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ANNEX 1 - ROUNDING

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ROUNDING

Table of Contents

1. Introduction

The approach described in this annex is intended as a practical way to address the rounding of values used in calculation operations as well as the rounding of reportable values. In particular, conformance to specification limits is assessed by comparison of the reportable value (rounded appropriately) to specified limits.

Values can be rounded to *n* significant digits (Section 5) or to *n* decimal places as shown in Table 1. Of these two approaches, rounding to decimal places is recommended to compare reported values to specification limits.

Table 1. Rounding of a reportable value (13.463) to *n* significant digits or *n* decimal places.

Precision (*n*)	Rounding to significant digits	Rounding to decimal places
3	13.5	13.463
2	13	13.46
1	10	13.5
0	N/A	13

Prior to providing recommendations about how to round off the reportable value, this annex discusses two critical aspects, i.e. the rounding of raw data and the rounding of intermediate calculated results.

2. Rounding of raw data

This section illustrates how the number of decimal places of raw data can influence final results. The copy/paste of data from Excel to CombiStats will be used as an introductory example. In Figure 1, the values are formatted in such a way that 3, 2 and 1 decimal places are visible in Excel tables. However, the 3 sets of data remain the same (some digits are only hidden). A copy/paste of the values to CombiStats results in 3 different sets of data and thus 3 different potency estimates, as CombiStats has copied the formatted values (visible digits).

	Dose	Rep.1	Rep.2	Dose	Rep.1	Rep.2	Dose	Rep.1	Rep.2
Excel tables	1/1	2.130	2.212	1/1	2.13	2.21	1/1	2.1	2.2
	1/4	1.073	0.973	1/4	1.07	0.97	1/4	1.1	1.0
	1/8	0.463	0.356	1/8	0.46	0.36	1/8	0.5	0.4
	1/16	0.228	0.197	1/16	0.23	0.20	1/16	0.2	0.2

	Dose	(1)	(2)	Dose	(1)	(2)	Dose	(1)	(2)
CombiStats tables	1/1	2.130	2.212	1/1	2.13	2.21	1/1	2.1	2.2
	1/4	1.073	0.973	1/4	1.07	0.97	1/4	1.1	1.0
	1/8	0.463	0.356	1/8	0.46	0.36	1/8	0.5	0.4
	1/16	0.228	0.197	1/16	0.23	0.20	1/16	0.2	0.2

Figure 1. Copy/paste of formatted data (Excel) results in 3 different CombiStats datasets.

This example shows that data copy/transfer from one program to another may have particular features requiring clear instructions in SOPs (e.g. in terms of data formatting) such that raw data submitted to analyses have the same precision.

When data are recorded manually, not all decimal digits should be reported, especially if they are in excess. Indeed, there is an increased risk of typing errors and reporting all digits may not be relevant, when considering the (lower) precision of the analytical procedure.

Rounding a value adds an error to that value. For example, when 2.130 is rounded to 2.1 (to 1 decimal place), all the values between 2.050 and 2.150 (interval: $\delta = 0.1$) are considered as equally alike and follow a rectangular (uniform) distribution. This distribution has a standard deviation equal to $u_r = \delta/\sqrt{12}$ (0.03 in this example).

In addition, the original value (2.130) comes with an error (u_a) due to the analytical procedure. Assuming $u_a = 0.05$ (fictitious data), the standard uncertainty is:

$$u_c = \sqrt{u_a^2 + u_r^2}.$$

In this example, $u_c = 0.06$ and the rounding step contributes to $(0.03/0.06)^2 = 1/4$ of the standard uncertainty. By rounding the value to 2 decimal places (2.13), the contribution of the rounding step to the standard uncertainty becomes negligible (0.3%). Rounding off to 2 decimal places may thus be considered as a good option.

Once the last decimal place that should be kept is determined, the values can be rounded according to the following rules:

- Leave the decimal digit as it is if the next digit is less than 5,
- Increase the decimal digit by 1 if the next digit is greater than or equal to 5.

Examples of values rounded to 2 decimal places:

$$2.13\underline{4}99 \Rightarrow 2.13,$$

$$2.13\underline{5}01 \Rightarrow 2.14.$$

Other approaches may be used to determine the most relevant number of decimal places of the input data. For multi-dilution assays as in Ph. Eur. 5.3, for example, CombiStats analyses could be run on a series of assays for various numbers of decimal places and the potency estimates compared. As the potency estimates will be reported with a limited number of decimal places, it is likely that input data rounded to n and n+1 decimal places will result in the same reportable values in most analyses. In this case, input data rounded to n decimal places may be used routinely (see Examples 1 and 2 for illustrations).

