White paper

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Minimum sample weight, USP <41>, OIML R 76, EURAMET cg-18, process accuracy, safety factor, relative measurement uncertainty

Minimum sample weights according to USP <41>, OIML R 76 and EURAMET cg-18

What should a sample weigh at least to obtain a reliable weighing result?

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Abstract

The smaller the weight of the sample, the larger the relative measurement uncertainty that the weighing is subject to. There are various concepts for specifying corresponding minimum sample weights so as not to exceed a specified relative measurement uncertainty.

Likely the most well-known concepts are those of the "United States Pharmacopeia", the "OIML R 76" and the "EURAMET Calibration Guide No. 18". These will be explained and compared with each other in the following. In addition, typical minimum sample weight values are listed for different Sartorius balance models.

The concept of minimum sample weight and specific implementations according to USP <41>, OIML R 76 and EURAMET cg-18.

Every balance has (at least) one weighing range from 0 to the maximum load Max with a scale interval *d*.
For a typical precision laboratory balance (Secura224-1S), for example, Max = 220 g and *d* = 0.1 mg.

Each measured value is subject to a measurement uncertainty, regardless of where it is taken in the weighing range. The measurement uncertainty is a parameter for identifying the value range, within which the true value of the measured variable lies. The uncertainty contribution is typically composed of two parts – a constant part that is independent of the measured value, and a part that increases with the size of the measured variable.
When roughly considered, the measurement uncertainty contribution, however, is at least in the order of magnitude of the display resolution, i.e. the scale interval *d*.

If you consider the uncertainty contribution in relation to the size of the sample weight, it is negligibly small in relation to a large sample weight – for example an assumed uncertainty of 0.1 mg for a sample weight of 100 g, results in a relative measurement uncertainty of 0.0001 % for the aforementioned Secura224-1S. However, the same (absolute) uncertainty contribution for a small sample weight of 1 mg corresponds to a relative uncertainty of 10 %.

Since very small sample weights are inevitably subject to large relative uncertainties, it makes sense to determine a so-called minimum sample weight, which ensures that no sample weights are taken for which a certain relative measurement uncertainty is exceeded.

Different regulations for different areas | applications govern different definitions of what is considered an acceptable relative measurement uncertainty and how the minimum sample weight is determined as a result. Likely the most well-known concepts are those of the **"United States Pharmacopeia"** (1), which is used in the pharmaceutical industry, the **"OIML R 76"** (2) for balances subject to legal metrology and the **"EURAMET Calibration Guide No. 18“** (3). These three concepts and the resulting (typical) values for minimum sample weights will be explained in more detail below.

However, minimum sample weights are always defined for net values in all three concepts. It is therefore not permitted to fall below these values due to differential weighing with a larger tare load.

Specific example: For a balance with a minimum sample weight of 1 g, it is not permitted to weigh an amount of 0.5 g substance in a vessel with a mass of 50 g in order to consider the difference between the weight of the empty vessel and the vessel including the substance (50.5 g – 50.0 g = 0.5 g) as a valid weighing value.

Figure 1: Weighing smallest amounts of substances on a microbalance.

Minimum sample weight according to OIML R 76 for legal metrology

The document "OIML R 76-1:2006" (2) is formally only a recommendation, but was adopted by many states and regions unchanged to determine requirements for balances which are subject to legal metrology. In Europe, for example, due to directive 2014/31/EU (4) (implemented in the member states in the form of the harmonised standard EN 45501 (5)), in the US in "Handbook 44" (6) and in China by "GB/T 23111" (7).

In all of these requirements, non-automatic weighing instruments are divided into accuracy classes, from which (taking the scale interval *d* of the balance and the number of verification scale intervals *n* into consideration) the minimum sample weight is calculated according to table 1.

The minimum sample weight is therefore determined according to OIML R 76 based on the accuracy class and the scale interval – it therefore does not have to be individually determined at the balance's installation location by means of a measurement. The minimum load is shown for balances that have an approval according to OIML R 76 on | in the display and on the identification plate. For an example, see fig. 2.

