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LOGFILE Feature 31/2020 – Two different pairs of boots: GMP for APIs and GMP for medicinal products

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Some essential differences between EU GMP Guide Part I (GMP for medicinal products) and Part II (GMP for APIs) are:

Objective and scope

The first difference follows directly from the scope of application of the two GMP regulations. While the EU GMP Guide Part I is clearly fully applicable from the first step in the manufacture of medicinal products, the requirements for the applicability of the EU GMP Guide Part II to the production of APIs are not always clear.

The question of the point at which the requirements of the EU GMP Guide are applicable to the different process steps in the manufacture of APIs depends on the type of API or the manufacturing process. A detailed overview can be found in the introduction to the EU GMP Guide Part II.

Quality management

The so-called quality unit as set out in the EU GMP Guide Part II,

which is independent of production, has an extended area of responsibility: it is also responsible for the quality control of the intermediates and APIs produced. The division into the three areas of quality assurance, production and quality control traditional for medicinal products is therefore no longer applicable here. The only distinction made is between responsibilities of the quality unit and the responsibility for production activities.

The step of release to the market of APIs and intermediates must also be performed by the quality unit. In contrast to medicinal products, the release may not only be performed by qualified persons in accordance with EU GMP Guide Part I chapter 2.6, but also by specified, authorised persons.

Water quality

In the manufacture of APIs, the process water must, at a minimum, meet the WHO requirements for drinking (potable) water quality. The minimum requirement here is therefore not – as required for the manufacture of medicinal products – in the specification of the European Pharmacopoeia for purified water (Aqua purificata). However, if the WHO requirements for drinking water appear to be insufficient, the active substance manufacturer should establish tighter specifications for

- Physical and chemical attributes
- Total microbial counts
- Objectionable organisms and/or
- Endotoxins

If a non-sterile API is to be used for sterile medicinal products,

water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

Containment

With the amendment of chapters 3 and 5 of the EU GMP Guide Part I, a further difference to the manufacture of medicinal products follows: The decision-making basis for determining whether production must be carried out in dedicated facilities or whether production can be carried out in shared facilities, and how in the case of shared facilities the technical and organisational measures to avoid cross-contamination are to be established is now set out in much greater detail for medicinal products.

In this context, the calculation of the acceptance criterion for cleaning validation should also be mentioned. According to the ICH Q&A paper on ICH Q7, an alternative calculation basis for the Maximum Allowable Carryover (MACO) by means of the Occupational Exposure Limit (OEL) is also acceptable in the area of APIs, whereas only the Permitted Daily Exposure (PDE) is accepted for the area of medicinal products.

In-process controls

As compared to the production of medicinal products, it is clearly established for the production of APIs that investigations of out-of-specification (OOS) test results are not normally needed for in-process controls (IPC) in accordance with the master batch record that are performed for the purpose of monitoring and/or adjusting

the process.

Blending of batches

The blending of batches is a special feature of the manufacture of APIs. The EU GMP Guide Part II defines blending as the process of combining materials within the same specification with the goal of producing a homogeneous intermediate or API.
By contrast, combining fractions of a single batch or combining fractions from several batches for further processing is considered to be part of the production process.

For the purposes of blending, each individual batch must comply with the specification and its compliance must have been tested. Blending can thus be used for example to increase batch size or to combine tailings (i.e. relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.
For blending, numerous requirements apply that are described in Chapter 8.4 of the EU GMP Guide.

Impurity profile

The impurity profile should be regarded as an essential quality characteristic for intermediates and APIs. An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. It should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of

each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the manufacturing process in question and is therefore to some extent characteristic of the manufacturer and thus of the origin of the API. It should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in starting materials, equipment operating parameters, or the production process. The acceptable impurity profile should be adapted to the current state of knowledge about the manufacturing process. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin.

Certificate of Analysis

The impurity profile is therefore part of the Certificate of Analysis (CoA), which as a whole documents the quality of the intermediate or API and identifies both the specified acceptance criteria and the actual results of analysis. The CoA should be signed by an authorised person of the quality unit and should identify the original manufacturer. This means that the original manufacturer of the product can be identified at any time, including for a repacker or reprocessor. If new CoAs have been issued as a result of new testing, the laboratory should also be indicated on the CoA. A copy of the original CoA should be enclosed with the new CoA.

Retest date

In contrast to medicinal products, APIs are not usually assigned an expiry date, but rather a retest date based on the results of stability

testing. However, a successful retest after expiry of the initially declared retest date qualifies only for direct use of the batch in the production of medicinal products, and expressly not for extension of the retest date by the initial validity period. Reprocessing in order to extend the retest date or to define a new date of manufacture after batch release is also not GMP-compliant and is therefore not acceptable.

Rejection and re-use

The requirements for the reprocessing and reworking of intermediates or APIs that do not meet the specification provided are specific to the API.

Reprocessing

Where the issue at hand here is only repetition of a process step that is part of the routine process and thus of the master batch record, the term used is reprocessing. Examples of reprocessing include repetitions of crystallisation, distillation, filtration, chromatography or milling. Introducing unreacted material back into a process and repeating a chemical synthesis step is also considered to be reprocessing, unless it is part of the established process in the master batch record. Against the background of quality considerations, however, a careful evaluation with regard to the formation of by-products and over-reacted materials should be carried out and documented prospectively. However, the continuation of a process step if the in-process control test has shown that the desired end point has not yet been reached is not to be considered reprocessing. Reprocessing is generally

acceptable, but should be included in the master batch record if it is used on a regular basis.

Reworking

If a material that does not conform to the specification is subjected to a new process step that is not part of the routine manufacturing process and therefore not part of the master batch record, the term used is reworking. This must be documented in a report, subjected to appropriate evaluation and provided with additional tests and stability samples to ensure that it is of equivalent quality to the routine process. A comparison of the impurity profiles for the reworked and routine product must also be taken into account. Concurrent validation is recommended for reworking. The cause of the deviation from the specification should also be investigated before any reworking is initiated.

Recovery

The recovery of reactants, intermediates, APIs or solvents is also acceptable under defined conditions and is probably more specific for the production of APIs than for the manufacture of medicinal products.

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