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GMP Focus

Managing Process Validation

A Drugmaker's Guide

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Introduction

Validation is a key element of the quality management system in a pharmaceutical company. For a long time, our understanding of pharmaceutical quality was such that one relied solely on the control of raw materials and final products. The intermediate process was guaranteed by established experience and the professional honesty of longtime employees.

Today, our understanding is almost the reverse. Well-tested raw materials from qualified suppliers are used in a process that must be so well controlled that, theoretically, absolutely nothing can result other than a product that conforms to the specifications. In contrast, the place of manufacture and staff carrying out production are interchangeable, as long as they are qualified.

Validation has thus become a basic component of the quality assurance system of pharmaceutical companies and their suppliers. This development is logical and appropriate not only in terms of pharmacovigilance, but also as regards economic aspects, because when serious quality defects are detected in the final product control, irreparable damage will already have been incurred.

Also because modern active ingredients and novel preparations are becoming ever more costly, rejection of the end product must be avoided by means of preventive measures such as validation. The assessment of a process in the context of validation is also important because the increasingly shorter periods people remain at a company and widespread job rotation prevent them from building up a body of experience and thus also prevent the continuity of information and quality.

Furthermore, in international pharmaceutical companies, production processes are frequently switched between different production sites. In order to guarantee reproducible quality in spite of this, processes must be validated.

Therefore, quality in a product is spoken of in terms of being "*produced* into" and not simply "*tested* into." Quality is the sum of properties of a product, not only those that are covered in the specifications.

This report looks at the significance of process validation in drug manufacturing and discusses different approaches to validation. It also provides guidance on managing validation efforts, including developing a master plan, protocol and documentation.

About the Author

Christine Oechslein is a 27-year veteran of the pharmaceutical industry, working primarily with Sandoz and Novartis. Over the course of her career, she has developed oral drug delivery systems, headed a lab for development of nasal and pulmonary dosage forms, and helped create a quality manual for Rx development.

Defining Process Validation

Process validation is only a part of a broad concept that includes qualification of equipment, facilities, computers, buildings, building and utility services engineering, staff and suppliers, and demands systematic documentation, archiving and change control.

When the definitions used by different regulatory agencies are compared, it is apparent that the term "validation" is interpreted in very different ways. According to the EU GMP Guidelines Part I, Chapter 1, *Pharmaceutical Quality Systems* (see Appendix A), validation comprises not only processes, but also equipment and materials – the term is thus used as a generic term and also includes qualification. By contrast, the FDA *guidance Process Validation: General Principles and Practices* (see Appendix B) extends the content of process validation to make it a superordinate term which incorporates not only process design in the development phase, but also plant qualification and continuous process verification during routine production.

This relative lack of precision and insufficient demarcation of the terms is found in many places in the international guidelines on the subjects of validation and qualification. Therefore, every company that addresses this group of topics must initially specify its own definition. It is best to regulate such fundamental aspects in the validation master plan (VMP) primarily so a common starting point will exist for smooth communication during the validation activities – both internally and to the outside (contract accepter, contract giver, authorities).

Who Must Perform Validation?

The demand for validation is no longer restricted solely to pharmaceutical companies, but also to their suppliers, especially the producers of active ingredients, excipients, packaging materials, plants and equipment, including computers.

However, drug manufacturers are responsible, under GMP standards, for ensuring that they work only with qualified plants and only use materials which are produced, packed and stored in accordance with GMP. For some of these, product standards have already been established (e.g., ISO 15378: *GMP for Primary Packaging Materials*) that represent the state of the art – so one should only deviate from them for a good reason.

In all other cases "how much GMP" and "how much validation" a pharmaceutical manufacturer expects from its supplier is a matter of intensive individual discussions and precise contractual agreements, which can differ greatly from product to product and from process to process.

What Faults Can Occur During Validation?

Validation is regularly subject to inspections, be it by customers or by the public authorities responsible.

Numerous shortcomings are still detected here: about 10% of all GMP complaints are connected with validations – thus occupying one of the top places in the "hit list" of all GMP defects!

Typical faults include:

- Validation plans are not created or not complied with;
- Details about the equipment used, critical process parameters, sampling data, number of validation batches or acceptance criteria are missing;
- Changes to validated processes are not included or not included properly;
- Deviations while validation is being performed are not documented, examined or commented on, or this is not done properly;
- No rationale for acceptance criteria is documented;
- Validation reports do not reflect the specifications from the validation plan, for example, reports contain acceptance criteria which were not specified in the validation plan;
- No risk-based approach is recognizable, i.e. the scope of the validation activities was not defined by means of quality risk analyses.