DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(6&7), 1029-1046 (1989)

OPTIMIZATION AND VALIDATION OF MANUFACTURING PROCESSES

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ABSTRACT

Validation in the definition adopted by a Joint FIP Committee means that every essential operation in the development, manufacture and control of pharmaceutical products is reliable, reproducible and capable of providing the desired product quality if stipulated production instructions and control procedures are followed.

A pre-requisite for, and an integral part of process-validation is that people, premises and equipment should be qualified. In other words, validation activities rely upon the check of technical and physical parameters when measuring devices are being calibrated, equipment is being qualified as well as on chemical, physical and biological parameters when processes are being validated.

As we know, validation starts with planning a new plant, a new machine or equipment as well as with the development of a new or changed product.

This way of development from the laboratory trial and the clinical trial until the production phase has to guarentee the manufacture of products conforming to the desired profile.

According to a new draft guideline prepared by the FDA this year, drug products which are produced for clinical trials have to comply with the GMP - regulations. For example, the drug product must be produced in a qualified facility and the process must be validated. This means that manufacturing processes for clinical trials should be validated at the end of the development phase, as soon as processes are at least partially optimized, even if scaling up has not yet been completed.

The results of all development studies i.e. the use of equipment, the tolerances of physical parameters in the manufacturing process and the approved specification of starting materials being summarized in such a validations-report, the latter mostly seems to be an optimization-report. This can be of special value when scaling up in the production facility is completed.

As far as a sufficient number of clinical trial batches are manufactured according to an approved procedure this process can be validated prospectively. The results of this validation as well as the Know - how gained during optimization provide the basis for the validation of production conditions.

The organisation of our validation activities in the manufacture of sterile and nonsterile drug products will be described in this presentation and some examples of process-validation will be given.

INTRODUCTION

The operation which is nowadays referred to as qualification or validation in the pharmaceutical industry is basically not a new idea. The performance of apparatus, was also tested in the past.

However, it is not only the equipment but also the production and control procedures which have always been subject to optimization, monitoring and verification, albeit with varying degrees of intensity. These activities were naturally less highly organized then and may have been carried out without reference

to an established test protocol or check-lists, perhaps even without documentation. However, it is precisely this system of formal records to document that a machine operates as expected or that a process does what it purports to do, a relatively new key element of validation.

Nowadays both the qualification of premises and equipment as well as process validation come under the heading VALIDATION.

Definitions of the terms qualification and validation refer to the "formal and systematic" process of establishing that equipment is operational and processes are suitable for the intended purpose. Formal and systematic means that validation must be carried out systematically according to written test protocols and that all results must be documented and evaluated. In other words, validation must be organized.

I would like to recall two definitions, one of the FIP the other one of the PIC :

In the sense of the guidelines (FIP/1980) (3), validation means establishing that every essential operation in the development and manufacture - including the control of pharmaceutical products - is reliable and reproducible ; and, when following stipulated instructions and control procedures, is capable of providing the desired product quality.

PIC "Basic Standards"(2) define Qualification and Validation as follows;

Qualification: The performing and recording of tests on a piece of equipment to demonstrate that it will in practice perform as intended.

Validation : The obtaining and documenting of evidence to demonstrate that a method can be relied upon to produce the intended result under any conditions within defined limits.

The most important facts of the FIP-Guidelines (3) are :

- Validation is an additional part of GMP and very significant for the safety of drug products

- Validaton is important for the development phase as well as for the manufacture and quality control of medicaments
- Fundamental changes of manufacturing and control procedures have to be validated as far as empirical data are not sufficient
- The manufacturer is responsible for proper validation
- The governmental inspector has to verify whether the manufacturer carries out a validation and whether the methods chosen are appropriate and in keeping with the present state of science and technical knowledge.

Responsibility

Assuming that validation (including qualification and calibration) is a component of GMP and thus contributes to ensuring the quality of drugs, and assuming that we accept that this form of quality assurance requires the joint efforts not only of the departments responsible for manufacturing and quality control, but also of those responsible for the technical aspects, then it is reasonable that these departments should also be enstrusted with the responsibility for validation.