Table 2. Parallel-line analysis using CombiStats with absorbance units (AUs) given with 4, 3 or 2 decimal places. Statistical analysis carried out on log(AUs).

4 decimal places to raw data

	Standard (20 IU/mL)			Sample 1			Sample 2		
Doses	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
1/1	0.5148	0.5317	0.5457	1.1406	1.3868	1.0514	0.9579	0.8664	1.0454
1/2	0.2835	0.2959	0.3620	0.5015	0.6659	0.5766	0.5860	0.4895	0.5467
1/4	0.1595	0.1542	0.1665	0.3280	0.3556	0.3459	0.2778	0.2690	0.2700
1/8	0.0939	0.0999	0.0827	0.1676	0.1580	0.1789	0.1280	0.1466	0.1330
1/16	0.0431	0.0460	0.0512	0.0972	0.0975	0.0943	0.0870	0.0717	0.0732

Potency	Lower	Est.	Upper	Lower	Est.	Upper
IU/mL	40	44	47	33	35	38

3 decimal places to raw data

Doses	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
1/1	0.515	0.532	0.546	1.141	1.387	1.051	0.958	0.866	1.045
1/2	0.284	0.296	0.362	0.502	0.666	0.577	0.586	0.490	0.547
1/4	0.160	0.154	0.167	0.328	0.356	0.346	0.278	0.269	0.270
1/8	0.094	0.100	0.083	0.168	0.158	0.179	0.128	0.147	0.133
1/16	0.043	0.046	0.051	0.097	0.098	0.094	0.087	0.072	0.073

Potency	Lower	Est.	Upper	Lower	Est.	Upper
IU/mL	40	44	47	33	35	38

2 decimal places to raw data

Doses	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
1/1	0.51	0.53	0.55	1.14	1.39	1.05	0.96	0.87	1.05
1/2	0.28	0.30	0.36	0.50	0.67	0.58	0.59	0.49	0.55
1/4	0.16	0.15	0.17	0.33	0.36	0.35	0.28	0.27	0.27
1/8	0.09	0.10	0.08	0.17	0.16	0.18	0.13	0.15	0.13
1/16	0.04	0.05	0.05	0.10	0.10	0.09	0.09	0.07	0.07

Potency	Lower	Est.	Upper	Lower	Est.	Upper
IU/mL	40	44	48	33	36	39

Example 1. Absorbance units (AUs) come with 4 decimal places, by default (Table 2). On the other hand, potency results should be rounded to the nearest integer. There is no difference between the potency results calculated with raw data given with 4 or 3 decimal places: estimates = 44 and 35 IU/mL for samples 1 and 2 (95%CL = {40, 47} and {33, 38} IU/mL, respectively). With raw data given with 2 decimal places, potency results can vary by up to 1 IU/mL. Therefore, 3 decimal places may be a good trade-off between number of decimal places of AUs and precision of reportable results. Additional sets of data should be evaluated to confirm the use of 3 decimal places in routine testing.

Table 3. 4-parameter logistic regression using CombiStats with absorbance units (AUs) given with 4, 3 or 2 decimal places. Statistical analysis carried out using the logit transformation.

	Raw data: 4 decimal places				**3 decimal places**				**2 decimal places**			
	Standard 1 IU/mL		Sample		Standard		Sample		Standard		Sample	
Doses	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
1/1	2.9129	2.9179	3.0171	2.9874	2.913	2.918	3.017	2.987	2.91	2.92	3.02	2.99
1/2	2.5793	2.6544	2.8016	2.8087	2.579	2.654	2.802	2.809	2.58	2.65	2.80	2.81
1/4	2.1306	2.2129	2.4020	2.4508	2.131	2.213	2.402	2.451	2.13	2.21	2.40	2.45
1/8	1.6515	1.6386	1.9180	1.9638	1.652	1.639	1.918	1.964	1.65	1.64	1.92	1.96
1/16	1.0730	0.9731	1.3650	1.2998	1.073	0.973	1.365	1.300	1.07	0.97	1.37	1.30
1/32	0.5860	0.6662	0.8612	0.8543	0.586	0.666	0.861	0.854	0.59	0.67	0.86	0.85
1/64	0.4631	0.3561	0.4978	0.4960	0.463	0.356	0.498	0.496	0.46	0.36	0.50	0.50
1/128	0.2669	0.2342	0.3407	0.3449	0.267	0.234	0.341	0.345	0.27	0.23	0.34	0.34
1/256	0.2286	0.1976	0.2424	0.2171	0.229	0.198	0.242	0.217	0.23	0.20	0.24	0.22
1/512	0.1765	0.2154	0.1784	0.1260	0.177	0.215	0.178	0.126	0.18	0.22	0.18	0.13

Potency results (rounded to 2 decimal places) are equal for 4, 3 or 2 decimal places of raw data.
Sample potency (IU/mL): Lower confidence limit = 1.39, Estimate = 1.46, Upper confidence limit = 1.53.

