# DEPARTMENT OF BIOLOGICAL <br> STANDARDISATION, OMCL NETWORK \& HEALTHCARE (DBO) 

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# PTS156: LOSS ON DRYING 

PRELIMINARY REPORT<br>Statistician: A. Daas (EDQM, Strasbourg)<br>Scientific administrator responsible at EDQM: S. Muñoz Botella<br>Deadline for comments: 4 June 2015

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# PROFICIENCY TESTING STUDY 156: Loss on Drying 

This preliminary report is distributed for comments. Only the final report is definitive and to be used for the assessment of competence.

Statistician: A. Daas (EDQM, Strasbourg) ${ }^{1}$
Scientific administrator responsible at EDQM: S. Muñoz Botella

## 1. Introduction

Proficiency testing is a tool for measurement of the performance of laboratories based on inter-laboratory comparisons. Participation in Proficiency Testing Schemes (PTS) provides laboratories with an objective means of assessing and demonstrating the reliability of the data they produce. Thus, participation in a PTS provides independent verification of the competence of a laboratory and shows commitment to the maintenance and improvement of performance.
Proficiency testing covers the overall performance of a laboratory. This includes the entire process from reception and storage of samples, the experimental work in the laboratory, the interpretation and the transcription of the data, the conclusions drawn from the data and the production of reports. Failure at any of these stages reflects the competence of the laboratory. Hence, a report on a PTS cannot be modified if the laboratory discovers a failure after the first preliminary report has been received. Comments from the laboratories are added to the final report, but tables, figures and conclusions are not modified unless the data submitted by the laboratory has been mistyped by the EDQM.

## 2. Aim of the study

PTS156 was organised by the EDQM, Council of Europe, 7 Allée Kastner, F-67081, Strasbourg, according to the EDQM Instruction IS7/06 (Management of Proficiency testing Scheme).
The aim of the study was to assess the performance of the laboratories with regard to the loss on drying. Of the 106 participants initially registered, 101 sent their results. Laboratories received one vial of sample A (containing 3300 mg of sodium aminosalicylate dihydrate) and one vial of sample B (containing 3100 mg of asparagine monohydrate). They were requested to determine the loss on drying, according to Ph. Eur. general method 2.2.32 and the respective Ph. Eur. monographs, as described in the study protocol (PA/PH/PTS (15) 1).

## 3. Samples

The substances used as testing sample were obtained from a commercial supplier. They were aliquoted and labelled at the EDQM. The feasibility study confirmed that they were suitable for the purpose of the study and there was no evidence of non-homogeneity. Vials of sample A, containing sodium aminosalicylate dehydrate, were the same vials used as sample B in PTS129.

[^0]The recommended storage and shipment conditions for both samples, was ambient temperature.

## 4. Statistical methods

Different approaches may be adopted to assign the content of the analyte in the samples. The methods commonly applied in the EDQM PTS are the use of a theoretical value or the addition of a known quantity of the analyte to the sample ("true" value) confirmed in the feasibility study or the use of a consensus value based on the results from the participants. To determine the consensus value, robust statistics are applied (e.g. the median value, mean interquartile range, Huber's robust mean) to avoid the influence of "outliers" on the overall mean.

The target (relative) standard deviation, $\mathrm{T}(\mathrm{R}) \mathrm{SD}$, is set based on experience, the reported or expected precision of the applied techniques and according to fitness-for-purpose.

The general computational procedures used for the statistical evaluation of the data are described in EDQM Instruction IS7/06 (Management of Proficiency Testing Scheme). This instruction can be found on the extranet site and can also be obtained from the Secretariat upon request.

### 4.1. Assigned value

The assigned value used in PTS156 for both samples was the consensus value, $17.01 \%$ for sample A and $12.01 \%$ for sample B. These values were very close to the values found in the feasibility study ( $17.1 \%$ and $12.0 \%$ respectively) and to the assigned value used for sample B in PTS129 (17.03\%). They were all within the limits of the corresponding Ph. Eur. monographs.

