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PROCESS VALIDATION: PRACTICAL APPLICATIONS TO PHARMACEUTICAL PRODUCTS

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ABSTRACT

"Process Validation: Practical Applications to Pharmaceutical Products" by Ira R. Berry, Vice President-Technical Services, Pharmacaps, Inc., Elizabeth, NJ, USA.

Process validation and control of pharmaceutical products has been discussed in many forums in recent years. This paper discusses the origin of process validation in the context of principles of quality assurance and Current Good Manufacturing Practice. The approach is practical and describes "what" and "how" to validate, with emphasis on written documentation and standard operating procedures.

The Current Good Manufacturing Practice (CGMP) regulations of the United States Food and Drug Administration (FDA) have specified the requirement for process validation and control of pharmaceutical products. These regulations also have stimulated discussion of the subject (1-7,11).

Regulatory Requirements

Proper review of process validation of pharmaceutical products starts with a review of some definitions and basic principles (10). The U.S. FDA defines process validation as "...a documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."

One section of the CGMP regulations especially highlights process validation.

Section 211.110 (9) reads:
"To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls and tests, or examinations, to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

These regulations highlight the necessity for a quality assurance program having the overall objective to provide confidence in a quality manufacturing and control process. Confidence is achieved and verified by process validation. The focal point to establish this confidence is the process and not the end product. Exhaustive finished product testing is, by itself, not a substitute for in-process controls and process validation.

Basic Principles of Quality Assurance

Quality Assurance is identified with Current Good Manufacturing Practice such that we cannot comply with one and not the other.

Principles of quality assurance must be followed by a drug manufacturer.

First, safety and efficacy must be designed and built into a product. The best product, within current state-of-the-art and realistic constraints, should be designed.

Second, quality cannot be inspected or tested into a product. The implication here is that deficiencies in product design or the manufacturing (and control) process cannot be corrected by inspection and testing. We cannot justify using these procedures to compensate for defective components, equipment and facilities and personnel who have no pride in their work or who are not trained sufficiently. There is no accurate manner by which all defective units in a product batch can be identified and segregated.

There are many factors which bear on product quality and their control is the third principle of quality assurance. Four basic sources of error or variation in a manufacturing operation are materials, equipment and facilities, procedures and personnel (8). Variations can occur in:

1. Materials (raw materials and packaging components)
    a. Different suppliers of a material
    b. Different batches from one supplier
    c. Within a batch

2. Equipment and Facilities
    a. Different machines or facilities for a process
    b. Differences between machines

c. Aging

d. Inadequate preventive maintenance

e. Inadequate working conditions

3. Procedures (manufacturing and control)

a. Not clear or specific

b. Inadequate

c. Negligence by chance

d. Differences between plants

4. Personnel

a. Insufficient understanding and training

b. Lack of interest

c. Dishonesty, carelessness, fatigue

d. Poor communication and cooperation

The fourth principle of quality assurance is that each step of a manufacturing process must be in control and provide assurance that the finished product will satisfy all quality and design criteria. This provides the foundation for process validation, with the establishment of process controls and in-process testing by design and challenge. The overall objective is to be able to monitor each batch in process to be certain that the process is following the correct path. The net result is batch uniformity and reproducibility which provides the safety and efficacy intended for the product. The fifth principle of quality assurance is that test results on a batch be expressed with specific data (numerical if possible) and not as "pass" or "fail". A product history based on batches that are indicated to either "pass" or "fail" in reference to individual specifications does not provide any

useful data. It would not be evident if acceptable batches fell in the middle, upper or lower limit of a specification. It is important to indicate a measurable result as it would not be wise to manufacture all batches performing at the limit of a specification. In these cases, it would not be unexpected for batches to fall over to the wrong side and out of specification resulting in batch failures.

Basic Principles of Process Validation

Founded on the regulatory requirements, and in compliance with quality assurance, the first principle of process validation is to design a protocol of "what to do" and "how to do it". Process variables should be monitored, and only one varied at a time, so that the effects can be evaluated. Trial batches should include the most severe challenges to the system. The validation program should be performed in the product development phase, before the product is available commercially.

