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ANNEX 3 – VERIFICATION OF OOS RESULTS
ANNEX 3.4 SPECIAL CONSIDERATIONS FOR ANIMAL TESTING IN CONNECTION WITH VERIFICATION OF OUT-OF-SPECIFICATION RESULTS

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SPECIAL CONSIDERATIONS FOR ANIMAL TESTING IN CONNECTION WITH VERIFICATION OF OUT OF SPECIFICATION RESULTS (OOS)

Table of Contents

1. Introduction

Retest programmes that involve animal testing should be designed to minimise the use and the suffering of the tested animals as much as possible, in line with Directive 2010/63/EU on the protection of animals used for scientific purposes.

This Annex focuses on reduction of animal use through the retest strategy. Other 3R approaches should be considered (e.g. testing the bulk instead of several final filling batches, or application of the humane endpoint for symptomatic animals), but are not described in this document.

This Annex differs from the principles described in the core document, since the scope is to minimise the use of animals in retesting (i.e. embracing 3R principles).

In contrast to the requirements of the core document, the retest strategy described in this document introduces further tolerances to be applied to the specification limit for the potency.

The retest programme depends on the type of product and assay (e.g. human vaccines and veterinary vaccines). Another element to consider for the retest programme is how the authorised specifications were set in consideration of clinical relevance: in some cases, the specification limits in vaccines give the lower/upper values or only lower specification limits.

An example of how to deal with OOS in the context of animal testing is provided below for information.

2. Example of Retest Programme for TBE

The following example describes an approach for the potency assay of a TBE vaccine with a one-sided potency specification for the estimate: the vaccine complies with the test if the estimated potency is not less than the limit approved by the competent authority, based on data from clinical efficacy trials (for this approach arbitrarily set as: potency estimate ≥ 1), but no upper limit is set. As for many *in vivo* tests, variability is high (Ph. Eur. validity criterion for 95% CI of this assay is 33-300% of estimate).

From the specification and the maximal acceptable confidence limits it is possible to calculate the theoretically lowest lower limit of the confidence interval that leaves a reasonable probability that the final result may be in specification.

It is assumed in these cases that the results of the MAH are within the specifications with the approved confidence limits.

Figure 1 - Possible outcomes of valid initial OMCL test

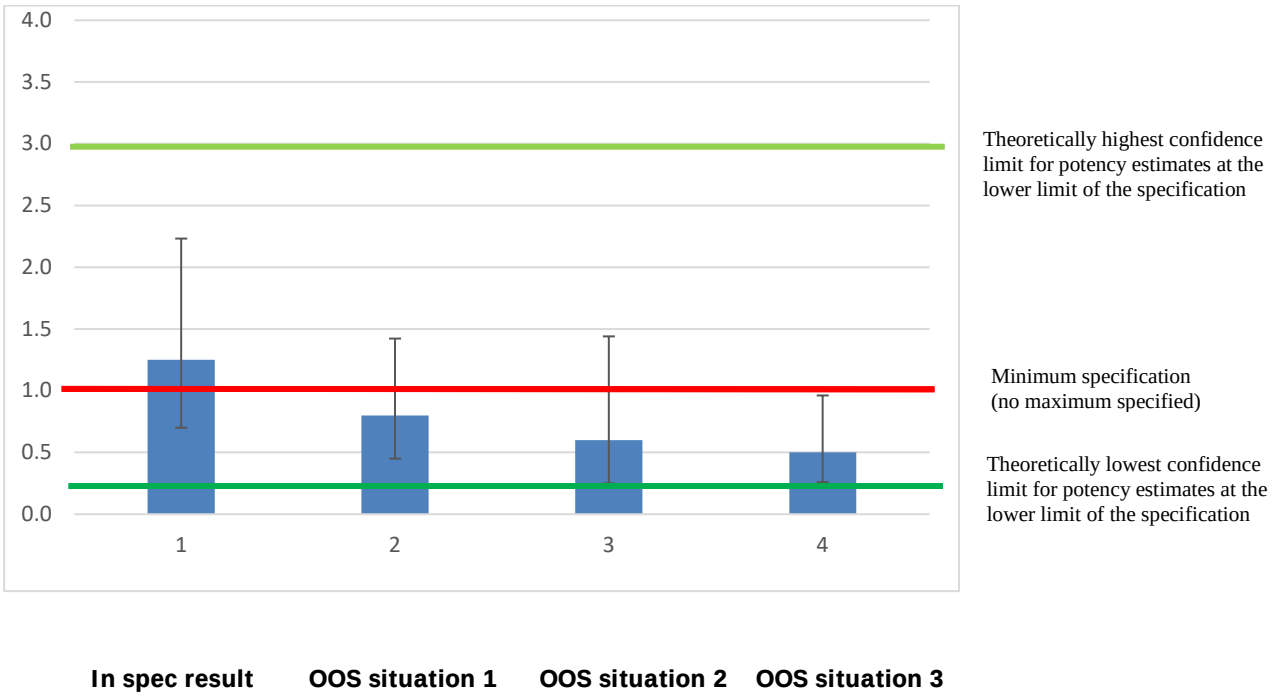

Figure 1: In the graph the red line represents the lowest acceptable estimate within the specification (1.0). The green lines represent the theoretical highest and lowest valid confidence limits if the estimated value is 1.0 (validity criterion for 95% CI of this assay is 33-300% of estimate). The bars on the individual assays represent the confidence limits of the individual assay estimates.

In OOS situations 2 and 3 the OMCL would need to repeat the test in order to confirm the OOS and appropriately evaluate the suitability of the batch.

In OOS situation 1, where the OMCL's estimate is below the minimum specification but the upper confidence limit is within specification and the lower confidence limit is above the theoretical lower limit, the results of manufacturer and OMCL are considered comparable. In this case (OOS situation 1) before launching a retest the OMCL can initiate a deeper review of the data from the MAH and from their own testing to determine if a retest can be avoided in view of the objectives of the abovementioned EU directive.

In the event of inconclusive results, batch release decisions should be based on scientific judgment and thorough investigation of:

- the trends in the data from the manufacturer looking for:
    - major changes or critical deviations during production or release testing
    - results of other production batches close to the acceptance limit
    - anomalies in other test parameters or processes that may have an impact (e.g. intermediate material at or beyond the approved shelf life, significant differences in process times)
- the trends in the OMCL data looking for:
    - consistency in test performance with past results for the product (e.g. variability, ED_{50} values of standard and test vaccines, width of confidence intervals, frequency of test performance)

- trends between MAH and OMCL data for previous batches (e.g. how do the results normally compare, are there systematic differences, is the current result in line with past observations or is it counter to the trend (if any)?)

If the MAH result is within specification and no abnormal trends, major changes, anomalies or critical deviations have been detected in the review of the data from the MAH and the OMCL, so that the evidence supports the manufacturer's in-specification result, the batch could be considered as compliant and no retests would need to be performed. This decision must be studied case by case. If there is any doubt concerning the compliance of the batch with the specification, this should be verified through testing at the OMCL.