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PRACTICE OF VALIDATION

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ABSTRACT

Validation may be described as a systematic study which helps to prove that the systems, facilities, and processes perform their job adequately and consistent by as specified.

MATERIALS

Wherever pharmaceutical products are manufactured, national reglementing authorities ensure that the good manufacturing practices (GMP) are respected. Responsibility lies in the hands of the medicine control authority. One of the conditions set in the international stade of pharmaceutical products is that all the countries involved have similar procedures and apply the same criteria. Toward this end, the convention for the mutual recognition of inspection in respect of the manufacture of pharmaceutical products (PIC) has been set up, signed firstly by the european association for free trading, then extensed to any country able to justify comparable controls. At the present time, turkey is negotiating integration. As it was absolutely necessary that all inspection should use the same criteria : the norms of the GMP were chosen. The guideline for the GMP of the PIC convention was drawn up along the lines of the CEE one.

Good manufacturing practices deal with that part of quality assurance which ensures that products are produced consistently and controlled to the quality standards appropriate to their intended use. GMP refer to "personnel, premises, equipment, documentation, production, quality control, contract manufacture and analysis, complaints, and product recall as well as self-inspection" validation is the action of proving, in accordance with the GMP principles, that any procedure, process, equipment, material, activity or system leads to the results expected". Total validation of manufacturing processes, in order to ensure continuous conformity of batches".

A manufacturer normally validates all production processes and supporting activities including cleaning operations, Our aim is to explain and promote the concept of validating manufacturing processes.

PROCEDURES

Validation may be described as a systematic study which helps to prove that the systems, facilities and processes perform their intended job adequately and consistent by as specified. A validated operation is one which has been proven and formally approved, as having the potential for the manufacture of uniform batches meeting the required specifications.

Two mayor types of validation are acknowledged : analysis and process. Analytical validation is not discussed here.

An adequate validation may be made in many ways :

2/1/ First question : What ?

This question requires a look at the definition of validation :

To run up : every thing that bears on the quality of a product has to be validated : i.e. development, preservation, manufacturing (process and equipment), premises, procedures, and staff.

The problem then is to master all of these. How should we begin ? Where should we stop ? How should we manage them ?

2/2 Second question : Who ?

Because it is compulsary, validation is required to obtain authorisation to launch a product on the market, and this according to the international texts on GMP. These

texts are very precise in two fields : sterilization and data-processing. In other fields, reference documents are inadequate. An effort by the firm in which everyone is involved should not be underestimated : investment is profitable.

2/3 Third question : When ?

It is accepted that the validation trial should be carried out successively on three batches, following standardised conditions.

Controls used to be made on finished products, but the concept of validation cannot be reduced to one single process on the end product.

Depending on the time when it is performed relative to production, validation can be :

- prospective validation which is carried out during the developmental stage and is the result of a risk analysis on the production process ; critical situations are identified, the risk is evaluated, potential causes are investigated, the trial plans are drafted, performed, evaluated. At the end, the results are acceptable, the process is judged satisfactory.

- concurrent validation is that carried out during normal production. The first three production scale batches must be monitored as thoroughly as possible concurrent validation combined with analysis including stability should be carried out to an appropriate extent throughout the life of the product.

- Retrospective validation is that which involves looking back at past experience obtained during production. It is not a quality assurance measure, it is useful in establishing priorities in the validation programme.

- Revalidation may be classified in cases of changes having a bearing on product quality, change in raw materials (density, viscosity) packaging material (glass for plastics), process (drying, mixing) equipment, area, and periodical revalidation. (scheduled intervals).

2/4 Fourth question : How ?

The basic principle is characterised by harmony between the results obtained and requirements. This supposes :

- specified requirements and objectives
- available means

- choices which are justified in relation to objectives
- each stage should begin when the previous is over

Certain dispositions have to be taken :

- how restrictions should be defined
- how norms should be identified
- how divergencies should be dealt with
- how modifications should be dealt with.

Controlling the evolution will involve :

- set data for decision-making
- evaluation before decision-making
- justifying the decision
- follow-up

The following scheme may be suggested :

- aim versus objective
- process as a whole, and the flow diagram
- validation protocol
- installation, drawings
- protocol versus report : procedures, sampling, testing, reporting, calibration, test data, results.
- evaluation and recommendations including frequency for revalidation.

expected results - specifications
demonstration - validating protocol
verification - validation
evaluation - report/conclusions
continuity - periodic validation

Quality = harmony between requirements expressed and results obtained

RESULTS

3/1 Essential notions

3/1/1 Production regularity - this will guarantee the controlled homogeneity of a batch or of several batches. The risks of heterogeneity are variable :

- according to the number of phases (direct tabletting or tabletting after granulation)
- according to the nature of products : physical characteristics (particle size) concentration, instability.
- according to the means of preparation (mixing, granulating, drying)

All these pise the problem of finding the sample which is representative of the batch. The size of the sample and the spot where it is to be taken must be clearly defined.

3/1/2 relationship between validation/GMP/Inspection

Development determines validation at the conception level, the GMP determine validation on the production level. Inspection verifies application.

3/1/3 Nature of the procedure

Whatever the procedure be, prospective, retrospective, periodic, it is important to refer to the sample, the parameters, the means, and the limits (mean, standard error, variation coefficient).

3/2 If we take the case of tablets prepared by granulation : granulation takes place in a granulator and drying in a drier - in this example, the parameters are : the quantity of liquid required to form granules, the capacity of mixer to be respected, the mixing time to allow for wetting, the quantity of binding - product, the drying of the granules.
The elements to be obtained for validation will be : batch size and sample size, temperature and length of wetting process, wetting intensity, drying
(temperature and length of time in drier), particle size, humidity and hardness of the granules.

