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Relationship between HPLC precision and number of significant figures when reporting impurities and when setting specifications

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Abstract

The rounding of an analytical result is a process that should take into account the uncertainty of the result, which is in turn assessed during the validation exercise. Rounding rules are known in physical and analytical chemistry since a long time, but are often not used or misused in pharmaceutical analysis. The paper describes the theoretical background of the most common rules and their application to fix the rounding of results and specifications. The paper makes use of uncertainty values of impurity determination acquired during studies of reproducibility and intermediate precision with regards to 22 impurities of drug substances or drug products. As a general rule, authors propose the use of sound and well-established rounding rules to derive rounding from the results of the validation package.

Keywords: Rounding; Significant digits; Impurity content; Validation

1. Introduction

The number of papers related to the validation of analytical methods is absolutely enormous and reflects the huge amount of work that industrial and academic laboratories as well as regulatory agencies spend in this kind of work. Concerning the pharmaceutical domain, the guidelines of the International Conference of Harmonisation (ICH) describe the way to present data in the pharmaceutical dossier aimed to be submitted to health authorities. These regulations are applicable in the three regions belonging to the ICH process, Europe, Japan and United States, but are also accepted in other countries. ICH guidelines Q2A and Q2B describe definitions [1] and methodology [2] of analytical validations, respectively. According to the key definition of Q2A, "the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose". Thresholds for reporting, identification and toxicological qualification of impurities are defined in ICH guidelines Q3A [3] and Q3B [4], covering drug substances and drug products, respectively. First of all, the *intended purpose* of the impurity determination is to ensure that no drug substance or drug product is released if the level of any specified impurity exceeds the specification limit assessed by toxicological and/or clinical studies or if the level of any unspecified impurity exceeds the threshold accepted by convention as the identification (in most cases 0.10%) or qualification limit (in most cases 0.15%). But the *intended purpose* is also to allow the applicant and the authorities to detect trends in the quality during manufacturing or during the storage of the products. We should expect an absolute coherence between thresholds and reporting limits introduced in the ICH impurity guidelines and data stemming from validation studies. Surprisingly, the final revision of Q3A (for the drug substance, DS) and Q3B (for the drug product, DP) states: "below 1.0%, the results should be reported to two decimal places; at and above 1.0% the results should be reported to one decimal place... the use of two decimal places for thresholds does not necessarily indicate the precision of the analytical procedure used for routine quality control purposes". This triggered by the authors the question: should not the rounding of any analytical data reflect its uncertainty? The authors of the present paper think that the quoted sentence can be understood as a "practical" compromise, but should trigger further scientific considerations

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on the relationship between analytical method performance and rounding of the final result, in order to achieve a full scientific consistency.

It is worth stressing that rounding of the final result has not only a pure scientific value, because the pharmacopoeias rule is: "round, then compare to the specification limits" [6]. According to this rule, in case of a test result of 0.21% the test does pass if the limit is "≤0.2%", whereas it does not if the limit is "≤0.20%". Rounding has therefore an impact on the final decision about the batch conformity, and not only on the numerical result.

In 2001, at the occasion of a symposium organized by the European Pharmacopoeia in Cannes, one of the authors tackled this topic but without entering into any theoretical and experimental considerations [7]. The purpose of the present paper is to support the claim made at that time and to show how the number of significant figures in reporting impurity levels can be related to the true precision of the method as assessed by validation studies. This paper has been intended as an effort to follow good scientific practices and not to design new rules: "as scientists, we are compelled to adhere to the fundamental conventions of mathematics or the chaos will be complete", as written by Bunnell [8] in one of the very rare publications dedicated to the reporting of quantitative analytical results.

It is common to find between pharmaceutical analysts rather confusing practices in assessing significant figures, but this should not be very surprising, taking into account that these simple concepts are not always taught and practised even in the academic and scientific worlds [9,10].

Results of several validation studies on impurity determination will be presented in order to show real examples of application of the rules. This paper only covers HPLC methods, that are, to a great extent, the most common analytical methods in pharmaceutical impurity determinations.