The minimum sample weight according to OIML R 76 is only defined for models that are approved for measurements in the context of legal metrology. However, it is not defined for devices without a type approval.

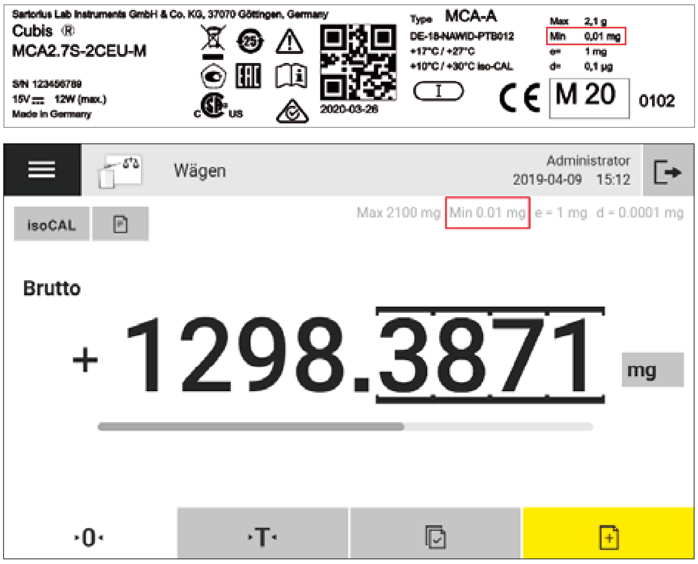

Figure 2: Specification of the minimum sample weight according to OIML R 76 on the identification plate (top) and in the display (bottom) of an MCA2.7S-2CEU-M. The minimum sample weight for this model is 0.01 mg (marked in red).

Since the minimum sample weight according to OIML R 76 is not dependent on current measured values, sample weights above this value may be taken for legally regulated applications if the balance complies with legally prescribed error limits.

The overview "Smallest possible and typical values for minimum sample weights according to USP <41>, OIML R 76 and EURAMET cg-18" lists the values for common Sartorius balance models. They must be complied with for all measurements subject to legal monitoring according to the respective legal requirements.

Accuracy class	Verification scale interval *e*	Number of verification steps *n* = Max/*e*	minimum load Min
I Special accuracy	0.001 g ≤ *e*	50 000 ≤ *n*[1]	100 · *d*
II High accuracy	0.001 g ≤ *e* ≤ 0.05 g 0.1 g ≤ *e*	100 ≤ *n* ≤ 100 000 5 000 ≤ *n* ≤ 100 000	20 · *d* 50 · *d*
III Medium accuracy	0.1 g ≤ *e* ≤ 2 g 5 g ≤ *e*	100 ≤ *n* ≤ 10 000 500 ≤ *n* ≤ 10 000	20 · *d* 50 · *d*
IIII Ordinary accuracy	5 g ≤ *e*	100 ≤ *n* ≤ 1 000	10 · *d*

Table 1: Minimum load depending on the accuracy class and the actual scale interval according to OIML R 76-1:2006.

[1] For balances with *d* < 0.1 mg, *n* may be < 50 000.

Minimum sample weight according to USP, chapter <41>

The "United States Pharmacopeia" (USP) is the official pharmacopoeia of the United States of America, which is published annually with two supplements by the United States Pharmacopeia Convention, a scientific and non-governmental organisation. The USP standards for pharmaceuticals are applied in more than 140 countries and are enforced in the United States by the Food and Drug Administration (FDA).

The USP places strict requirements on balances that are used for exact weighing in order to reduce faulty analyses in pharmaceutical processes to an acceptable and negligible level. These requirements are binding and are set out in USP chapter <41> on the topic of "Balances".

Specifically, the following requirements are placed on balances:

- Balances must be calibrated throughout the operational range
- Balances must meet the defined requirements for accuracy and repeatability

Calibration

The USP requires that the balance must be calibrated. Sartorius recommends having periodical calibrations performed with traceability of the measurement results to the national standard.