The second principle of process validation is to establish the variation of process parameters that can be allowed for individual batch runs. This is accomplished by trial batch runs and evaluation of resulting data to monitor the process variables and establish product standards. Component and product specifications provide guidance and allow us to evaluate whether or not materials are proper. However, we should be able to identify the variation from specifications that will cause batch failures.

The third basic principle of process validation is that extensive finished product testing is not sufficient to assure product quality. The manufacturing (and control) process must be challenged to provide adequate process controls and in-process

tests and specifications, in addition to finished product specifications. Under process validation, there is strong emphasis on process controls - which are specifications in the manufacturing part of the process such as adjustments for temperature and pressure and recording charts - and in-process controls which are specifications in the testing part of the process such as assays on batches in process.

Steps in Process Validation

The first step for process validation of pharmaceutical dosage forms is to verify that the basic manufacturing operation is in operation and qualified. There must be systems and procedures to assure compliance with CGMP. A system of standard operating procedures is used to satisfy this requirement and covers areas such as receipt of raw materials, stability program, cleaning, housekeeping, maintenance, calibration and personnel. Basic principles and ideas for these SOPs can be described (1).

The second step in process validation is to establish measurable characteristics that describe a product. Each characteristic has a test and specification so that a test result will indicate whether or not a batch will perform as expected. Some typical product characteristics are:

1. Physical

   Size, color, shape, pH, thermal analysis, specific gravity.

2. Chemical

   Potency and purity of actives and degradation products.

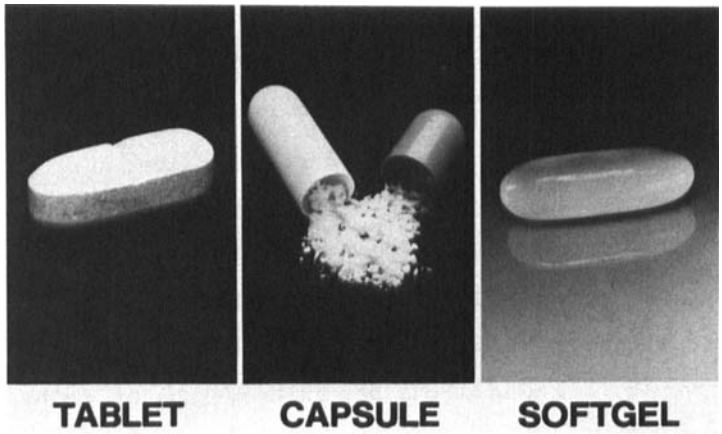

PHOTO 1

3. Microbiological

Limits, sterility.

4. Performance

Dissolution time is an in vitro test often used as an indicator of bioavailability. The test is standard for solid dosage forms such as tablets and two-piece hard gelatin capsules. However, it is poorly understood and different for softgels (3) and test results should be evaluated differently. After a tablet enters the stomach, it first disintegrates into small particles and then dissolves in the gastric juice for absorption into the blood. In the case of hard gelatin capsules, the shell opens first then the solid contents of the capsule dissolve and are available to be absorbed. For softgels, the actives are in solution or contained within a liquid or semi-liquid vehicle such that as soon as the shell ruptures, or opens, the contents are available immediately for absorption. It is this property which has provided improved bioavailability of many drugs - some of which are poorly soluble and poorly absorbed, in low dosage and with a narrow therapeutic index.

The third step in process validation is to establish specifications for raw materials, packaging components, in-process batches and finished product. Specifications are ranges of variation that are permissible, assigned to product characteristics based on testing and challenge. They are used to prevent batch failures understanding all variations which may occur normally in a manufacturing process. It does not necessarily follow that if an individual specification is not satisfied that the batch will fail. However, specifications permit assurance of product batch uniformity and reproducibility. Examples of raw material specifications can be given (1).