### 4.2. Target standard deviation

The target value for the standard deviation (TSD) was set at $0.25 \%$ to be in line with the values applied in previous studies on the same technique. The results of the study confirm that the uncertainty of the assigned value is negligible compared to the TSD and can be ignored in the interpretation of the z -scores.

### 4.3. Scoring

The $z$-score gives a bias estimate of the result. Absolute $z$-scores less than 2 are acceptable. A zone of doubtful performance exists for absolute z -scores between 2 and 3 . Those do not necessarily have to be unacceptable since there is some uncertainty how close the consensus value is to the true value. An absolute $z$-score of 3 or more can be interpreted as an unacceptable performance. Corrective action should also be triggered when $z$-scores are frequently in the doubtful zone or of identical sign.
For the purposes of this exercise, the calculation of the z -score was made for each laboratory according to:

$$
z=\frac{\bar{x}-\hat{x}}{\hat{\sigma}}
$$

Where $\bar{x}$ is the mean value reported by the individual laboratory,
$\hat{x}$ is the assigned value, and
$\hat{\sigma}$ is the target value for the standard deviation.

### 4.4. Outliers

As a first step, a check for high standard deviations (Cochran's test) and for outlying means (Grubbs' test) was carried out. An outlier is a value that is so unlikely in the light of the overall distribution of results, that it would have an unreasonable impact on the calculation of certain statistics (e.g. the overall mean and the overall standard deviation). These tests do not necessarily detect values that are obviously unacceptable to a trained eye. Standard or relative standard deviations printed on a black background are only to indicate that these values are high compared to the (R)SDs found in other laboratories, but they do not necessarily imply that they are unacceptable. The purpose of $(\mathrm{R}) \mathrm{SD}$ s is to provide participants with comparative material so that they can interpret their own data in the light of the performances of other laboratories and draw their own conclusions. It is also important to be aware that the SD for precision is not the same as the SD for accuracy on which the z -scores are based. The latter is a fixed criterion, independent of the statistical distribution of the results.

## 5. Results

The raw data reported by the participants for both samples are reported in Tables 1.1 and 1.2. The mean value, the standard and the relative standard deviation and the $z$-score are reported in Tables 2.1 and 2.2. The distribution of the z -scores is illustrated in the bar-charts in Figures 1 and 2. The distribution of the mean values and of standard deviations is illustrated in the corresponding histograms in Figures 3 and 4.

For sample A only laboratory 75 reported questionable results ( $2<\mid z-$ score $\mid<3$ ). The mean result reported by this laboratory was also shown to be an outlier according to Grubbs' test. Laboratories $35,46,60,62$ and 76 showed poor apparent precision and were shown to be outliers according to Cochran's test.

For sample B, all the results reported were satisfactory. The mean results reported by laboratories $11,28,46$ and 97 were shown to be outliers according to Grubbs' test. Laboratories 46 and 97 showed poor apparent precision and were shown to be outliers according to Cochran's test.

To determine the loss on drying, laboratory 34 did not use an oven according to general method 2.2 .32 but a moisture analyser. Therefore their results were not considered for the calculation of the consensus value.

## 6. Potential source of errors

- Errors in weighing samples.
- Water up-take by the samples during testing.
- Errors in the use of equipment:
- Control of the drying time to constant weight/mass.
- Control of the temperature.
- Calculation and reporting errors.


## 7. Comments sent together with the results by the laboratories

Laboratory 1
Date sample was received: 28/02/2015.
Laboratory 11
Tests for both samples were carried out by the same analyst.
Laboratory 30
Loss on drying was carried out in accordance with the procedure described in the protocol PTS156 (document PA/PH/PTS (15) 1).

Laboratory 34
Loss on drying test was performed using a moisture analyser (Mettler HX 204) in replacement of Ph. Eur. 2.2.32 oven method.

Laboratory 36
Sample A: drying at $105^{\circ} \mathrm{C}$ for 2 h .
Sample B: only two results are reported.
Laboratory 38
Sample A was dried in an oven at $105{ }^{\circ} \mathrm{C}$ for 2 hours. Both samples were cooled in desiccator for 1 hour before weighing. Phosphorous pentoxide was used as desiccant.

