OMCL Network of the Council of Europe
QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (14) 92

Evaluation and Reporting of Results
Annex 2D

Full document title and reference	Evaluation and Reporting of Results – Annex 2D Special Considerations for Animal Testing in Connection with Verification of Out of Specification Results (OOS) PA/PH/OMCL (14) 92
Document type	Guideline
Legislative basis	/
Date of first adoption	August 2014
Date of original entry into force	October 2014
Date of entry into force of revised document	/
Previous titles / other references / last valid version	/
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

ANNEX II D OF THE OMCL NETWORK GUIDELINE

"EVALUATION AND REPORTING OF RESULTS"

**<u>SPECIAL CONSIDERATIONS FOR ANIMAL TESTING
IN CONNECTION WITH VERIFICATION
OF OUT OF SPECIFICATION RESULTS (OOS)</u>**

Introduction

To be in line with the directive 2010/63/EU on the protection of animals used for scientific purposes, retest programmes to confirm out of specification results that involve animal tests should be designed to minimise the use and the suffering of test animals as much as possible, while on the other hand assuring that the quality of the tested medicinal product (e.g. the clinical efficacy of a tested vaccine) is appropriate for the intended use.

Retest Programme

The approach described here is an example of how supplementary analysis of manufacturers' batch release data as well as consideration of clinical relevance may contribute to deriving a conclusion without unnecessary additional testing in animals at the OMCL.

The following describes an approach for a vaccine with a one sided potency specification for the estimate: the vaccine complies with the test if the estimated potency is not less than that approved by the competent authority, based on data from clinical efficacy trials (for this approach arbitrarily set as: potency estimate $\geq$ 1, but no upper limit. Like 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 (blue bars represent the estimate)
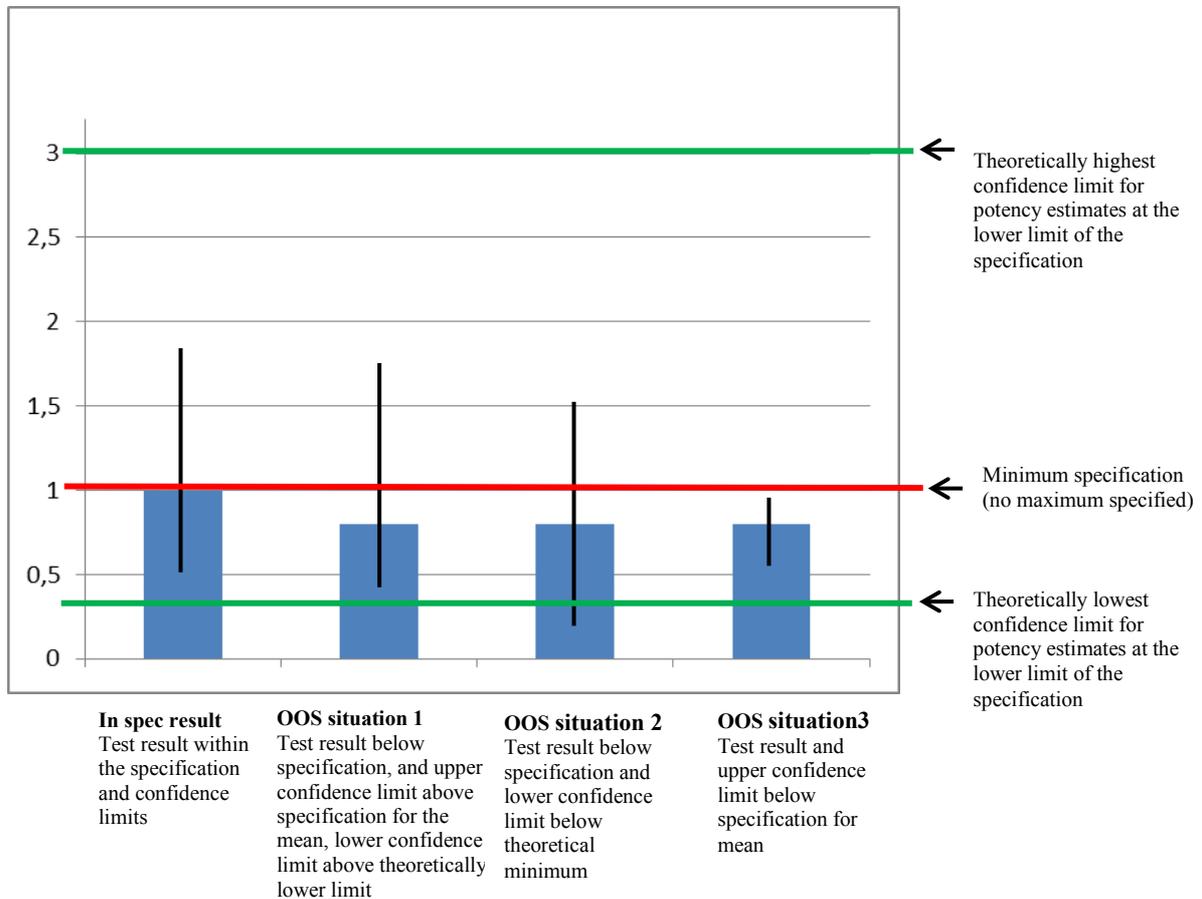
Figure 1: In the above table the red line represents the lowest acceptable estimate within the specification (1.0). The green lines represent the theoretical highest and lowest possible confidence limits if the estimated value is 1.0 (validity criterion for 95% CI of this assay is 33-300% of estimate). The bars on the individual assay represent the confidence limits of the individual assay estimates (which must meet the validity criterion for the confidence interval for the observed estimate (in this case, 33-300%), otherwise the reason for poor repeatability has to be investigated).

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 OMCLs 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, clinical efficacy would still be expected.

In such cases, 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 above mentioned EU directive.

The investigation should consider:

- 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 (eg. intermediate material at or beyond the approved shelf life, significant differences in process times etc.)
- the trends in the OMCL data looking for:
    - consistency in test performance with past results for the product (e.g. variability, ED50 values of standard and test vaccines, width of confidence intervals, frequency of test performance)
    - relation in trends between MAH and OMCL 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 the specification and if abnormal trends, major changes, anomalies or critical deviations have not 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 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.

Figure 2 – 1 example of a possible decision tree

```
                    ┌─────────────────┐
                    │   Perform 1     │
                    │  determination  │
                    └─────────────────┘
                             │
                             ▼
                          ╱──────╲                    ┌──────────────┐
                        ╱  Result  ╲      Yes          │ Sample passes │
                        ╲  in spec? ╱────────────────▶ └──────────────┘
                          ╲──────╱
                             │
                             │ No
                             ▼
```

Perform 1 determination

Result in spec ? → Yes → Sample passes

No

Upper CL above spec/lower CL above theoretically lowest limit? → Yes → Evaluate supplementary data from the manufacturer and the OMCL with attention to trends, anomalies, changes, deviations in tests or production → Result of analysis supports manufacturer's in spec result?

No/Inconclusive

Yes

No → Perform 1 additional determination

Perform 1 additional determination

Result in spec ? → Yes → Combine 1st and 2nd OMCL result

No

Combine 1st and 2nd OMCL result → Combined Result in spec ?

Combined Result in spec ? → No → Sample fails

Combined Result in spec ? → Yes → Sample passes