Example 2. This example is similar to Example 1, except that the AUs are spread over a wider range of values, i.e. from 0.1 to 3.0, limiting the effect of rounding of raw data on final calculated results (Table 3). Assuming that potency results should be rounded to 2 decimal places, they are equal to 1.46 IU/mL (95%CI = (1.39, 1.53) IU/mL) for AUs given with 4, 3 or 2 decimal places. Two decimal places may be a good trade-off between number of decimal places of AUs and precision of reportable results. Additional sets of data should be evaluated to confirm the use of 2 decimal places in routine testing.

In summary, it appears that when input data can be entered/copied automatically to the analysis tool, users seldom think about rounding the data even when they contain decimal digits in excess. However, a rounding step may be envisaged in order to reflect the actual precision of the analytical procedure or instrument.

In addition, this rounding step may be motivated by other considerations, e.g.:

- The analysis uses all the decimal digits of the input data. However, due to data formatting, a limited number of decimal places is visible. If input data are not available electronically later on (e.g. hard copy only), only formatted values can be re-entered, and it is not possible to reproduce the same analysis results. Rounding and formatting input data to the same relevant number of decimal places will avoid such a situation.
- Input data are entered manually. A relevant number of decimal places should be specified to ensure harmonisation of practices (data submitted to analyses have the same precision) and mitigate the risk of typing errors (which increases with the number of digits).

3. Calculation steps

In Examples 1 and 2, a series of calculation steps are carried out automatically, according to the selected regression model (e.g. parallel lines, 4-parameter logistic regression). As the software does not round intermediate results, no cumulative rounding errors are introduced (best practice). In-house calculation spreadsheets should be developed on the same principle, i.e. no rounding of intermediate results. However, intermediate results, if displayed, can be formatted to a readable number of decimal places.

Note. The software may use either a single-precision or double-precision number format, which differ, in particular, in the number of available decimal places (6 to 9 versus 15 to 17, respectively). Although both formats may have a higher precision than the precision of input data (e.g. absorbance units) and no consequences for the reportable value (usually rounded to a limited number of decimal places), they may lead to slightly different calculated values. In summary, knowing whether single-precision or double-precision (as in CombiStats) is used may be of interest in cases where calculated results should be reproduced using different software.

The next recommendations may be followed for calculation steps carried out manually (e.g. with the help of a pocket calculator), in order to limit cumulative rounding errors. The rounding rules applied to the reportable values in the various examples are explained in Section 4. Rules for counting significant digits are given in Section 5.

- **For mathematical or physical values** characterised by a long list of decimal digits (e.g. π = 3.141592653589793), a practical approach may consist in applying the same number of significant digits. Three or four significant digits are suggested in Table 4 (t-percentiles and square roots are given as examples because they are involved in the calculation of confidence limits often used to assess the validity of assay results).

Table 4. Rounding of mathematical or physical values.

Values rounded to	π	$t_{95,\,1}$	$t_{95,\,2}$	$\sqrt{2}$	$\sqrt{3}$
3 significant digits	3.14	12.7	4.30	1.41	1.73
4 significant digits	3.142	12.71	4.303	1.414	1.732

$t_{P,\,df}$: two-sided t-percentile for a P% confidence level and number of degrees of freedom (df).

- **For addition (e.g. a step in averaging) or subtraction**, input data can be rounded to the same number of decimal places. This number can be chosen such that the uncertainty of the rounding step is negligible compared to the standard uncertainty of the analytical procedure (Section 2). For input data with known different precisions, different numbers of decimal places may be kept.

Example 3. Rounding of the mean of {98.754, 100.283, 101.61}. The calculated mean is equal to 100.2157. For the mean used as an intermediate calculated result, the maximum number of decimal places of the input data may be used (mean = 100.216), or, for input data with the same number of decimal places, i.e. {98.754, 100.283, 101.610}, the number of decimal places plus one (mean = 100.2157).

