really differ?

There are still significant misinterpretations about the differences between testing, calibration, verification and validation. In summary, validation proves that the overall process works for a specific application. This includes specific equipment, software and qualified people and, in analytical processes, it also includes sample-specific calibration standards. A prerequisite for validation is that the individual parts used for the process are qualified during testing and calibration. ISO/IEC Guide 2 (1991) explains the term "verification" as assessment and provision of evidence to confirm that specified requirements have been met. In regard to the management of the measuring equipment, verification provides a logical way of checking if the deviations between the values from a measuring instrument and its corresponding known values are not greater than the limits of acceptable error, consistently. Performance verification of analytical instrumentation is the process of comparing the test results with the performance specification. It includes testing and requires the availability of clear specifications and acceptance criteria. Therefore, "validation" is defined as an evaluation process to ensure compliance with specified requirements. Whereas "verification" is related to the individual phases or modules, "validation" is related to a complete process.

Development of process and analytical validation models: The key elements

For the first time in the middle of 1970s, two FDA officials named Ted Byers and Bud Loftus, proposed the concept of validation in the pharmaceutical industry in order to improve the quality of the products [3]. However, it is now a regulatory requirement and is described in general and specific terms in the FDA's Code of Federal Regulations - CFR21 parts 210 and 211 as well as in the EMA's GMP guide-Annex 15. Although, the first validation attempts were performed according to the processes involved in manufacturing of pharmaceutical products, the concept of validation quickly spread to associated processes including the analytical methods used to test the products.

Process validation activities are described in three different stages: Process Design (PD), Process Qualification (PQ) and Continued Process Verifications (cPV). During PD, a commercial manufacturing process is defined based on the gained knowledge during the development and scale-up stages. During PQ, the design of the process will be evaluated to verify whether the process is capable of commercial manufacturing. At last, in the cPV stage, the ongoing assurance will be achieved via routine production, confirming that the process remains under control. In January 2011, the FDA issued a new guidance document for the industry, entitled "Process Validation: general principles and practices" [4]. This guideline described that the understanding and controlling of the variations are the key to ensure a process would lead to a fit-for-purpose product. It suggests that the manufacturers should understand the sources of the variation, be able to detect the presence and degree of the variation, understand the variation effects on the process and on the product characteristics. They should also consider variation control in a way that is suitable for the related quality risk to the process and the product. Consequently, it is obvious that the absolute focus on the qualification efforts will possibly not lead to a rational quality-related result without consideration of the manufacturing process and its associated variations.

Arrangement between process and analytics: A three-stage approach

Just as process validation can benefit from a product life-cycle approach, so can analytical method validation. This was suggested by Nethercote et al. in 2010 when they proposed that there are a number of key factors that are important in a Quality by Design/Lifecycle approach [5].

These key factors are summarized as the following:

- Importance of having predefined objectives
- Need to understand the method, i.e. being able to explain the method performance as a function of the method input variables
- Need to ensure that the controls on method inputs are designed as such that the method will deliver quality data consistently in all intended environments in which it is used
- Need to evaluate method performance from the method design stage throughout its life cycle of use

By reviewing the above-mentioned factors, one can understand that the method validation can be described as the gathering and assessment of information and data, collected from the design phase during method lifecycle of use. Therefore, it establishes scientific supports that a method is proficient of consistently delivering the quality data [6]. In a simple way, the three-stage approach to analytical life-cycle validation can be illustrated in the Fig. 2 where the concept of having an analytical target profile (ATP) is defined. It is important that "Stage 3" of the activities is involved in both the routine performance monitoring and the effective assessments of the change.