On the one hand responsibility presupposes knowledge, experience and enthusiasm on the part of those involved and on the other hand it presupposes acceptance and acknowledgement by the management who must be aware of the necessity and value of validation.

Validation can thus be seen as a form of teamwork which should be managed by the person whose plant or laboratory houses the apparatus requiring qualification or the processes which need to be validated. The plant manager is the person most familiar with the equipment and the processes which have to be validated, as is the laboratory manager in quality control with the analytical equipment and test methods. In other words, each of these managers should be actively involved in validation in his own area.

Optimization and Validation in Development Phase (1)

When development reaches the stage where drug products are produced for clinical trials, then compliance with GMP regulations is required. For example, the drug product must be produced in a qualified facility using equipment which has been qualified, and processes must be validated. This means that the development phase has been finished, the manufacturing processes for clinical trials have already been optimized, and procedures are described. According to a new draft guideline prepared by the FDA this year, drug products which are produced for clinical trials have to be validated (6).

The quality of design should be defined as early as possible during the development phase because changes from batch to batch cost time and money. The gained experience from such changes are indeed the results of optimization, but cannot be defined as validation. A continously changed process which has not been laid down cannot be validated.

Objectives of development are :

- Definition of the quality of design
- Setting specifications of starting materials - not only those of the pharmacopeia, which mostly are not quite complete as far as physical parameters are concerned
- Setting product specification
- Definition of critical parameters which have to be controlled by IPC
- Optimization
- Scaling up and
- Transfer of experience

Objectives for optimization are

- Find the cause of weak points of the formulation during development which sometimes are detected later during manufacture

- Improve quality-aspects
- Work out tolerance limits for process parameters
- Improve manufacturing procedures for cost-saving

Examples for optimization are the following parameters

- Flow properties
- Dissolution
- Disintegration
- Thermal stability
- Filterability
- Preservation
- Viscosity of semisolid preparations
- Particle size in suspensions
- Physical stability of emulsions
- Pharmacokinetics as
  - Bioavailability and
  - Drug release

Results of optimization should comprise

- Confirmation of the formula
- Decision to start manufacture of clinical trials
- Description of manufacturing process for clinical trials
- Basis for validation in development phase

Scaling up can be defined as the

- Transfer of manufacturing processes from laboratory to pilot plant and from there to production with the guaranty not to change important quality aspects
- Optimization in production for quality and economical reasons
- Validation in production phase

The results of all development studies - for example the use of equipment, the tolerances of physical parameters in the manufacturing process, data about physical and microbiological stability, and the approved specifications of starting materials being summarized in a report - can only be a substitute for a validation report if testing is not done according to a validation protocol. At any rate such an optimization report can be of special value when scaling up and validation in the production facility are to be completed.

A process can be validated prospectivelly if a sufficient number of clinical trial batches are manufactured according to an approved procedure. The results of this validation as well as the Know-how gained during optimization provide the basis for the validation of production conditions (Fig. 1).

Requirements for Process Validation

Thorough specialist knowledge, experience, an interest in the quality of the product being made and a certain amount of scientific enthusiasm are the vital characteristics of the team-members. The team should call on specialists to assist with other specific questions.

Equipment or plant cannot be inspected/qualified if, for example, too little thought has been given to the equipment specification, the points to be tested or the test criteria, or if these are incomplete or even non-existent. In the same way a process cannot be validated if it has not been described, or if the description is incomplete, or if the equipment which is to be used is not qualified. Process validation thus depends on optimized processes and corresponding manufacturing and testing specifications. But optimization is not the same as validation!