3/3 If we take the case of a semi-solid form : the critical phases and control parameters must be noted during development. The critical phases depend on formulation and are as follows :

- manufacturing temperature which influences gel viscosity.
- stirring speed which influences emulsion size
- length of stirring time which effects homogeneity
- cooling temperature
- homogenating conditions which influences the size of particles.

The control parameters will show the size of the sample and where it was taken measurements should always be taken as an average, using standard error and variation coefficient.

In this way, verification will be as follows :
gel ==> manufacturing temperature ==> viscosity
cream ==> agitation speed ==> particle size
ointment ==> length of agitation ==> homogeneity
emulsion ==> cooling temperature ==> particle size

CONCLUSIONS

Validation is the action of proving in accordance with the GMP, that any procedure, process, equipment, material, raw materials, activity or system leads to the results expected. Total validation of manufacturing processes, in order to ensure continuous conformity of batches is required for immunological, veterinary, and medicinal products.

Validation means demonstrating that the principles of procedure are controlled and that there is correspondence between procedure versus formula. Validation is confirmed through the results obtained form representative samples taken from the batches at critical stages.

Reference 1

Good Pharmaceutical
Manufacturing
Practices

English translation of "Bonnes Pratiques de Fabrication et de production pharmaceutiques" (B.P.F.)

Second edition - October 1985
Ministère de la Santé
Direction de la pharmacie
République Française

CHAPTER 10

VALIDATION

Validation is an operation intended to demonstrate that every process and procedure used for production, packaging or control of products does actually lead to the expected results.

Validation is an element of the system of quality assurance which guarantees, for a given medicine :

- the reliability and reproducibility of the principal process provided in the dossier;
- the attainment of quality as specified during routine production, packaging and control.

In view of the variety of problems posed by each of the pharmaceutical operations, only general recommendations can be made.

10.1 VALIDATION OF A NEW PRODUCTION PROCESS

10.1.1. During the phase of development, the following steps are to be taken :

- make a list of the various parameters concerned ;
- work out the tests and methods of control adapted to the monitoring of the principal parameters ;
- define the limits within which each parameter may vary without compromising the quality of the final product ;
- define and validate control methods for raw materials, packaging materials, semi-finished ans finished products ;
- verify that specifications for raw materials and packaging materials are adequate ;
- carry out the studies necessary to demonstrate the reliability, efficacy, reproducibility and adequacy of the procedures specified in the dossier for the main stages of manufacture and packaging.

10.1.2. The results and know-how acquired during the phase of development will form the basis of the validation procedures to be implemented before the full production phase begins.

10.1.3. At the launch of full production, the validation procedures must be applied to the conditions of production definitively adopted.

10.1.4. Different verifications must thus be carried out on several successive batches before acceptable reproducibility can be ensured :

10.1.4.1. Verifications of the principal parameters pertaining to the functioning of the equipment and installations and their suitability to the manufacture of the product.

10.1.4.2. Verification, by appropriate means, of the control of :

- the functional parameters of the equipment and installations ;
- the environmental conditions likely to affect manufacture if they diverge from those defined in the procedures.

10.1.4.3. Special verification, by appropriate tests, of the critical operation phases likely to have repercussions, even distant, on the quality of the finished product.

10.1.4.4. Verification of the quality of the products obtained at the end of each of the principal operations.

10.1.5. The evaluation of the results obtained constitutes the cardinal element of validation, once the conditions of manufacture and
quality control of the semi-finished and finished products are mastered and that the safety and efficacy of the process are guaranteed.

10.2. **RETROSPECTIVE VALIDATION**

10.2.1. If the formulation, process and equipment have not required modification, it is possible to obtain an acceptable validation by a rigorous and critical examination of both the experimental data which has been accumulated during previous manufacture and controls.

10.2.2. If required, this experimental data may be supplemented by :

- more specific tests carried out on samples derived from batches of routine production ;
- control of critical parameters of the equipement ;
- special studies.

10.3. **REVALIDATION**

A revalidation, partial or general, must be carried out in certain cases, such as :

- change of the formulation, manufacturing process or batch size ;
- considerable changes in the equipment described in the process ;
- use of new equipment ;
- considerable modifications in manufacturing conditions ;
- major servicing of the equipment or installations ;
- change in methods used for quality control ;
- finally, when quality control results for the semi-finished or finished product reveal anomalies requiring revalidation.

Reference 2

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

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PHARMACEUTICAL PREPARATIONS

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specification

A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform.

Specifications serve as a basis for quality evaluation.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessariliy specific to a given product or materials but of a more general nature (e.g., equipment operation, maintenance and cleaning ; validation ; cleaning of premises and environmental control ; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

system

A regulated pattern of interacting activities and techniques that are united to form an organized whole.

validation

The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Part One. Quality management in the drug industry : phylosophy and essential elements

In the drug industry at large, quality management is defined[1] as the aspect of management function that determines and implements the "quality policy", i.e., the overall intentions and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are :

[1] This definition conforms with that contained in International Standard ISO 9000.

- an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes, and resources ; and
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

Sanitation and hygiene

A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *hygiene* please refer to section 10, "Personnel", and for *sanitation* to section 11, "Premises".)

Validation

Validation studies are an essential part of GMP and should be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of processing, testing, and cleaning procedures.

Process validation

Critical processes should be validated, prospectively or retrospectively.

When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing.

The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process, should be validated.

Complaints

Principle. All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

A person reponsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.

There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.