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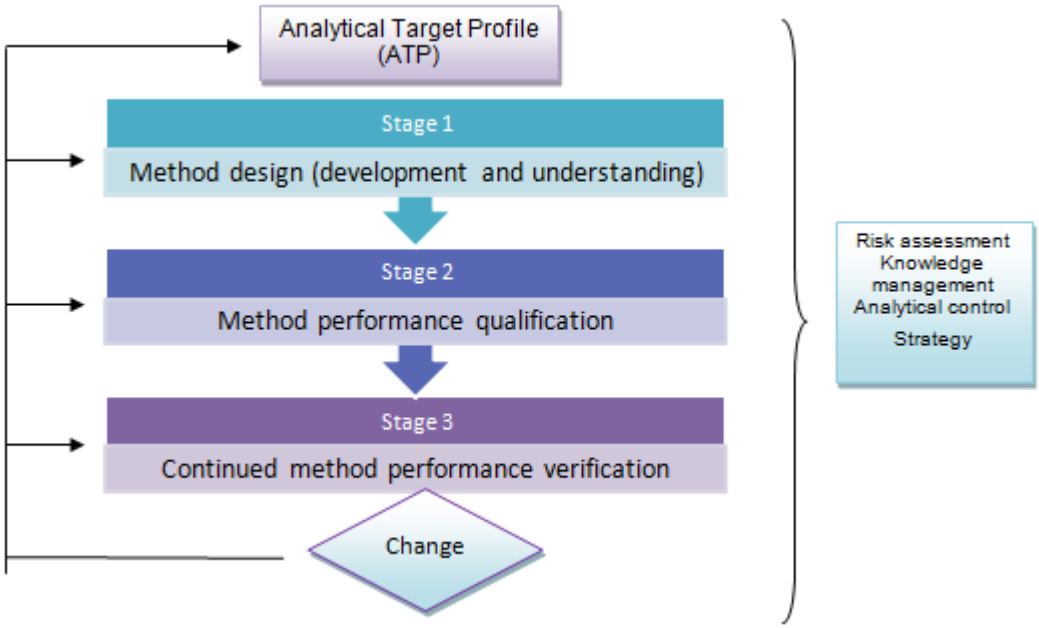


Fig. 2. Three-stage approach to analytical life-cycle validation.

Computerized System Validation (CSV): A necessity for the today's manufacturers

When GLP and GMP regulations were first introduced, computers were not that widely used in the industries; therefore, no special attention was paid to the use of computer hardware and software. Computers were treated like any other laboratory and production instrumentation and were covered under the regulations of GLPs in the US Code, such as 21 CFR Part 58 and 58 on design, maintenance and calibration of equipment.

The Parenteral Drug Association (PDA) has published two technical reports on validation of computer systems. Technical Report 18 is for the generic applications (PDA 1995) and Report 31 is on Validation and Qualification of Computerized Laboratory Data Acquisition Systems (PDA 1999). This report is a good guideline for the validation of any computerized system used in the laboratories. Table 1 shows the milestones in CSV:

Table1. Stages in the development of in Computerized System Validation

1982	US FDA publishes first two Compliance Policy Guides on computerized drug processing
1983	US FDA publishes The Blue Book: Guide to Inspection of Computerized Systems in Drug Processing
1983	US PMA establishes the Computer System Validation Committee
1985	First widely publicized FDA 483 observations concerning computer systems
1986	PMA publishes a concepts paper on computer validation
1987	FDA technical report on Software Development Activities
1987	FDA Compliance Policy Guide: Computerized Drug Processing: Source Code for Process Control Applications
1988	Consensus paper: Computerized Data Systems for Nonclinical Safety Assessments
1989	UK DOH GLP Monitoring Unit publishes The Application of GLP Principles to Computer Systems
1989	US EPA publishes draft on Good Automated Laboratory Practice. Release of final version in 1995
1993	FDA releases draft regulations on the use of electronic records and electronic signatures
1994	The UK Pharmaceutical Industry Computer Systems Validation Forum (PICSVF) releases first draft guideline on "Validation of Automated Systems in Pharmaceutical Manufacture," known as Good Automated Manufacturing Practices (GAMP)
1995	The OECD develops a draft paper entitled The Application of GLP Principles to Computer Systems
1997	FDA releases regulation on electronic records and signatures: 21 CFR Part 11
1999	PDA publishes Technical Report entitled Validation and Qualification of Laboratory Data Acquisition Systems
1999	FDA publishes the industry guide: Computerized Systems Used in Clinical Trials
2000	The US EPA releases the proposed Cross-Media Electronic Reporling and Record-keeping Rule (CROMERRR)
2001	The FDA publishes its draft industry guidance on validation for 21 CFR Part 11
2002	FDA publishes guidance for industry: General Principles of Software Validation
2002	The Pharmaceutical Inspection Convention (PIC) develops a draft edition of good practices for computerized systems in regulated GxP .