It is not sufficient to produce operating instructions and operating and testing specifications; staff must also have an opportunity to become familiar with the new machinery or a new process. This applies not only to production staff but also to

OPTIMISATION AND VALIDATION IN DEVELOPMENT PHASE

Determination of
- Product profile
- Specifications for starting materials
- Test methods for starting materials and drug product
- Manufacturing process (draft)
- Critical steps

Optimisation
- Process parameters
- Tolerance limits
- Preservation

Manufacturing process for Clinical Trials/ Validation development phase
- Validation protocol (prospective)
- Validation results (Equipment, IPC, stability, quality testing)
- Validation report

Scaling up
- Equipment
- Process

Optimisation

Manufacturing Process for Production
- Validation on the basis of results of the development phase
- Validation protocol (prospective)
- Validation data
  - Calibration of measuring devices
  - Qualification of (premises and) equipment
  - Results of IPC
  - Results of quality testing
- Validation report

FIGURE 1

Optimisation and Validation in Development Phase

maintenance and quality control personnel. Qualified staff, i.e. personnel properly trained and familiar with the job, are a prerequisite for or a part of validation.

Where new premises are constructed or new equipment is brought in, installation qualification and calibration of the measuring devices must precede operational qualification, which in turn must precede process validation of, for example, an aseptic filling, a cleaning or a manufacturing process.

Preparation for Qualification and Validation Activities

Although, according to operating regulations, all manufacturing processes including equipment have to be validated, priorities have to be established. As a rule, manufacturing processes for products which have already been on the market for some time can be validated retrospectively, whilst new products should be validated prospectively. In general validation of the manufacture of parenteral drug products has a higher priority than those of non-sterile oral dose forms, for example, and validation must thus be carried out prospectively.

Policy and Organization of Validation (5)

What follows is a description of the validation policy in our Health Care Sector, including the organizational set-up and the way validation is carried out. This means that the description applies to just one pharmaceutical manufacturer and not to the West German Pharmaceutical Industry as a whole.

Some seven years ago our Quality Assurance Committee which consists of the heads of production, quality assurance, engineering, pharmaceutical technology and the GMP section created a validation steering committee. The latter also consists of representatives from the above departments and reports to the QA Committee (Fig 2).

The validation committee's first task was to draw up specifications for the validation policy and for the organization

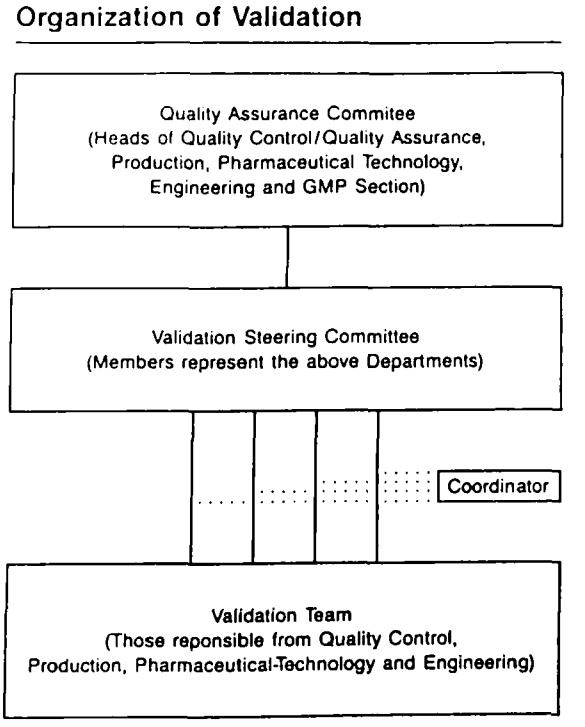


FIGURE 2
Organization of Validation

of the validation procedure. The committee's routine tasks include ensuring that the validation policy is observed, discussing new developments in this field and suggesting priorities for prospective and retrospective validation.

One important decision made by this committee concerned responsibility for carrying out validation which was expressly given to the various departments, the plants and laboratories concerned and not to a corporate validation group. Another new feature was that responsibility was to reside not with quality assurance alone but with the team as a whole. The activities of the GMP section which coordinates all validation work in production were defined and the need for this section to be provided with information was emphasized.