## Laboratory 51

It would have been useful to have the Material Safety Data Sheet together with the samples or with the documentation.

## Laboratory 65

With regards to the respective monographs, it would be preferable to express the results with only one digit after the decimal place

## Laboratory 81

Our results are according to the instructions given in the protocol and Ph. Eur. 2.2.32.

## Laboratory 82

Oven used not certified across temperatures required by trial. Thermocouple certified in range of $100^{\circ} \mathrm{C}$ used to determine oven drying temperature.

Laboratory 83
The test was performed on 0.5 g for both substances.
Laboratory 95
Sample A: as no time was prescribed for the determination of the loss on drying, the test item was dried to constant mass (altogether 3.5 hours).

Laboratory 99
A drying cabinet from Memmert type UNB400 was used.

## 8. Conclusion

$99 \%$ of the participants reported satisfactory results. This overall performance is higher than that obtained in previous studies on loss on drying, including those where the same substances were used as testing samples.

## 9. Availability of additional samples

Following completion of the study and upon request, the EDQM can provide additional samples to laboratories that want to monitor the success of their corrective measures. Requests should be sent to Ms. Muriel Guissé. A handling fee of $€ 100$ will be charged for these additional samples.

## PTS156 - Table 1.1

Raw data reported by the participants


## PTS156 - Table 1.2 <br> Raw data reported by the participants

| Assigned value: Target SD: | Sodium | $\begin{gathered} \hline \text { Sample } \\ \text { inosalicy } \\ 17.01 \\ 0.25 \\ \hline \end{gathered}$ | dihyd | Sample B <br> Asparagine monohydrate <br> 12.01 <br> 0.25 |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Replicates: | 1 | 2 | 3 | 1 | 2 | 3 |
| Lab |  |  |  |  |  |  |
| 53 | 17.01 | 16.90 | 16.99 | 12.04 | 12.00 | 11.96 |
| 54 | 16.87 | 16.96 | 16.89 | 11.92 | 11.91 | 11.98 |
| 55 | 16.96 | 16.98 | 16.95 | 12.10 | 12.18 | 12.11 |
| 56 | 17.03 | 17.03 | 17.02 | 12.03 | 12.03 | 12.01 |
| 57 | 17.08 | 16.99 | 17.06 | 11.94 | 11.95 | 11.97 |
| 58 | 16.98 | 17.05 | 17.10 | 12.06 | 11.98 | 11.99 |
| 59 | 17.07 | 17.07 | 17.06 | 11.95 | 11.97 | 11.97 |
| 60 | 17.54 | 17.03 | 17.05 | 12.03 | 12.04 | 12.14 |