A vital element of process validation is setting sufficient process controls with appropriate in-process testing and specifications, to provide assurance that each product batch remains in control and within established specifications. Some process controls for the softgel encapsulation process, which we will use as an example, are speed of die rotation, temperature of molten gelatin, gelatin ribbon thickness and relative humidity in the encapsulation room. In-process tests include checking the fill weight and softgel seam and wall thickness.

This leads to the fourth step in validation, which is to establish a written manufacturing procedure and challenge the manufacturing process. Prior, equipment and process have been implemented so as to meet product specifications consistently. Equipment has been installed and qualified to satisfy operating requirements such as speed of movement, temperature and pressure. A validation protocol should be written to include a list of all parameters to be challenged. Some examples of these parameters are listed in figure 1.

1.0 EQUIPMENT
- 1.1 Sanitation procedure
- 1.2 Cleaning agents
- 1.3 Temperature variation and control
- 1.4 Pressure variation and control
- 1.5 Speed variation and control

2.0 FACILITIES AND PERSONNEL
- 2.1 Air temperature
- 2.2 Humidity
- 2.3 Air pressure
- 2.4 Air quality
- 2.5 People differences

3.0 CALIBRATION
- 3.1 Balances and scales
- 3.2 Pressure gauges
- 3.3 Thermometers
- 3.4 Speed of movement e.g. mixers, conveyors
- 3.5 pH meters

4.0 COMPONENTS
- 4.1 Water quality
- 4.2 Different suppliers
- 4.3 Different batches from the same supplier
- 4.4 Variations within a batch
- 4.5 Container washing, drying and sterilization
- 4.6 Closure washing, drying and sterilization
- 4.7 Container/closure integrity

5.0 BULK MANUFACTURING PROCESS
- 5.1 Weights
- 5.2 Temperature
- 5.3 Pressure
- 5.4 Mixing times
- 5.5 Mixing speeds
- 5.6 pH
- 5.7 Time limitations
- 5.8 Microbial control
- 5.9 Bulk product storage conditions

6.0 FILLING AND PACKAGING
- 6.1 Product temperature
- 6.2 Line speed
- 6.3 Fill weight
- 6.4 Time limitations
- 6.5 Microbial control

7.0 STERILIZATION
- 7.1 Bioburden
- 7.2 Load in chamber

8.0 LYOPHILIZATION
- 8.1 Product characteristics prior to freezing
- 8.2 Thermal analysis
- 8.3 Product characteristics after freezing and thawing
- 8.4 Tray suitability
- 8.5 Chamber shelves temperature uniformity
- 8.6 Condensor refrigeration and ice capacity
- 8.7 Vacuum pump pressure reduction capability

8.0 LYOPHILIZATION (Cont.)
- 8.8 Internal stoppering mechanism capability
- 8.9 Shelf and product temperature
- 8.10 Chamber pressure
- 8.11 Product cycle, i.e. product temperature, shelf temperature and chamber pressure over time
- 8.12 Sterilization
- 8.13 Pressure regulating gas

9.0 LABORATORY
- 9.1 Physical tests
- 9.2 Chemical tests
- 9.3 Microbiological tests
- 9.4 Performance tests

Figure 1. Some validation parameters for consideration. (adapted from I.R. Berry "Process Validation - A.U.S. Viewpoint", Manufacturing Chemist, January 1983, p. 34)