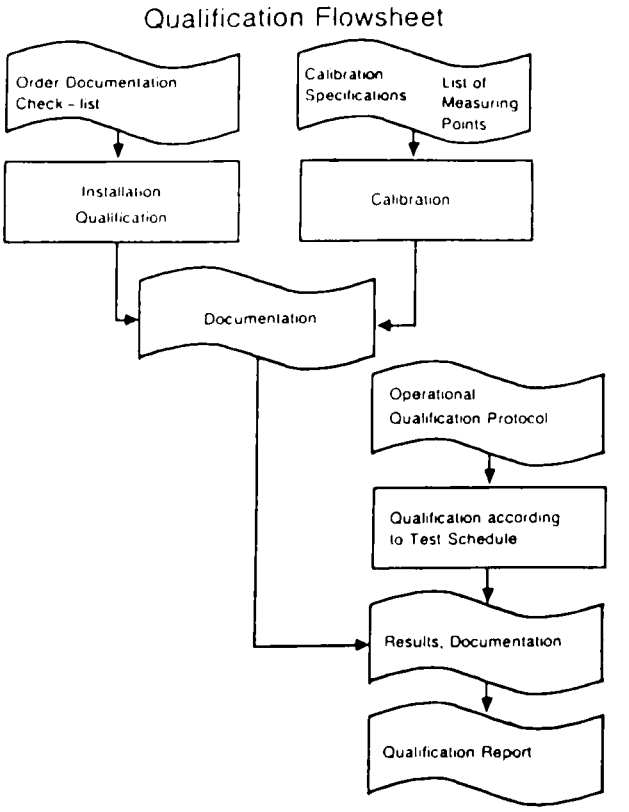


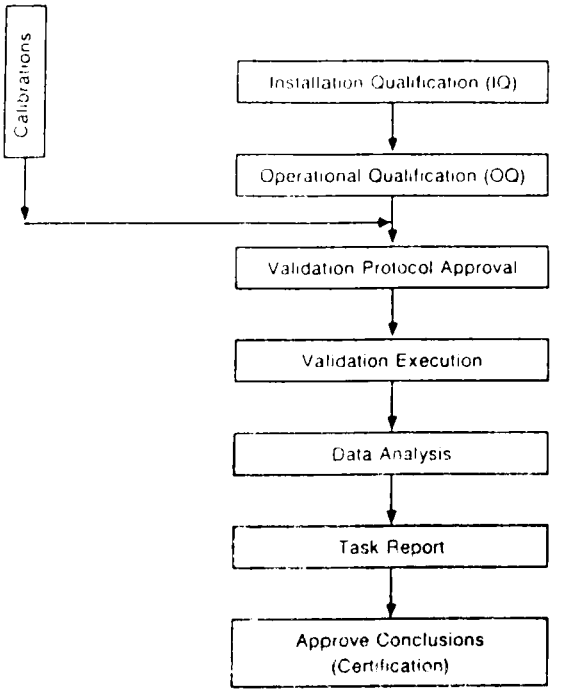
FIGURE 3

Qualification Flowsheet

The Validation Procedure

The following flowcharts show the various steps involved in qualifying equipment or validating processes (Fig. 3,4).

The validation coordinator of the GMP section is informed of a new project while it is still at the planning stage and thus has time to decide on dates and protocols for qualification and validation. A validation team is nominated, the scope of the validation project is defined, the coordination office in conjunction with the validation team draws up qualification and



Chapman, Prospective process validation

FIGURE 4
Prospective Process Validation

validation protocols which are then discussed, supplemented or corrected and finally approved by the team members.

Qualification and validation protocols are numbered systematically and each consists of a title page, a page listing dates, a page listing the points to be tested together with the test methods, the frequency and specified values or tolerance limits (Fig. 5) plus appendices such as report forms and drawings. The title page (Fig. 6) contains a description of the equipment or process, the name of members in the validation team, the type of validation being carried out (prospective, retrospective) and the reason for validation.