2. Theoretical considerations

Every physicochemical measurement is always affected by random error and may be affected by systematic error. Therefore, a result is fully expressed only if its uncertainty is also given. This is of course also true for the HPLC determination of impurities contained in drug substances and drug products.

As for any physical measure, forgetting the systematic error and only focusing on the random error, the impurity level I (assumed to follow a normal distribution) from p independent determinations results ($x_i(\%)$, $i = 1, \ldots, p$), obtained for any individual impurity, could normally be reported in percentage (m/m) with regard to the active substance as (1):

$$I(\%) = \bar{x}(\%) \pm \frac{s}{\sqrt{p}} t_{p-1,\alpha} \quad (1)$$

$$s^2 = \frac{\sum(\bar{x} - x_i)^2}{p-1} \quad (2a)$$

and

$$\mathrm{CV} = 100\frac{s}{\bar{x}} \quad (2b)$$

where $\bar{x}$ is the arithmetic mean value of the p independent determinations x_i; s the estimate of the standard deviation; $t_{p-1,\alpha}$ the Student parameter for $p-1$ degrees of freedom at a level of risk α (generally 0.05) and CV is the coefficient of variation (%).

The right part of the second term of Eq. (1) is the limit of error (or "confidence limit" in the statistical jargon), or, according to another terminology, the expanded uncertainty, that is the standard uncertainty (standard error in the present case) multiplied by a fixed number k [11] or an appropriate distribution coefficient (Student's t, most often). In all the discussion below, the term "uncertainty", symbolized by u, will be used to mean expanded uncertainty, because this is the definition that better complies with this concept.

In an equivalent manner, an individual impurity determination x_0 from a validated analytical method should be reported, in an equivalent manner, as:

$$x_0 \pm u \quad (3)$$

u represents the expanded uncertainty, of which a mathematical expression can be written as:

$$u = ks = k\frac{x_0 \mathrm{CV}}{100} \quad (4)$$

where k is the coverage factor; s the standard uncertainty (standard deviation) of the analytical method and CV is the precision coefficient of variation of the analytical method (s and CV are estimated in the scope of the method validation).

If the measurand is known to be normally distributed with known standard deviation, a coverage factor of $k = 3$, of common use in statistical process control [12], ensures a 99.7% confidence level. If the distribution is not known, but can be assumed as unimodal, recent developments of the Bienaymé–Tchebychev theorem (cf. Vysochanskii and Petunin [13]) enable us to propose approximate coverage factors (in general, 3 for a 95% confidence interval). These arguments will justify the use of the coverage factor of $k = 3$ throughout the manuscript.

In the common practice of the pharmaceutical analysis, we mean in general routine quality control, uncertainty is not evaluated routinely for each impurity determination; the uncertainty value obtained during validation studies is considered as the reference indicator of the precision of the method. In passing, we recall that suitability parameters have to be introduced in the QC monograph; they should support the performance of the method as assessed in the validation package. Two main arguments support the relevance of the uncertainty estimate from the validation unit. Firstly, the operating conditions (instruments performance, balances and volumetric apparatuses) are strictly controlled according to common standards. Secondly, when performed in accordance with the guidelines in force [2,5], validation studies include, as a minimum, intermediate precision and, often also, reproducibility that capture all the sources of variability (day, operators, instruments and laboratories). Two practical factors, amongst the others, have an insidious impact on method reproducibility. The first is the effect of the "integration method", that is the algorithm and the set of parameters used to integrate the chromatogram: a different threshold can lead a laboratory to systematically increase or decrease impurity peak

areas with reference to the correct values. The second factor is the chromatographic resolution, that can lead to split or merge two separate but very close peaks as a result of different column or instrument performance. For these reasons, uncertainty of the test result should be assessed not only as repeatability, but as reproducibility, or at least intermediate precision. Once uncertainty u is available, the next step is the rounding of the result in order to keep only the *significant figures*. The objective of rounding is to remove digits that do not carry any relevant information, and can therefore be misleading for the reader. At this level, rounding of experimental results should not be confused with rounding of arithmetic results operated by computers, that is done only because of the limited size of the figure representation.