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Lifecycle approach in process validation: From R&D through clinical trials to commercial scale regulation

As a fundamental concept, "validation processes are not supposed to be considered as a one-time experience and should be considered as an activity that covers the product lifecycle, linking process/method development, validation of commercial manufacturing process and its maintenance during routine commercial production" [1]. Process development, commercial manufacturing capabilities and the quality system must be integrated in order to achieve effective and compliant commercial operations. This approach implies that the process validation starts before the time when consistency batches are manufactured and continues during the commercial phase. Validation activities requires an interdisciplinary approach to integrate expertise from a variety of disciplines like engineering, chemistry and microbiological sciences, statistics, manufacturing and quality assurance and needs appropriate planning with full support of the upper management. The quality and the regulatory organizational units shall be part of the product cross-functional team from the beginning of the process of validation study design.

Risk-based approach validation strategy: Quality Risk Management system

To answer this very important question: "what needs to be validated and when is the right time?", a Quality Risk Management (QRM) system must be developed adjacent to the product lifecycle during the different validation stages. The entire product attributes and operational parameters should be assessed in terms of their utility related to the specific processes and their effect on the product (in-process) should be re-assessed, as new data become available. This will help to identify critical operational parameters. Therefore, validation activities may focus on those processes that tend to have the greatest quality risks. This means that higher degrees of controls are necessary for the attributes with the higher risks [7]. For instance, some of the factors that may affect the product safety, identity, strength, quality and purity are bioburden, endotoxin levels, glycoform distribution (in cell culture and fermentation process), product homogeneity (e.g., mixing) which represent some quality risks that are needed to be identified as a part of the product development.

Validation of vaccine production steps: Identification of the critical steps

Vaccines can be manufactured from a variety of different compounds like antigens, live attenuated or inactivated (killed) whole organisms, crude fractions or purified immunogens including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, and polynucleotides (such as the plasmid DNA vaccines). It may also be a combination of the above-mentioned antigens [8]. Considering the complexity of the related processes, specific studies such as stability studies of in-process intermediates and process solutions may be performed separately from the full-scale conformance lots. For this purpose, process validation could be divided into validation of individual related groups of operations or unit operations rather than considering the entire process. These studies may be performed at a pilot scale, prior to the manufacturing of consistency lots of the finished product, including for example recommended lifetime, holding time and acceptable ranges for the step yields. In certain cases, parameters established prior to commercial consistent batches can be evaluated and confirmed by on-going validation studies, carried out according to the protocols established during the commercial manufacturing or during the production of consistent commercial batches (e.g. determination of the membranes and resins lifetime, holding times, inactivation and detoxification, purification yields, impurities removal). According to the FDA's PV guideline, the determination of the re-use level of some materials such as column resins or molecular filtration media can be estimated in quality control studies. The extended lifetime for the re-use of such materials should be confirmed and verified by the ongoing process performance qualifications which must be performed during the commercial manufacturing. The acceptable limits of variability must be surveyed and optimized processing parameters should be chosen from the obtained results. Depending on the circumstances, controlled experiments like scale-down processes may be arranged to find the data necessary for the identification of the minimum and maximum limits of the process parameters [9]. A complete list of vaccine production validation and the key common steps and critical factors which are needed to be considered as part of the validation studies, are presented in Table 2.

Table 2. A summary of the key common steps and critical factors in the validation studies.

Process Step	Key Steps to be considered
Propagation	- Propagation from retrieval of the working cell bank (WCB) to culture harvest; Culture media used at each step, with details on preparation and sterilization - Inoculation and growth of initial and sub-cultures (volumes, time, temperature of incubation) - Culture transfers and precautions taken to control contamination -In-process testing which determines inoculation of the main culture system and absence of adventitious agents, including tests on culture cells -Main culture system including operating conditions and control parameters (e.g., temperature of incubation, static vs. agitated, aerobic vs. anaerobic, culture vessels vs. fermentor, volume of fermentor, or number and volume of culture vessels) -Parallel control cell cultures, if applicable, including number and volume of culture vessels (cell factories).
Fermentation	- Volume of air flow through headspace of fermentor (e.g., in Tetanus toxin production) -Speed of the impeller at the fermentor culture of anchorage-dependent cell substrates - antigen stability under the conditions of fermentation (e.g., pH higher than 7.4 in Pertussis antigen production) - Live and dead cell ratio at trypsinization of cell cultures
Harvest	- Speed of chilling of the culture - Capacity/volume/speed and temperature of separation/centrifugation/cross flow filtration; - Preservative added, if applicable