| 61 | 16.87 | 16.89 | 16.80 | 11.94 | 11.92 | 11.96 |
| 62 | 17.49 | 17.04 | 17.28 | 11.85 | 12.01 | 12.10 |
| 63 | 16.77 | 16.88 | 16.87 | 11.97 | 11.96 | 12.02 |
| 64 | 17.14 | 17.04 | 16.97 | 12.23 | 12.00 | 12.04 |
| 65 | 16.93 | 17.06 | 16.96 | 12.18 | 12.01 | 12.04 |
| 66 | 16.91 | 16.92 | 16.92 | 11.97 | 11.97 | 11.96 |
| 67 | 17.06 | 17.16 | 17.07 | 12.01 | 11.95 | 11.98 |
| 68 | 17.01 | 17.06 | 17.02 | 11.95 | 11.95 | 11.96 |
| 69 | 17.41 | 17.28 | 17.56 | 11.82 | 12.02 | 11.95 |
| 70 | 17.00 | 16.96 | 17.00 | 11.84 | 11.82 | 11.88 |
| 71 | 16.88 | 16.87 | 16.83 | 11.90 | 12.00 | 12.00 |
| 72 | 17.01 | 17.01 | 17.02 | 12.03 | 12.05 | 12.00 |
| 73 | 17.02 | 16.99 | 17.00 | 12.00 | 12.01 | 11.95 |
| 74 | 17.08 | 17.08 | 17.00 | 12.04 | 12.16 | 12.03 |
| 75 | 16.31 | 16.28 | 16.29 | 11.97 | 11.93 | 11.94 |
| 76 | 17.24 | 17.27 | 17.66 | 12.04 | 12.18 | 12.03 |
| 77 | 16.89 | 16.86 | 16.86 | 12.05 | 12.04 | 12.04 |
| 78 | 17.06 | 17.13 | 17.01 | 12.03 | 12.10 | 12.23 |
| 79 | 16.82 | 16.78 | 16.89 | 12.02 | 12.07 | 12.03 |
| 80 | 17.06 | 17.02 | 17.00 | 11.95 | 11.95 | 11.94 |
| 81 | 17.09 | 17.10 | 17.22 | 11.98 | 11.98 | 11.98 |
| 82 | 16.82 | 16.82 | 16.76 | 11.95 | 11.94 | 11.94 |
| 83 | 16.94 | 16.95 | 16.91 | 11.94 | 11.96 | 11.96 |
| 84 | 16.99 | 16.99 | 16.98 | 11.95 | 11.94 | 11.94 |
| 85 | 17.10 | 17.09 | 17.08 | 11.97 | 11.96 | 11.96 |
| 86 | 17.07 | 17.01 | 17.04 | 12.05 | 12.03 | 12.00 |
| 87 | 16.91 | 16.96 | 16.90 | 11.98 | 11.99 | 11.91 |
| 88 | 16.90 | 16.89 | 16.89 | 11.96 | 11.95 | 11.95 |
| 89 | 16.89 | 16.94 | 16.88 | 12.07 | 12.07 | 12.04 |
| 90 | 17.20 | 17.29 | 17.25 | 12.00 | 11.98 | 11.85 |
| 91 | 16.95 | 16.89 | 16.92 | 12.01 | 11.98 | 12.03 |
| 92 | 17.17 | 17.08 | 17.04 | 11.90 | 11.91 | 11.82 |
| 93 | 17.01 | 16.99 | 17.00 | 12.03 | 12.04 | 12.06 |
| 94 | 17.04 | 17.04 | 17.06 | 11.99 | 11.95 | 11.97 |
| 95 | 17.07 | 16.91 | 17.03 | 11.90 | 12.00 | 12.06 |
| 96 | 17.09 | 17.07 | 17.05 | 12.09 | 12.08 | 12.02 |
| 97 | 16.83 | 16.84 | 16.86 | 12.12 | 12.36 | 12.59 |
| 98 | 17.09 | 17.05 | 17.08 | 12.10 | 12.09 | 12.07 |
| 99 | 16.95 | 17.00 | 16.99 | 12.03 | 12.08 | 12.04 |
| 100 | 16.94 | 16.92 | 16.87 | 12.02 | 12.02 | 12.02 |
| 101 | 16.90 | 16.94 | 16.96 | 12.04 | 12.01 | 12.03 |

n.r. = not reported. Results are listed with the same number of decimals as reported by the participants.