At this point, it has not to be ignored that rounding is an alteration of the original value and therefore introduces a new error. If the number is rounded to the n-th decimal figure, rounding uncertainty u_r is uniformly distributed from 0 to 10^{-n}: $u_r \sim U(0, 10^{-n})$.

In consequence,

$$E(u_r) = \frac{10^{-n}}{2} \tag{5}$$

and

$$\mathrm{Var}(u_r) = \frac{(10^{-n})^2}{12}, \text{ that is to say } s_r = \frac{10^{-n}}{\sqrt{12}}. \tag{6}$$

Then, the second element to be kept in mind when rounding is that we should control the rounding uncertainty, so that it does not become too big with reference to the original uncertainty. In accordance with the law of propagation of uncertainty[1], the total uncertainty after rounding (effective standard deviation of the measurement process) is given by the following equation [14]:

$$s' = \sqrt{s^2 + \frac{(10^{-n})^2}{12}} \tag{7}$$

Provided these notations and equations, different rounding rules, commonly referenced, can be presented and discussed. To highlight the discussion, two numerical examples will be used with their corresponding u values (in both cases, given before rounding): (a) 0.34378 ± 0.02575 and (b) 2.51878 ± 0.03185.

At this point, it cannot be overemphasized that the rounding rules must be applied only after obtaining the final result, in our case the percent impurity amount.

2.1. Rounding rules

Rule 1: "round the number so that the last retained decimal digit is between $u/30$ and $u/3$".

Or, in an equivalent definition: "round so that the uncertainty is in the range 3–30 in the last two digits". This rule is very common in experimental physical chemistry and is reported in the classical textbook of Shoemaker et al. [14] even though some authors pointed out that rounding is not always correctly performed even in scientific papers [10]. A 1993 Belgian standard on sampling also adopted and justified this rule [15]. It is worth noting that Shoemaker et al. clearly stated that uncertainty should be here understood as the expanded value.

This rule can be expressed mathematically by the following inequality:

$$\frac{u}{30} \leq 10^{-n} \leq \frac{u}{3}, \quad \text{with } n \in N \tag{8}$$

By using the Eq. (4), the inequality (8) becomes:

$$\frac{ks}{30} \leq 10^{-n} \leq \frac{ks}{3}$$

or, also:

$$\frac{k\mathrm{CV}x_0}{3000} \leq 10^{-n} \leq \frac{k\mathrm{CV}x_0}{300} \tag{9}$$

It must be noted that, according to the rule, the more is the coverage factor, the less decimal figures are reported.

When using the previously advocated coverage factor of $k = 3$, a particular case of rule 1 can be drawn:

$$\frac{\mathrm{CV}x_0}{1000} \leq 10^{-n} \leq \frac{\mathrm{CV}x_0}{100} \tag{9a}$$

which is equivalent to:

$$2 - \log(\mathrm{CV}) - \log(x_0) \leq n \leq 3 - \log(\mathrm{CV}) - \log(x_0), \quad \text{with } n \in N \tag{9b}$$

This inequality can finally be expressed using the floor function (which corresponds to the integer part of the number and noted $\lfloor y \rfloor$) as:

$$n = \lfloor 3 - \log(\mathrm{CV}) - \log(x_0) \rfloor \tag{10}$$

According to Eq. (7), the increment of the uncertainty due to rounding according to rule 1 is 4.0% for $k = 3$ (case where $10^{-n} = s$).

The inequality (9b) enables us to calculate n to be introduced in the QC monograph specifications for different CV values and impurity levels x_0 (vide infra).

Rounding of numerical examples according to rule 1: (a) 0.344 ± 0.026 and (b) 2.52 ± 0.03.

Rule 2: "round the number to not greater than $\sigma/2$ and not less than $\sigma/20$ (or s, when σ is not available)".

This is the rule stated in the ASTM standard E29-02 [16]. It is worth stressing that this rule differs from the first one not only for the 2 instead of the 3 of the denominator of the limits, but also for the choice of the standard deviation instead of the expanded uncertainty as reference value.

