

7.D Revalidation

Here you will find answers to the following questions:

- What does revalidation mean?
- At what intervals should periodic revalidation be carried out?
- What kind of changes makes revalidation necessary?

A validation status once reached is not static, but is subject to everyday dynamics: all companies develop, undergo restructuring and change their targets. The staff changes, responsibilities change, SOPs are updated, buildings and equipment are adapted and maintenance work is carried out, etc. Even if the influence of each individual measure on the validation status is reviewed as part of a systematic change control program (see chapter 19.C *Change control*), a conjunction of various events can nonetheless cause processes to gradually become “devalidated”. Other factors like compliance erosion in staff, inadequate maintenance work, calibration intervals that are too long due to pressure for time and economy measures, can also mean that the preconditions for the validity of a process are no longer met. To prevent this from endangering the product quality, critical process steps must be revalidated at regular intervals. This means that a completed validation must not be viewed as a one time exercise, but rather the validation status should be periodically reviewed according to an established review cycle.

Regardless of the periodic revalidation of critical processes, validations (or parts thereof) must always be repeated if changes are made to buildings, facilities, equipment, processes, techniques or at the manufacturing site.

Definition of revalidation

Revalidation means the repetition (of parts) of the validation

- after changes that were found to require validation in accordance with the decision during the change control,
- for critical processes (e.g. sterile or aseptic), at established intervals
- as described in a USA quality system document which addresses the subject of revalidation

Figure 7.D-1 Definition of revalidation

7.D.1 Time intervals for periodic revalidations

The legal drug product provisions allow the user a certain amount of leeway for carrying out revalidation. Chapter 5, paragraph 5.24 of the EU GMP Guideline says the following on the subject:

"Processes and procedures should undergo periodic critical re-evaluation to ensure that they remain capable of achieving the intended results." The exact definition of "periodic" is left to the manufacturer.

The validation master plan is the appropriate document to establish a company's concept for revalidation. When fixing the revalidation intervals, the following must be taken into consideration:

- the individual process risk and product risk
- the number of batches manufactured per year
- any other control measures used, e.g. SPC (statistical process control)

Depending on the product, the process and the manufacturing frequency, intervals of between two and five years may be advisable. If a process is continuously monitored with other methods, e.g. using statistical process control, then longer intervals may also be justifiable. If no critical change is made to a process during a period under review, an interpretation and evaluation of the process and product data for this period can be accepted as revalidation of the process. The USA FDA would expect the concept of revalidation to be documented in a written Quality System that provides sufficient details to define when and how a revalidation should be performed (see chapter D.2 *Guideline on General Principles of Process Validation*).

7.D.2 Incidences requiring revalidation

7.D.2.1 Changes to the manufacturing instructions

Process validation is carried out on the basis of *approved manufacturing instructions*. If at a later stage these manufacturing instructions are intended to be changed, it is necessary to check, document and possibly show through revalidation, that this change has no effect on the product quality (see chapter 19.C *Change control*). Examples of changes to the manufacturing instructions are:

Changes to the product composition

It can have serious impacts on the reproducibility of the manufacturing process, if ingredients, like APIs or critical excipients are changed, or even if only their percentage of quantity is changed: the original validation result is therefore no longer relevant. Critical excipients are to be understood as those, which are either present in the formulation in very large proportions, or whose properties (e.g. particle size, density, moisture) significantly influence the physicochemical behavior of the

Incidences requiring revalidation

- planned changes to the manufacturing instructions
- changes in product composition
- changes in production process or the sequence of operations
- changes in primary packaging material
- changes in batch size by more than a factor of 10
- extension of the ranges of critical process parameters
- planned changes of raw material (e.g. drug substance) suppliers
- changes in manufacturing sites
- significant changes to process equipment
- extensive maintenance measures on manufacturing machines
- trends observed in IPC or quality control
- occurrence of quality problems (e.g. OOS) during manufacturing or quality control

Figure 7.D-2 Incidences requiring revalidation

batch. This includes excipients that do not have any (or only slight) inherent pharmacological efficacy, but which have a desired effect in the final product (preservative, anti-oxidants, complex formers, polymers with retarding effects on the API).

Before such changes are made, it is necessary to carry out prospective validation studies based on three new batches with the changed product composition. It is important to know that, even if the validation result is favorable, some of these changes must be presented to the regulatory authorities *before* the changes are implemented in routine production (chapter 19.C.1 *Principles of change control*).

Changes in production process or the sequence of operation

Just like the formulation for a validated process, the exact sequence of operation for all subsequent production batches is binding. It must be taken into account in the validation protocol, if it is already planned from the outset to allow different process or sequence variants.

In practice and for operational reasons, there may be a subsequent wish for process changes: for example, it may be suggested, that a drying step is performed in a shelf or tray dryer, since the required fluid bed dryer is constantly in use. Switching between different blending methods is a frequent but very delicate problem as well. In any case, such process changes must be revalidated in the context of a prospective validation.

Apparently harmless variations to be made in the *sequence of operation* must be highlighted as equally critical: for example, which phase is placed in the vessel and which is mixed in afterwards can be crucial for the quality of a cream.

Changing the chronological order of two processing steps is also a change in the sequence of operation which requires validation (e.g.: first heat then evacuate, or first evacuate then heat? Is it permissible to mix in a flow regulation medium before interim storage of the tablet mass or only immediately before producing tablets?).