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	- Final holding temperature - Volume of inactivating/detoxifying agent, holding time and temperature in the fermentor, in case inactivation/detoxification is done during harvesting.
Purification	- Yields and purity at each step - Removal or dilution of product related and non-product related impurities, e.g., contaminating cell proteins or nucleic acids, endotoxin, processing reagents, etc.
Concentration	- The acceptable range of yield - Quality and quantity of extractables - Filter sanitization process
Inactivation and Detoxification	- Concentration of chemicals, pH, and temperature of culture, duration of inactivation
Viral clearance	- pH, solvent/detergent concentration, heat duration
Sterilizing Filtration	- Sorption, which varies by filter type and media present (occupation of non-specific or specific binding sites on the filtration matrix) - Different behaviors depending on concentration and content – a detergent-dependent protein will filter very differently if there are still micelles present.
Formulation of Bulk Product	- The quality and quantity of adjuvant - Simulation of the aseptic process
Manufacturing of Consistency Lots	- Qualification of facility, equipment, utilities, and related processes - Consistency Lots (Process Performance Qualification)
Dry and Moist Heat Sterilization Process	- Temperature distribution to detect potential cold spots (e.g., sampling ports, inlet and outlet filters), by performing temperature profile studies with a sufficient number of probes to be representative of the empty vessel or chamber (e.g. 10 probes). Temperature uniformity must be proven - Temperature penetration and biological challenge studies are normally performed simultaneously. For moist heat, biological indicators with moist heat resistant spores are used. For dry heat, endotoxins are employed. The locations and number of the biological indicators placed should be clearly described and justified in the corresponding validation protocol and need to be representative of the types of items to be treated - Validation of moist heat sterilization processes of heat resistant items, buffer solutions or empty vessels should demonstrate a six log inactivation of a heat-resistant biological indicator system (e.g. using 106 microorganism spores challenge, with a D value >1.5 minute). A temperature of 121.1ºC for at least 15 minutes is usually required in all parts of the load - Validation of depyrogenation processes should demonstrate that a temperature profile of 250° C is attained, and an endotoxin 3-log reduction in the load is accomplished

Aseptic process validation: The famous media fill process

Along with any validation activity, aseptic processes validation or media fill processes that consist of challenging filtration systems, the environment, equipment and personnel should be performed in terms of aseptic processing assurance. Aseptic process validation must be performed only after all applicable qualification studies have been completed and approved. Products that cannot be filter-sterilized in any stage of the process (e.g. vaccines like DPT and MMR), have the highest risk of contamination and the validation strategy needs to consider the aseptic processing during all the manufacturing stages. Overall, when the aseptic processes are designed, the manufacturer should consider the following aspects to lower the contamination risks:

Use of single-use closed system technology for the aseptic connections, including aseptic transfers from lower class rooms. These systems have no exposure to the environment

Isolator technology

Automated sterilization in place process (SIP) is recommended whenever possible for main production equipment, product valves and product transfer lines

It is critical to notice that the media fills should be a representative of the routine production and include possible worst-case situations such as engineering interventions. Different product presentations can be grouped together [9]. The minimum quantity of vials for media fill operation should fulfill the WHO requirements (WHO TRS 961) and must be adequate for valid evaluations [12].

Cleaning validation strategies: Establishment of the acceptance criteria

Manufacturing processes have to be designed and carried out in a way that prevents cross-contamination as much as possible. Since most pieces of equipment are being used to manufacture different products, cleaning procedure must be able to remove residues from the equipment, up to an acceptable level. The cleaning methods utilized in any production line shall consistently control the residuals of potential carryover of different products, cleaning agents and contaminants into subsequent product that is going to be manufactured in the same line to an acceptable predetermined level. Different production lines may have different cleaning requirements based on the process steps and the subsequent products to be manufactured. Hence, the higher risk of having a finished product cross-contaminated, the more requirements for validation of the cleaning procedure to assure the product safety. In order to design and justify an adequate cleaning validation strategy, it is essential to understand the nature and risks of the potential product residues to the patients, the manufacturing steps, the equipment and the utilities involved. It basically depends on the following considerations:

Dedication of the equipment multipurpose usage

The manufacturing step (e.g. early, intermediate or final step)

Series of batches in-campaign or a product changeover

Possible residue level from potential build-up of same product impurities

Cleaning agent residue, if used

Presence of components with a potential for accumulation /adsorption /precipitation etc., given the possible concentrations, materials and conditions