[1] The following statistical model enables to describe the rounding process: $x_{\text{rounded}} = x_{\text{unrounded}} + 10^{-n}u_r$. Hence, one can deduce the expression of the variance of a rounding result:

$$\mathrm{Var}(x_{\text{rounded}}) = \mathrm{Var}(x_{\text{unrounded}} + 10^{-n}u_r) = \sigma^2 + \frac{10^{-2n}}{12} + 2\mathrm{Cov} \approx \sigma^2 + \frac{10^{-2n}}{12}$$

This rule can be expressed mathematically by the following inequality:

$$\frac{s}{20} \leq 10^{-n} \leq \frac{s}{2}, \quad \text{with } n \in N \tag{11a}$$

that can be rewritten:

$$\frac{\mathrm{CV}x_0}{2000} \leq 10^{-n} \leq \frac{\mathrm{CV}x_0}{200} \tag{11b}$$

In the same manner than for rule 1, n can be written as:

$$n = \lfloor 3 + \log(2) - \log(\mathrm{CV}) - \log(x_0) \rfloor = \lfloor 3.3 - \log(\mathrm{CV}) - \log(x_0) \rfloor \tag{12}$$

It can be added that rules 1 and 2 (cf. Eqs. (10) and (12)) are equivalent only with a coverage factor of $k = 1.5$. For a coverage factor of $k = 3$, rule 2 tends to give more decimal figures than rule 1; the increment of the uncertainty due to rounding is 1.0% (cf. case where $10^{-n} = s/2$).

Rounding of numerical examples according to rule 2: (a) 0.344 ± 0.008 (s) and (b) 2.519 ± 0.011 (s).

Rule 3: "round so that the uncertainty is not more than three times the last retained digit".

This rule can be expressed mathematically by the following inequality:

$$u \leq 3 \times 10^{-n} \leq 10u, \quad \text{with } n \in N \tag{13}$$

This rule may be translated in:

$$\frac{k\mathrm{CV}x_0}{300} \leq 10^{-n} \leq \frac{k\mathrm{CV}x_0}{30} \tag{14}$$

that is to say, with a coverage factor of $k = 3$:

$$n = \lfloor 2 - \log(\mathrm{CV}) - \log(x_0) \rfloor \tag{15}$$

This rule is described in the Belgian standard cited in the case of "data without uncertainty" (the authors interpret this as "with uncertainty not expressed"). This rule is also consistent with a common definition of significant digits: "in practice, it is usual to quote as significant figures all the digits which are certain, plus the first uncertain one" [17]. By rounding according to rules 1 and 2, on the contrary, "the last significant digit is largely uncertain (by 3 or more) and the next to the last may be slightly uncertain (by as much as 3)" [15]. The increment of the uncertainty due to this last rule rounding is as much as 200% (case where $10^{-n} = 10s$).

Rounding of numerical examples according to rule 3: (a) 0.34 ± 0.03 and (b) 2.52 ± 0.03.

NB: Another rule can be found in literature corresponding to rule 1 with $k = 3/5$ but it will no longer considered in this work, as leading to too much significant figures.

With these three rules in mind, the number of decimal figures to be retained in the final result can be easily computed. Table 1 reports rounding to be operated according to the stated rules as a function of the impurity level and of the coefficient of variation.

Table 1
Expression of impurity content

Number of retained decimal digits	CV (%)											
	Rule 1[a]				Rule 2[b]				Rule 3[c]			
	2.5	5	10	15	2.5	5	10	15	2.5	5	10	15
Impurity content (%)												
0.05	3	3	3	3	4	4	4	3	2	2	2	2
0.10	3	3	3	2	4	4	3	3	2	2	2	1
0.50	2	2	2	2	3	3	3	2	1	1	1	1
0.80	2	2	2	1	3	3	2	2	1	1	1	0
1.00	2	2	2	1	3	3	2	2	1	1	1	0
2.00	2	2	1	1	2	2	1	1	1	1	0	0

Retained decimal digits as a function of the impurity level and of CV according to the three examined rules. If $\bar{x}$ is the mean impurity content, CV is the coefficient of variation of the method and k is the coverage factor ($k = 3$ in the table).