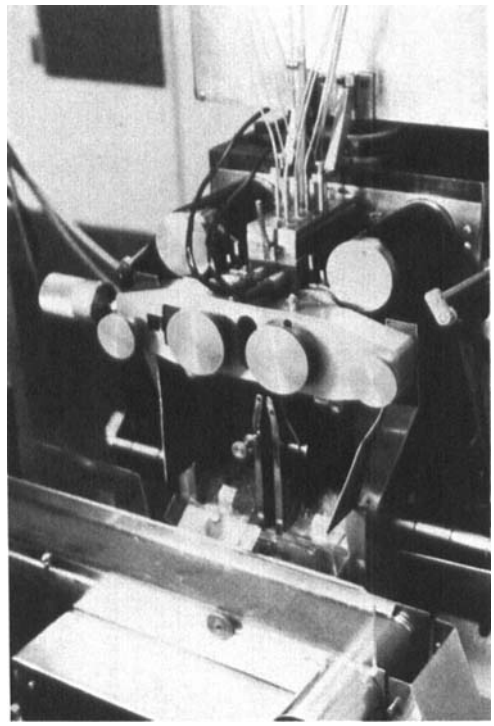

PHOTO 2

Let's pick a specific example and examine how validation may be accomplished. Assume that we are manufacturing a softgel for the first time. The review quickly, softgels consist of a liquid or semi-liquid fill material that is enclosed within a plasticized gelatin shell. These softgels are formed, filled and hermetically sealed in one continuous operation. Softgels are made by molten gelatin formed into two sheets, or ribbons, each of which is passed over a die of the desired shell shape and size. At the point where the two rotating dies meet, the softgels are formed, filled and sealed with the actives in solution or a semi-liquid vehicle. The fill remains in this state as a liquid and does not solidify later. Softgels are then cleaned and dried, inspected, tested and packaged.

With the occurrence of tragic episodes resulting from criminal tampering with two-piece hard gelatin capsules, manufacturers of one-piece soft gelatin capsules have decided to assign a new name to that dosage form. This name is "softgels". During the past several years, manufacturers of one-piece, liquid filled and hermetically sealed soft gelatin capsules have attempted to educate the industry and consumer of the differences from two-piece, powder filled and unsealed hard gelatin capsules. In fact, we have pointed out that the only similarity between the two dosage forms is that they both require the use of gelatin as a raw material. Also, manufacturers have been in communication with the Food and Drug Administration and other regulatory, legislative and compendial agencies to differentiate the two types of capsule in any law, regulation and consumer press. These efforts were not successful toward the end of assuring that the public is aware of such information. Therefore, industry decided to delete the word "capsules" from all references to this dosage form and adopt the term "softgels". Softgels are defined as one-piece hermetically sealed soft gelatin shells, containing medication in a liquid or semi-liquid state, that have been formed, filled and sealed in one continuous operation. Use of the word "capsules" will be assigned to the hard gelatin dosage form only. The new term has been published in the current Pharmacopeial Forum (12). Any reference to the dosage form of soft gelatin capsules in this text has been changed to use the new name "softgels".

Four important elements of process controls for softgel encapsulation are speed of die rotation, temperature of the molten gelatin mass, ribbon thickness and relative humidity in the encapsulation area. It is important to perform testing along with these process controls. In-process tests include

softgel fill weight, wall thickness and seam thickness. The controls and tests described here also can be related to other dosage forms such as tablets and hard capsules. The validation protocol for this portion of the manufacturing process might include the process variables described above.

In order to validate the process, we can adjust the encapsulation machine so that each process variable will be at its optimum level, at the midpoint of each range, and then produce softgels. We can then challenge the process by intentionally changing adjustments to affect only one process variable at a time and to reach and then exceed the acceptable upper and lower limits of each specification. Specific points for each range should be chosen, at which softgels are produced. All process variables must be monitored during these runs.

After the entire manufacturing (and control) process has been challenged, and finished product shown to conform to all process controls and testing in-process, finished product and stability, the process is validated. At this point, however, there are two additional steps that must be followed.

The fifth step in validation is that the need for revalidation must be evaluated before a significant change is made in the validated process. Stages of the manufacturing process to be considered include: specifications, formulas and procedures, suppliers, equipment and facilities.

The sixth step includes all the above and indicates accurate recordkeeping, or documentation, at all stages of validation and subsequent manufacture. Proper recordkeeping is necessary to comply with CGMP and to achieve process validation.

Concluding Remarks

Process validation of pharmaceutical products is important to satisfy the regulatory requirement and also to follow good business judgement. It provides assurance that a product can be manufactured reproducibly to satisfy label claims for safety and efficacy. It enables determinations to be made during a product batch run to indicate whether or not the final product will meet specifications. The key and emphasis are process controls in combination with in-process testing.

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