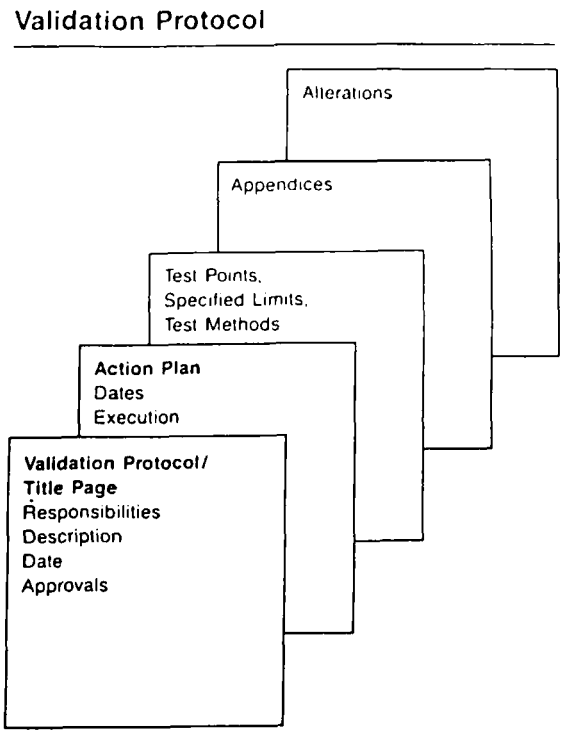


FIGURE 5

Validation Protocol (a)

The actual qualification or validation protocol comprises a list of the points to be tested. These must be selected specifically either for the equipment or for the product and process involved and must particularly take into account the critical process parameters. The compilation of a list which is as complete as possible and the selection of the correct test methods with a small standard deviation will determine the success of failure of a validation procedure. It is worth giving a good deal of thought to the test points.

All departments involved in testing receive a copy of the entire protocol according to which they carry out their tests, preferably on schedule.

Validation protocol

- Title page -

Company Dept Title:
System No: Page of
Edition No Valid from

Building /Room-Nr.:

Type of validation
( ) prospective
( ) retrospective

Reason for validation
( ) new process/ equipment
( ) modified process/ modified or repaired equipment

Description of equipment/process:

Validation team: Production
Pharm. Technology
Quality Control
Engineering

For distribution to: Validation team
Departments which carry out tests
GMP-sections

Appendices: List of measuring points
Report forms
Drawings

Signatures:

FIGURE 6
Validation Protocol (b)

Test Results

The results of the individual tests are sent to the head of qualification / validation and to the coordinating office which is also responsible for monitoring the schedule.

Once the results have been submitted and evaluated, the head of validation and the coordinating office have to produce a summary in the form of a final qualification / validation report which is then submitted to the team for approval. A concluding report must be written for every object which has to be qualified and for every process which has to be validated and is filed internal together with the corresponding test protocol and all