[a] $n = \lfloor 3 - \log(\mathrm{CV}) - \log(x_0) \rfloor$.

[b] $n = \lfloor 3 + \log(2) - \log(\mathrm{CV}) - \log(x_0) \rfloor = \lfloor 3.3 - \log(\mathrm{CV}) - \log(x_0) \rfloor$.

[c] $n = \lfloor 2 - \log(\mathrm{CV}) - \log(x_0) \rfloor$.

3. Methods

3.1. Design

The typical study design of the inter-laboratory studies is a two fold nested design with a number S of fixed sites from 2 to 5, N random days per site (at least) and n independent replicates per day (in general, $n = 3$) as illustrated in Table 2 [18].

The repeatability, intermediate precision and reproducibility standard deviations of the analytical method can be deduced from within-day, between-day and between-laboratories variance components estimated in a two-fold nested ANOVA framework [19,20].

In the scope of this study, the reproducibility CVs (including within-day, between-day and between-laboratories variance components) have been retained as far as they capture the total method variability when used by different habilitated laboratories.

3.2. Long-term stability studies

Long-term stability data have been used for deducing estimates of intermediate precision CVs of impurity methods for DPs; the designs of those studies were in accordance with the ICH recommendations in force (at least three batches of product, assayed at time: 0, 3, 6, 9, 12, ... months).

The intermediate CVs of interest have been calculated from the residual standard deviations from the ANOCOVA model used for testing for poolability of the batches [21,22],

Table 2
Inter-laboratory study designs

Site 1 (R&D)			Site 2 (Manuf #l)			...	Site S (Manuf #S-1)		
Day 1	...	Day N	Day 1	...	Day N		Day 1	...	Day N
×		×	×		×		×		×
×		×	×		×		×		×
×		×	×		×		×		×

after verification of the absence of any lack-of-fit in the model.

All the statistical calculations (estimates of intermediate CVs) have been done using the SAS© v8.2 statistical software.

4. Results and discussion

In order to gain a realistic estimate of the precision of a typical HPLC impurity method, data were assembled from the development package of different new drug substances and drug products just before phase 3, that is just before the industrialisation phase, according to the company strategy. All results were obtained by previously validated methods, and suitability test always prescribed that the S/N ratio of a peak representing 0.05% of the content of the active substance be more than 10. A typical chromatogram is represented by Fig. 1. Pharmaceutical forms were tablets, capsules and solutions for injection with concentration varying from 1 to 400 mg/unit.

The first type of data represents the pooled intermediate precision from stability studies performed on three drug products according to ICH guidelines, then at 1, 3, 6, 12 months and over. These data include four impurities. It is authors' company strategy to collect these data before one initiates the technology transfer between R&D development and production, because they represent realistic precision data, obtained during day-to-day work for several years, and then give a better estimation of realistic acceptance criteria for analytical transfer studies than validation data. It is worth noting that the concept of intermediate precision can include quite a large range of analytical diversity, in terms of equipment, people and time, and intermediate precision data from stability studies lasting years are at the upper limits of this diversity, therefore very close to reproducibility.

The second type of data comes from inter-laboratory studies. These kinds of studies always include, in our organization, the development laboratory responsible for development and validation of the method and usually also the development stability studies, and the QC laboratory of the receiving production site. According to this scheme, inter-laboratory studies have two goals: the evaluation of robust value of the reproducibility and the demonstration that the receiving site (generally, the industrial QC laboratory) is able to reproduce the performance of the HPLC method as obtained during the validation. At the end of the study, the conformity to acceptance criteria ensures that the receiving laboratories operate with equivalent performances to those of the emitter laboratory, in particular with regard to previously highlighted integration and resolution challenges. This last point is an important prerequisite in the context of this work.

Data includes six drug substances and nine drug products, for a total number of 22 impurities. Tables 3 and 4 show the results of the studies.

Data include impurity levels between 0.06 and 0.76%, with precision, expressed as CV in percent, between 3.06 and 28.00%. Lower levels are more populated than higher ones are, but this reflects the need of the highest possible quality of the active substances.