PTS156 - Table 2.1
Scoring of the participating laboratories

|  | Sample ASodium aminosalicylate dihydrate |  |  |  | Sample B <br> Asparagine monohydrate |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Mean | SD | RSD | z-score | Mean | SD | RSD | z-score |
| Lab |  |  |  |  |  |  |  |  |
| 1 | 16.89 | 0.04 | 0.21 | -0.48 | 12.07 | 0.01 | 0.05 | 0.25 |
| 2 | 17.13 | 0.04 | 0.23 | 0.48 | 11.97 | 0.01 | 0.08 | -0.16 |
| 3 | 17.07 | 0.02 | 0.10 | 0.24 | 11.99 | 0.01 | 0.10 | -0.07 |
| 4 | 17.08 | 0.01 | 0.08 | 0.29 | 12.11 | 0.01 | 0.12 | 0.40 |
| 5 | 17.07 | 0.03 | 0.19 | 0.25 | 12.00 | 0.03 | 0.22 | -0.04 |
| 6 | 17.18 | 0.09 | 0.53 | 0.69 | 12.10 | 0.06 | 0.46 | 0.36 |
| 7 | 17.10 | 0.01 | 0.07 | 0.37 | 12.23 | 0.13 | 1.02 | 0.89 |
| 8 | 17.07 | 0.00 | 0.00 | 0.24 | 11.96 | 0.01 | 0.08 | -0.20 |
| 9 | 16.86 | 0.04 | 0.24 | -0.59 | 11.96 | 0.08 | 0.63 | -0.20 |
| 10 | 17.04 | 0.13 | 0.78 | 0.12 | 11.88 | 0.01 | 0.10 | -0.51 |
| 11 | 16.95 | 0.10 | 0.60 | -0.23 | 12.39 | 0.10 | 0.81 | 1.51 |
| 12 | 17.02 | 0.01 | 0.03 | 0.05 | 11.94 | 0.02 | 0.17 | -0.28 |
| 13 | 17.04 | 0.01 | 0.03 | 0.11 | 11.97 | 0.02 | 0.13 | -0.17 |
| 14 | 17.02 | 0.03 | 0.19 | 0.05 | 12.07 | 0.04 | 0.33 | 0.25 |
| 15 | 16.89 | 0.02 | 0.12 | -0.49 | 11.98 | 0.02 | 0.17 | -0.12 |
| 16 | 16.86 | 0.03 | 0.15 | -0.59 | 11.95 | 0.01 | 0.10 | -0.23 |
| 17 | 16.98 | 0.01 | 0.07 | -0.11 | 11.93 | 0.02 | 0.15 | -0.32 |
| 18 | 16.86 | 0.03 | 0.17 | -0.61 | 11.95 | 0.02 | 0.17 | -0.23 |
| 19 | 17.04 | 0.02 | 0.12 | 0.13 | 11.93 | 0.02 | 0.17 | -0.31 |
| 20 | 17.01 | 0.02 | 0.10 | 0.00 | 12.07 | 0.01 | 0.10 | 0.25 |
| 21 | 17.04 | 0.02 | 0.09 | 0.13 | 11.93 | 0.02 | 0.17 | -0.33 |
| 22 | 17.08 | 0.06 | 0.33 | 0.29 | 12.05 | 0.02 | 0.17 | 0.16 |
| 23 | 16.95 | 0.02 | 0.12 | -0.24 | 11.95 | 0.01 | 0.05 | -0.25 |
| 24 | 17.06 | 0.03 | 0.15 | 0.21 | 11.99 | 0.03 | 0.25 | -0.07 |
| 25 | 17.05 | 0.12 | 0.70 | 0.17 | 11.98 | 0.07 | 0.58 | -0.12 |
| 26 | 17.02 | 0.02 | 0.12 | 0.04 | 12.02 | 0.08 | 0.63 | 0.05 |
| 27 | 17.01 | 0.02 | 0.12 | 0.00 | 12.00 | 0.01 | 0.05 | -0.05 |
| 28 | 16.93 | 0.11 | 0.62 | -0.32 | 12.30 | 0.04 | 0.29 | 1.16 |
| 29 | 16.92 | 0.04 | 0.22 | -0.35 | 12.06 | 0.05 | 0.41 | 0.20 |
| 30 | 17.08 | 0.03 | 0.18 | 0.28 | 11.96 | 0.00 | 0.00 | -0.20 |
| 31 | 17.08 | 0.07 | 0.41 | 0.29 | 12.08 | 0.02 | 0.19 | 0.29 |
| 32 | 16.89 | 0.03 | 0.17 | -0.49 | 12.04 | 0.03 | 0.22 | 0.12 |
| 33 | 16.99 | 0.07 | 0.43 | -0.09 | 12.02 | 0.02 | 0.19 | 0.05 |
| 34 | 17.37 | 0.04 | 0.21 | 1.44 | 12.18 | 0.14 | 1.17 | 0.67 |
| 35 | 17.22 | 0.18 | 1.05 | 0.85 | 12.15 | 0.04 | 0.36 | 0.56 |