For a reportable value to be rounded to 1 decimal place, for example, a truncated value should be determined first to avoid “double rounding errors”. An effective way to do this is to truncate the calculated value to 1 more digit than the reportable value (truncated mean = 100.21). Therefore, the reportable value is equal to 100.2.

Example of “double rounding errors”: 100.2499 is first rounded to 100.25 on the lab notebook. This value is then rounded to 100.3 instead of 100.2. To report the value correctly, it should be truncated first (100.24) and then rounded (100.2).

Example 4. Rounding of the standard deviation of {98.754, 100.283, 101.61}. A different approach may be used for uncertainty estimates (such as standard deviations) than for individual and mean results. Specifically, the recommended approach is to round off to a given number of significant digits instead of decimal places.

The calculated standard deviation is equal to 1.4292. For an intermediate calculated result, a maximum of 4 significant digits may be kept, i.e. SD = 1.429. For a reportable value, no more than 2 significant digits should be kept. Therefore, the truncated value should be equal to 1.42 and the reportable value 1.4.

Note. The (relative) standard deviation can be used as an assay validity criterion, in which case the (R)SD value should be rounded to the prescribed number of decimal places. For example, some monographs indicate that repeatability should not be "greater than 3 per cent for an assay and not greater than 5 per cent for an impurity test". Repeatability estimates should be rounded to the nearest percent value.

The 95% confidence limits of the mean value are equal to mean ± $t_{95,\,2}$ × SD / sqrt(3). Using the intermediate results calculated above, we obtain 100.216 ± 4.303 × 1.429 / 1.732 = {96.666, 103.766}. The mean value and associated confidence limits should be reported with the same number of decimal places: 100.2 {96.7, 103.8}.

- **For multiplication or division**, input data (y) can be rounded to reach the same relative precision, which is calculated as $\delta_p = 100 \times \delta / y$, where δ is the precision interval defined in Section 2.

Example 5. Product of 101.54 by 10.2547. The first value has a relative precision of about one-hundredth (100 × 0.01 / 101.54 = 0.0098% ≈ 0.01%), the second value a relative precision of about one-thousandth (100 × 0.0001 / 10.2547 = 0.00098% ≈ 0.001%).

For input data aligned on the same relative precision (0.01%), the calculated result is 101.54 × 10.255 = 1041.293. For an intermediate calculated result, the same relative precision as the input data may be used (product = 1041.3).

For a reportable value to be rounded to the nearest unit, for example, the truncated value is equal to 1041.2 and the reportable value is equal to 1041.

- **For the $\log_{10}$-transformation**, input data should be represented using the scientific notation M × 10^E with 1 ≤ M < 10. The number of decimal places of $\log_{10}$-data should be equal to the number of digits contained in M.

Example 6. Input data are cell concentrations / mL {3.674 10^6, 7.83 10^5, 1.282 10^6}. As M has 4 digits for most concentrations, $\log_{10}$ values are rounded to 4 decimal places, i.e. {6.5651, 5.8938, 6.1079}.

The arithmetic mean is equal to AM = 6.1889 $\log_{10}$ and can be back-transformed (anti-$\log_{10}$) to report the geometric mean concentration (GMC). In this respect, AM is an intermediate result.

The geometric mean is GMC = 1 544 899 (1.544899 10^6) to be rounded to the nearest thousandth, for example. Then, the truncated value is 1.5448 10^6 and the reportable value is 1.545 10^6.

4. Final calculated result

There are several examples of final calculated results in the previous sections, which were rounded according to the following rule:

Rounding rule: knowing the last decimal place to which to report the value, the final calculated result is rounded as follows (Table 5):

- Leave the decimal digit as it is if the next digit is less than 5,
- Increase the decimal digit by 1 if the next digit is greater than or equal to 5.

Table 5. Examples of final calculated result rounded to 2 decimal places.

Final calculated result	Truncated value	Reportable value
2.13499	2.134	2.13
2.13501	2.135	2.14

The final calculated result is truncated to the underlined digit that follows the decimal place to which it should be rounded. This approach avoids "double rounding errors", e.g. 2.13499 rounded to 2.135 on the lab notebook and then to 2.14 (instead of 2.13). Truncation is suggested but other approaches that can mitigate the risk of "double rounding errors" can be envisaged.

Table 6 provides a summary of the final calculated results, truncated and reportable values obtained for the examples of the previous sections.

Table 6. Rounding of final calculated results of Examples 1 to 6.