One evident remark is that there is no strong relationship between precision and impurity content level ($r = -0.1$ between level and CV), and this confirms that often very good precision can be obtained by modern instruments at levels lying between 0.05 and 2.00% (or more) and corresponding to what is found in general for classical chemical entities. It is worth stressing here again that CV values represent reproducibility or intermediate precision acquired on long time intervals and not simply repeatability values.

Precision data were then used to obtain the correct number of decimal digits to be retained in the result. The authors chose rounding rule 1 just because as the most assessed in physical chemistry and because they think that the added uncertainty due to rounding is still acceptable, as lower than 5%. Rule 2 would lead of course to retain more digits. Conversely, rule 3 would produce to too few decimal figures and, in consequence, to an unacceptable erosion of the precision of the report results, itself meaning increased risks of incorrect decisions (customer and producer risks). Fig. 2 shows the distribution of the

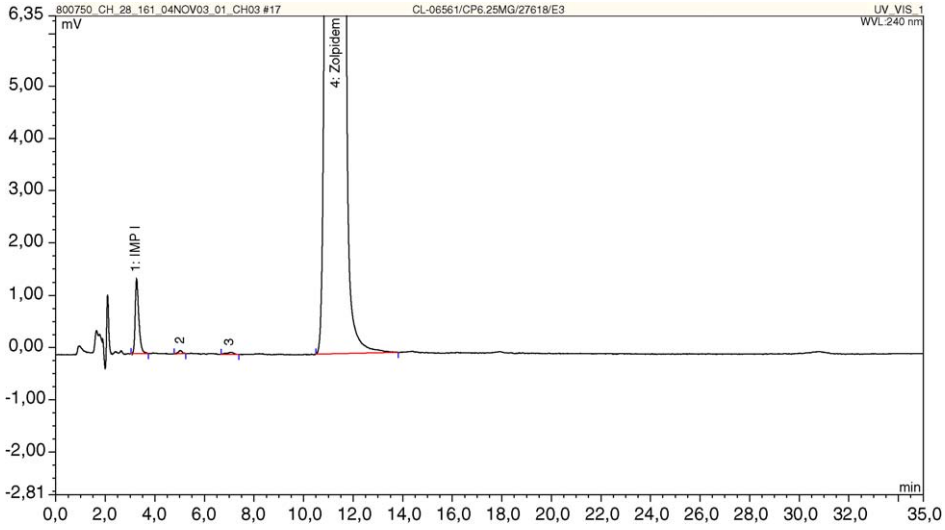

Fig. 1. Typical chromatogram of an impurity test.

Table 3
Results on precision of impurity assay methods in the drug substance

Method	Impurity	Impurity amount[a] (%)	Standard uncertainty (S.D., %)	Relative uncertainty[b] (CV, %)	Comments
DS-A	Imp. DS-A1	0.49	0.06	11.94	All opposite CVs are reproducibility from inter-laboratory studies
DS-B	Imp. DS-B1	0.28	0.02	8.95	
	Imp. DS-B2	0.18	0.02	11.32	
DS-C	Imp. DS-C1	0.50	0.04	7.66	
	Imp. DS-C2	0.76	0.04	4.90	
	Imp. DS-C3	0.41	0.04	10.24	
DS-D	Imp. DS-D1	0.20	0.01	6.03	
	Imp. DS-D2	0.20	0.01	5.87	
DS-E	Imp. DS-E1	0.19	0.02	8.90	
DS-F	Imp. DS-F1	0.278	0.009	3.06	

[a] Impurity amounts and S.D.s have been rounded according to rule 1.
[b] CVs have been conventionally rounded to two decimal places.