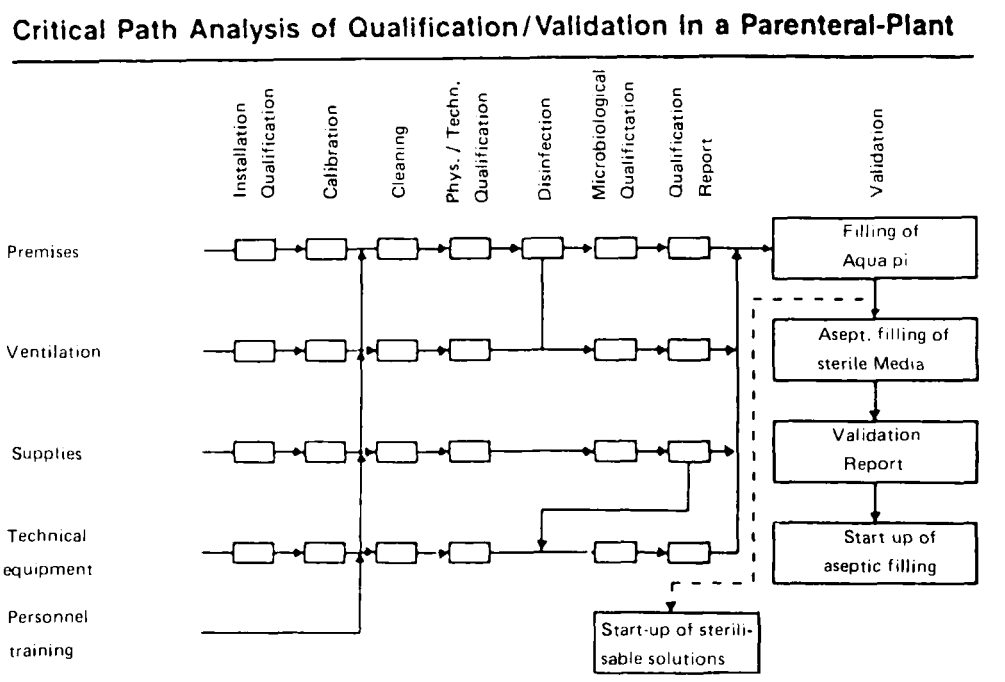


FIGURE 7

Critical Path Analysis of Qualification / Validation in a Parenteral - Plant

results. Where necessary, a summary of all the tests carried out during process validation and their results is produced for registration purposes for the Health Authority.

Validation Activities in a New Plant

A critical path diagram (Fig. 7) has been used for major projects, particularly in sterile areas, so that the interactions between the individual stages can be taken into account more effectively.

MANUFACTURE OF TABLETS FROM FLUIDIZED BED GRANULATES/ PROCESS VALIDATION

Basic requirements: SOP's available, personnel trained

1. Installation Qualification of Equipment and Calibration of Measuring Devices

2. Operational Qualification of Fluidized Bed Granulator/ Check-points
   - Temperature and Quantity of air
   - Spraying-rate and -pressure
   - Temperature of product and outgoing air

3. Granulate
   - Humidity
   - Weight per volume
   - Actual and percentage of theoretical yield

4. Container rotating machine
   - Revolutions per minute
   - Mixing-time

5. Tablet press
   - Pressure
   - Number of tablets/hour

6. Non-lacquered tablets
   - In process Control
     - Weight of single tablets
     - Thickness
     - Friability
     - Hardness
     - Disintegration
   - Actual and percentage of theoretical yield
   - Quality testing according to specification including microbial purity

7. Cleaning of Equipment according to SOP
   Testing of simulated product (Maize starch) for effectiveness of cleaning. Samples are drawn from different points of the fluidized bed granulator and from tablet press to test for absence/presence of the product made before.

FIGURE 8

Manufacture of Tablets from Fluidized Bed Granulates / Process Validation

Microscopic examination of these three different types of indomethacin powders indicated that there were tremendous differences in particle size distributions (Figure 1). Figure 1b showed that the majority of the particles prepared via a high throughput micronization process were below 10 μ. However, a few larger particles (20 - 80 μ) were also found in the sample. Indomethacin powder micronized via a low throughput process exhibited a very uniform particle size distribution (Figure 1c). Particles were below ten microns on average. Further examination of data presented in Table 3 revealed the fact that batch 4 (Formulation III), which utilized low throughput micronized powder, gave a higher yield of pellets (98.2%) and a higher assay of indomethacin content of the finished pellets (33.1%) than batch 3 (Formulation II) (high throughput micronization process). These results seem to indicate that the distribution of particle sizes within a sample of indomethacin powder may affect the yield from this layering process.

To substantiate this hypothesis, the particle size distributions of the three different types of indomethacin powders tested were examined using a laser scanning analyzer.[i] Data are presented in Table 4. As expected, indomethacin powder micronized via a high throughput process (used to prepare batch 3) showed a particle size distribution ranging from 2 to 75 microns. However, 31% of the total amount of the particles were larger than ten microns. On the other hand, indomethacin powders, micronized via a low throughput process (used to prepare batch 4; Formulation III) exhibited a very narrow particle size distribution of indomethacin ranging from one to thirteen microns. Since the two batches of IS pellets prepared from the micronized drug samples were manufactured using similar processing

and documented approach is adopted, then validation can not only make a valuable contribution to quality assurance but can also be an economical procedure.

Retrospective validation and validation transfer can also be considered in the same light. In such cases an organizational input is required to compile plant and laboratory data from a large number of batches of the same product.

I feel that the authorities'need for information can be satisfied by a clear and succinct registration document stating the nature, extent and result of the validation procedure.

In conclusion it must be said that our experience has shown that preference should always be given to a well-organized validation procedure carried out by a team rather than to an uncoordinated testing of individual parameters which is not based on a written plan.

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