Example	Rounding to nearest	Final calculated Result	Truncated Value*	Reportable Value
1	1	43.5286	43.5	44
2	0.01	1.45913	1.459	1.46
3	0.1	100.2157	100.21	100.2
4	0.1	1.4292	1.42	1.4
5	1	1041.293	1041.2	1041
6	1000	1 544 899	1 544 800	1 545 000

* The final calculated result is truncated to the underlined digit to mitigate the risk of double rounding errors.

Rounding of the mean and confidence limits: the mean value and associated confidence limits should be reported with the same number of decimal places. It should be the number of decimal places of the assay validity criteria or product specification limits, when such criteria or limits exist.

Rounding with specification limits: in some cases, specification limits can be provided both in test units and as percentages, e.g. 8.1-9.9 g/L (90-110%), which can lead to opposing conclusions depending on how the results are managed. As an illustration, the calculated concentration is 9.949 g/L:

- Rounded to 9.9 g/L (PASS) (limits are assumed to be inclusive in this example);
- Calculated as a percentage, 100 × 9.949 / 9 = 110.54% rounded to 111% (FAIL).

Therefore, the laboratory should document which specification limits (test units or percentages) should be used to assess their routine data in a consistent way. When both limits exist, those in test units are recommended in this guideline.

In some Ph. Eur. monographs, the specification limits can be stated as follows:

The mean value must be between 85 per cent and 115 per cent of the label claim.

Content: 90.0 per cent to 110.0 per cent of the content stated on the label.

In this case, it is recommended to convert the intermediate calculated value as a percentage and compare it to the limits, taking into account the requested number of decimal places (see Table 7 for an illustration).

Table 7. Rounding according to specification limits in %.

Limits*	Rounding to nearest	Label claim	Calculated value	Truncated value (%)	Reportable value (%)
85-115%	1%	50	42.347	84.6%	85% (PASS)
90.0-110.0%	0.1%	40	42.347	105.86%	105.9% (PASS)

* Limits are assumed to be inclusive in this example.

As another example, specification limits for impurities may be expressed with different numbers of decimal places in monographs, in which case reportable values should be rounded accordingly, e.g.:

- Impurities A, B, C: for each impurity, not more than 0.15 per cent. Reportable percent values should be rounded to 2 decimal places;
- Unspecified impurities: for each impurity, not more than 0.10 per cent. Reportable percent values should be rounded to 2 decimal places;
- Total: not more than 0.3 per cent. Reportable percent value should be rounded to 1 decimal place.

Rounding when there is no specification limit: different approaches may be envisaged depending on, for example, the precision of the method, expected range of results, or use made of the rounded values:

- Result are measurements (e.g. pH-value, temperature) that can be rounded to reflect the precision of the instrument (in some cases, the relevant number of decimal places is displayed by the instrument).
- Results are calculated using a simple formula: the precision of reportable values may be aligned on the lowest precision of the input data.
- Results are calculated using a regression analysis: the precision of reportable values may be chosen taking into consideration the precision of the titre of the standard preparation or precision of the input concentration/dilution levels.
- Alternatively, there may be other usages of the analytical procedure of interest or similar products to which specification limits are applied. The same rounding rule can be followed, for the sake of consistency of reporting of results in the laboratory.
- The expected range of values goes from 100 to 300 g/L. With such a range, rounding off to the nearest unit may be sufficient for most subsequent data usages or analyses (e.g. use of control charts, comparison of data distributions). For an expected range of values between 42 and 45, rounding off to 1 or 2 decimal places may be more relevant.

5. Significant figures

Rules for counting significant figures indicate that:

- all non-zero digits and any zeros contained between non-zero digits count, e.g. ***10038*** has 5 significant figures (in bold italic);
- leading zeros indicate order of magnitude only and thus do not count, e.g. 0.00***25*** has 2 significant figures;
- trailing zeros count if there is a decimal point, e.g. 0.0***9700*** and ***1250*** have 4 significant figures;
- trailing zeros may or may not count if there is no decimal point, e.g. ***200*** could have 1, 2 or 3 significant figures. In fact, the significance of trailing zeros can only be identified from knowledge of the source of the value. However, unless specified, the highest number of significant figures should be kept. In the case of the above example, this means 3 significant figures, which assumes that results are reported to the nearest integer (e.g. 194, 199, 202, 208).

The use of scientific notation can simplify the identification of the significant figures as shown in Table 8.

Table 8. Use of scientific notation for easier determination of the significant figures.

Number	10038	0.0025	1250	0.09700	200
Scientific notation	***1.0038*** x 10^4	***2.5*** x 10^{-3}	***1.250*** x 10^3	***9.700*** x 10^{-2}	***2.00*** x 10^2
Significant figures	5	2	4	4	3