Table 4
Results on precision of impurity assay methods in the drug product

Method	Impurity	Impurity amount[a] (%)	Standard uncertainty (S.D., %)	Relative uncertainty[b] (CV, %)	Comments
DP-A	Imp. DP-A1	0.40	0.02	6.00	All opposite CVs are intermediate precision from stability studies
	Imp. DP-A2	0.31	0.03	8.59	
DP-B	Imp. DP-B1	0.16	0.01	7.51	
DP-C	Imp. DP-C1	0.063	0.006	9.18	
DP-D	Imp. DP-D1	0.50	0.04	7.66	All opposite CVs are reproducibility from inter-laboratory studies
	Imp. DP-D2	0.76	0.05	6.50	
	Imp. DP-D3	0.41	0.04	10.24	
DP-E	Imp. DP-E1	0.20	0.02	8.83	
DP-F	Imp. DP-F1	0.177	0.007	3.85	
DP-G	Imp. DP-G1	0.116	0.007	5.73	
DP-H	Imp. DP-H1	0.20	0.02	12.42	
DP-I	Imp. DP-I1	0.184	0.007	4.02	

[a] Impurity amounts have been rounded according to rule 1.
[b] CVs have been conventionally rounded to two decimal places.

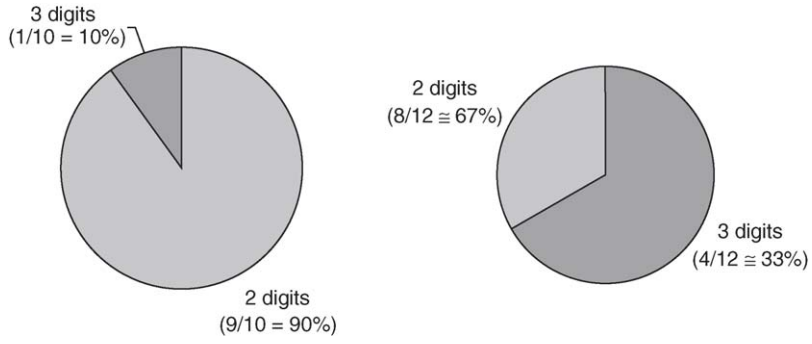

Fig. 2. Number of retained decimal figures to be applied to results of the validated methods according to rule 1. Left: drug substances data. Right: drug products data.

number of decimal digits to be retained in the cases shown in Tables 3 and 4.

5. Conclusions

In physical chemistry, the number of significant digits should be obtained case-by-case taking into account the result and its uncertainty. According to the compendial rules [6], the result of a test should be expressed with the same number of decimal digits as the specification limits; which means, as unfortunately not sufficiently said, that the number of decimal digits reported in specifications are supposed to reflect precision. Case-by-case does not mean, in pharmaceutical quality control, analysis-per-analysis, but method-by-method, after validation.

Technology transfer should of course ensure that the receiving laboratories work with the same performance shown during validation. Rounding is therefore part of the important job represented by specification setting during development [7]. Too many digits not only gives a misleading impression of precision, but also increases the risk to reject good batches, and, in the opposite sense, too little digits means the risk to accept bad batches.

Procedures to be used for choosing how to round results, in particular for impurity tests, have been presented. Data show that for most studies, rounding to two decimal figures, as prescribed by ICH guidelines, is statistically sound, not irrespective to, but taking into account validation data.

In some cases three figures could also be given: this could be not useful for the routine reporting, but useful for the use of analytical results in further calculation, such as control charts or stability trend evaluation. Now, regarding the total impurity content, it is important to remind oneself that the sum has to be performed on the non-rounded individual values, the rounding on the content taking place just at the end of the calculation. Furthermore, the number of significant figures retained for the sum is not more than the last significant digit of any datum (this is also true for the mean).

This being said, it is important to note that one of the goals of this publication was to show that the impurity acceptance criteria, finally set up in the QC monograph, should definitely be based on the actual results obtained from the analytical validation and not systematically implemented whatever the actually demonstrated reproducibility (as we may have the impression when examining pharmacopoeia monographs). On the contrary, if, as it can be the case for analytical methods using delicate extraction, or for low UV responding impurities, etc., we get a poorer CV, we can very easily justify a report with less significant figures on reckoning on the data shown in Table 1.

Analytical validations are time consuming. We can expect, at least, that they are performed not for complying to some regulatory requirements but first of all to produce a sound rationale for setting up specifications. Finally, we would like to stress that the approach developed here is very general and can be applied to any kind of physical measurements.

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