| 36 | 16.91 | 0.02 | 0.09 | -0.39 | 12.00 | 0.01 | 0.12 | -0.04 |
| 37 | 17.09 | 0.04 | 0.22 | 0.31 | 12.06 | 0.01 | 0.10 | 0.19 |
| 38 | 17.09 | 0.03 | 0.20 | 0.32 | 11.89 | 0.01 | 0.05 | -0.49 |
| 39 | 17.17 | 0.04 | 0.24 | 0.63 | 12.20 | 0.01 | 0.08 | 0.76 |
| 40 | 16.90 | 0.04 | 0.21 | -0.44 | 12.00 | 0.03 | 0.21 | -0.05 |
| 41 | 16.99 | 0.06 | 0.37 | -0.08 | 11.98 | 0.02 | 0.13 | -0.13 |
| 42 | 17.11 | 0.00 | 0.00 | 0.40 | 12.02 | 0.01 | 0.05 | 0.05 |
| 43 | 17.02 | 0.01 | 0.03 | 0.05 | 11.95 | 0.01 | 0.05 | -0.25 |
| 44 | 17.03 | 0.01 | 0.06 | 0.08 | 12.00 | 0.04 | 0.29 | -0.05 |
| 45 | 16.93 | 0.06 | 0.38 | -0.33 | 11.93 | 0.07 | 0.56 | -0.33 |
| 46 | 17.28 | 0.18 | 1.02 | 1.09 | 12.49 | 0.34 | 2.73 | 1.91 |
| 47 | 16.80 | 0.12 | 0.70 | -0.83 | 12.14 | 0.03 | 0.29 | 0.52 |
| 48 | 17.07 | 0.00 | 0.00 | 0.24 | 11.97 | 0.02 | 0.19 | -0.15 |
| 49 | 17.09 | 0.01 | 0.06 | 0.32 | 11.94 | 0.01 | 0.08 | -0.28 |
| 50 | 16.91 | 0.02 | 0.14 | -0.41 | 12.02 | 0.03 | 0.22 | 0.04 |
| 51 | 17.07 | 0.05 | 0.30 | 0.25 | 12.02 | 0.02 | 0.13 | 0.03 |
| 52 | 17.06 | 0.00 | 0.00 | 0.20 | 11.99 | 0.00 | 0.00 | -0.08 |
| 53 | 16.97 | 0.06 | 0.35 | -0.17 | 12.00 | 0.04 | 0.33 | -0.04 |
| 54 | 16.91 | 0.05 | 0.28 | -0.41 | 11.94 | 0.04 | 0.32 | -0.29 |
| 55 | 16.96 | 0.02 | 0.09 | -0.19 | 12.13 | 0.04 | 0.36 | 0.48 |
| 56 | 17.03 | 0.01 | 0.03 | 0.07 | 12.02 | 0.01 | 0.10 | 0.05 |
| 57 | 17.04 | 0.05 | 0.28 | 0.13 | 11.95 | 0.02 | 0.13 | -0.23 |
| 58 | 17.04 | 0.06 | 0.35 | 0.13 | 12.01 | 0.04 | 0.36 | 0.00 |
| 59 | 17.07 | 0.01 | 0.03 | 0.23 | 11.96 | 0.01 | 0.10 | -0.19 |
| 60 | 17.21 | 0.29 | 1.68 | 0.79 | 12.07 | 0.06 | 0.50 | 0.24 |
| 61 | 16.85 | 0.05 | 0.28 | -0.63 | 11.94 | 0.02 | 0.17 | -0.28 |

PTS156 - Table 2.2
Scoring of the participating laboratories


Means, SDs and RSDs are calculated at the EDQM on the basis of reported individual values.
Mean values that are indicated as outliers using Grubbs' test are printed on a black background.
SDs and RSDs that are indicated as outliers using Cochran's test are printed on a black background.
Absolute $z$-scores greater or equal to 3 are printed on a black background (none in this study).
Absolute $z$-scores greater than 2 are printed on a grey background.

## PTS156 - Figure 1

Bar-chart of z-scores (Sample A)



## PTS156 - Figure 3 Histograms of laboratory means and standard deviations (Sample A)



Numbers in the boxes are the laboratory codes.

PTS156 - Figure 4
Histograms of laboratory means and standard deviations (Sample B)


Numbers in the boxes are the laboratory codes.


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