Likewise, it must first be proven through validation that the quality of a product is not affected if, for example, a manufacturing step is carried out in three *sub-batches* on equipment with smaller dimensions, for capacity reasons, and these three sub-batches are then *combined* after successful IPC.

In practice, there are often *prolonged holding times* for intermediate stages or in-process material because processing has been delayed for planning reasons. These holding times, above all the appropriate packaging, storage, and possibly analysis before further processing, can be critical for sensitive products and therefore require validation.

Changes in primary packaging material

The primary packaging material for which sufficient long term stability data is already available, is defined in the approved and validated manufacturing instructions. In practice, it is also usual (but not compulsory) to store long term stability samples from the three validation batches, in order to support or supplement the available data.

On the one hand, a change in the primary packaging material may influence the validation status of the packaging process, as the changed packaging material may require different machine settings and can have different process ability properties (e.g. changing the film thickness of a blister film or of a sachet bag, changing the dimensions of ampoules, vials, stoppers, changing the material of films, stoppers, closures, etc.). On the other hand, the influence on the stability of the product must also be reviewed.

Before such a change is introduced, extensive clarifications are first required which extend far beyond the scope of revalidation. Ultimately, changes to the primary packaging materials must be indicated to the regulatory authorities in advance.

Planned changes of raw material suppliers

The quality of the raw materials determines not only the stability of a product, but also the technological behavior during processing. Unfortunately, it is not yet possible to *exhaustively* describe raw materials in the specifications in terms of their quality attributes and requirements, meaning that there may be some surprises during processing if the supplier is changed, despite the raw material being in line with the specifications (see chapter 17.A *Contract manufacture*).

Qualified raw material suppliers must be defined at the time of validation of an approved formulation. Since the validation is to be carried out using conditions as close to reality as possible, it is advisable to use the different suppliers' raw materials in the validation batches.

If another supplier is to be approved at a later date, he must first be qualified (see chapter 17.A.3.1 *Selection of one or more contract acceptors*), and the production process concerned (or sub-step) must be revalidated.

For contract manufacturers, it is also important to obtain the approval of the customer *before* the change is implemented.

7.D.2.2 Extension of the ranges of critical process parameters

During a validation study, the operating ranges for critical process parameters within which the process is valid, are verified. If it is planned to extend these ranges at a later time, it must be proven that the process still reproducibly leads to a product with the desired quality. However, justifying the planned extension of the limits soon leads to a crisis in the line of argumentation – initially the processing step in question was originally designated as “critical”, i.e. a slight change would have a big influence on the product quality. Now and before extending any ranges, it must be proven and documented that the processing step is not so critical after all.

As the extension of the acceptance limits for critical processing steps can have a far-reaching influence on *all* subsequent steps, it is generally not sufficient to validate only the processing step in question – rather, all subsequent processing steps must also be validated either prospectively or concurrently.

7.D.2.3 Changes in manufacturing site

Revalidation is required if the manufacturing site is changed to a different, possibly newly constructed manufacturing unit of the same company, for example, or to a subsidiary or contract manufacturer, as the results of the original validation cannot be compared with manufacturing conditions in a changed environment. The same facilities or equipment is not generally available at the new manufacturing site (at best they are constructed in the same way). In the case of relocation to a new manufacturing hall, the original equipment will have been disassembled in the meantime, and must be qualified again and started up at the new site. Not only that, but usually the manufacturing, sampling and IPC tasks at the new manufacturing site will be carried out by different staff and possibly different raw materials suppliers will also be permitted.

All these aspects show why a process must be revalidated when the manufacturing site is changed (prospectively or concurrently if allowable under applicable laws or regulations).

However, before validation studies are performed, the following basic requirements must be fulfilled at the new manufacturing site:

- Qualification of the facilities and equipment
- Calibration and maintenance performed according to standard operating procedures
- GMP training of all staff involved
- Environmental monitoring
- Effective change control system implemented

7.D.2.4 Serious quality problems

If out of specification results (OOS results) occur during the quality control, the underlying error must be searched for based on a written, OOS-SOP (see chapter 14.H *Out-of-specification results*). If it comes to light that the error occurred during the manufacturing process, then measures must be taken to prevent the error from occurring again. In particular, the corresponding manufacturing step can no longer be considered to be validated, if the same error occurs repeatedly. Corrective measures must therefore be taken (e.g. changing the manufacturing instructions, adding additional control steps, staff training, adjusting the frequency of calibrations or maintenance). Validation should then show that these measures have been successful – namely, that the manufacturing process is again running in a controlled manner.

The same applies if repeated problems or quality deviations have already been observed during routine manufacturing, e.g. during IPC. The causes of trends, which are observed during a retrospective batch assessment (e.g. during the Annual Product Review (see chapter 15.F *Annual product review/ Product quality review*)), must also be investigated critically, even if they have not yet led to OOS situations. Both point to the fact that changes in the manufacturing process have occurred, which is why it must be revalidated.

Summary

A completed validation study must not be viewed as a one time exercise, as changes can occur constantly in everyday manufacturing. Such changes may be planned, in which case their influence on the validation status must be assessed in the context of a change control program. Other changes are unintended (e.g. through a conjunction of changes which are considered to be uncritical), and only come to light through trends or even deviations from the specifications. In this case, measures must be taken to bring the process under control again. The effectiveness of these measures must be proven through revalidation.

Critical manufacturing processes must also be reviewed periodically according to an internally established cycle.