Potential contaminants characteristics like toxicity and solubility

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Potential for live and inactivated microorganisms to be mixed
Elements added later to the process would kill/modify/oxidize new materials coming in, or downstream steps that would purify any possible level of contaminants Disposable vs. reusable product-contact equipment/accessories.
Automated CIP vs. manual cleaning Use of 100% fresh water, or re-circulated water for washing/rinsing purposes of product contact surfaces.
Levels of cleaning are defined as the following:
Level 0: is considered in batch-to-batch changeover in an identical process (the same intermediate and API) and change to early steps of another product
Level 1: is considered in changeover between the intermediates of one product to final/intermediate of another, change in early step to intermediates of another product and changeover from early steps to final step of the same product
Level 2: is considered in changeover of one API to another API, changeover of any intermediate to any API, changeover from early steps to final step of the same product and the product changeover in the case of any equipment that are going to be used in final production steps
In level 0, no validation is required, although the cleaning intervals and methods should be determined. However, it is necessary to determine a maximum campaign length after which the cleaning must be carried out. In level 2, the validation performance is necessary.
In a multipurpose setting, a prioritized matrix/bracketing approach of selected compound residues to be verified after cleaning, could be based on the toxicity and the safety data, in order to reduce the validation scope while ensuring a proper cleaning validation study. The setting limits approach might include a product-specific cleaning validation or might group the products into families with the same characteristics and then a worst-case product could be chosen. Grouping of the products is usually based on the risk-assessment approach and according to the product solubility, potency, toxicity and detectability. The carry-over of the product residues should meet the defined requirements and could be categorized according to one of the following rules:
Rule one: it is not allowed that more than 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the next product (according to ICH impurity document).
Rule two: it is not allowed that more than 10 ppm of any product to be carried over to another product.
In both criteria, it is considered important that no residue should be visible on the surfaces of the equipment after executing of the cleaning procedures. Spiking studies should determine the concentration at which the most active ingredients are visible. If the acceptable limit is lower than the detection limit (LOD) of the analytical, the equipment must either be dedicated or an alternative and more sensitive method must be developed and utilized for the residue detection. In case of manufacturing certain products containing hazardous substances, separate, dedicated and self-contained facilities should generally be used. In this case, there is no need for the full cleaning validation studies. Dedicated production areas include facilities, air handling equipment and/or process equipment. Dedication of the equipment must be performed for products that have gummy or insoluble residues which are difficult to be removed. Furthermore, for equipment which are difficult to be cleaned and for biologicals and potent (high pharmacological activity) or highly toxic and cytotoxic pharmaceutical products, the dedication of the equipment is mandatory. In case of potent and biological products, the detection of the residues is often difficult, as it may be far below the predicted acceptable limits. Moreover, in case of production of steroids or cytotoxic anti-cancer drugs or highly sensitizing active pharmaceutical ingredients, like penicillin or cephalosporin, the dedication rule is mandatory. These mentioned products are not advisable to be manufactured in a same facility where a vaccine is going to be produced.

Revalidation: When is it necessary?

Once the system or the process has been validated, it is expected that it remains in control, provided that no changes are made. In the event that modifications are made, or equipment is replaced or relocated, partial or full revalidation studies could be needed (11). These situations must be strictly handled through the appropriate Deviation Handling, Corrective Action and Preventing Actions (CAPA), Change Control management and Risk Assessment. Whenever there is not a sign and document for an implemented significant change in a system or process and also when a quality system review assures that the system/process is consistently producing the products with their determined specifications, there is usually no need for the revalidation studies [12]. This revalidation approach could be described as event/change-driven. WHO recommends that the systems and the processes should be periodically evaluated to authenticate that they are still operating in a valid manner. In case of high risk processes, such as aseptic processes, sterilization and depyrogenization processes, the validation studies are expected to be performed twice a year or at least, yearly.

WHO Pre-Qualification process: Expectations from the validation studies point of view

When a manufacturer tends to participate in a WHO PQ process, it must focus on the sufficiency of the subsequent validation-related aspects. Such related aspects are implementation of the risk assessment in the validation studies as mentioned in section 5, conformance of current validation activities, policies for routine validation and revalidation, change control and deviation management policy, critical validation deviations (e.g. failure to have a cleaning validation of the critical steps), inactivation process validation, uncontrolled risk of cross-contamination and continued process verification through trend analysis [13].
To perform a typical validation study efficiently, all the relevant departments such as quality assurance, quality control, and of course, production should be involved directly. The related study should be carried out according to a perfect schedule. After determination of the critical steps of the process, appropriate validated methods must be employed to analyze the collected samples. The results will be compared with the acceptance limits, defined in the "quality by design" stage, before commencing of the study. It is also essential to take the necessity of revalidation into account as applicable.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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