Accuracy

The accuracy requirement is a general requirement, i.e. if the requirement for accuracy is not met, the balance in its current state is not suitable for the accurate weighing of substances to be weighed. The accuracy test is used to determine the balance's systematic errors, which may not be greater than 0.10 % according to the USP requirements.

Repeatability and minimum sample weight

The requirement for repeatability restricts the weighing range to a working range usable for the corresponding purposes in the form of a minimum sample weight. The minimum sample weight is calculated from the standard deviation *s* of a repeatability measurement with at least 10 repetitions according to:

$$m_{\text{min, USP}} = \begin{cases} 2\,000 \cdot s & \text{if } s \geq 0.41 \cdot d \\ 2\,000 \cdot 0.41 \cdot d & \text{otherwise} \end{cases}$$

The minimum sample weight according to USP is therefore determined pragmatically so that any sample weights are larger than random deviations by a factor of 2 000 (or than its standard deviation, to be mathematically correct). The second line in the formula above only limits this to a minimum value of $2\,000 \cdot 0.41 \cdot d = 820 \cdot d$, as otherwise a measured standard deviation of $s = 0$ g would result in a minimum sample weight of $m_{\text{min,USP}} = 0$ g.

The minimum sample weight according to USP, chapter <41>, therefore not only takes the characteristics of the balance in the form of the scale interval *d*, but also the actual condition or ambient conditions in the form of the standard deviation of the repeatability measurement. The minimum sample weight can therefore reasonably be determined only at the balance's site of use and should be repeated if there is a change to the installation location. Even under ideal conditions, the minimum sample weight according to chapter <41> USP is always at least $820 \cdot d$ – this value must never be fallen short of.

The overview "Minimum and typical values for minimum sample weights according to USP <41>, OIML R 76 and EURAMET cg-18" lists realistically achievable values for common Sartorius balance models – provided the installation conditions are good.

Remark: It is generally not recommended to repeatedly adapt the current working range to the minimum sample weight value resulting from the last repeatability measurement – since the standard deviation is a statistical variable, it can always vary slightly from measurement to measurement. So if users get obtain a standard deviation of, for example, if users get the standard deviation of, for example, $s = 5$ µg from a repeatability measurement, set the minimum sample weight for their balance accordingly to $2\,000 \cdot s = 10$ mg, and then weigh samples down to this value, they risk that at the next repeatability measurement $s = 8$ µg is obtained, and therefore a minimum sample weight of $2\,000 \cdot s = 16$ mg results.

In this case, it would now be questionable whether past sample weights between 10 mg and 16 mg met the USP requirements. We therefore recommend defining a "desired minimum sample weight" for each balance, which is reliably adhered to – checking the balance according to USP then ensures that the actual minimum sample weight is smaller than the defined one. The permissible minimum sample weight should be visibly marked on balances that are used under USP provisions. Some Sartorius balances permit the minimum sample weight to be specified in the service menu. Net sample weights below the minimum sample weight can therefore not be made (see section regarding the SQmin function).

Minimum sample weight according to EURAMET Calibration Guide No. 18

The "Calibration Guide No. 18" (in the following "cg-18" for short) is a calibration guideline for non-automatic weighing instruments published by EURAMET (the European Association of National Metrology Institutes) (see (10)). Unlike the two preceding sections, the cg-18 is not obligatory. However, it is a very comprehensive consideration of the topic of "Calibrating balances" and, above all, the associated uncertainty calculation. Its global acceptance by accreditation bodies, specialists and users continues to grow.

The biggest difference from the concepts of both preceding sections is that cg-18 takes the user's process requirements into consideration. In many countries, Sartorius issues accredited or non-accredited calibration certificates according to cg-18, which also specify the "Uncertainty in use", i.e. the measurement uncertainty for the user, in the form of a linear equation.

A typical "Uncertainty in use" for a typical laboratory balance (Secura224-1S) on a calibration certificate can, for example, look like this:

Uncertainty of the weighing result $U_{gl}(W)$:
$U_{gl}(W) = 0.00024\ g + 3.88 \cdot 10^{-6} \cdot R$

This equation makes it possible to calculate the expanded measurement uncertainty $U_{gl}(W)$ for each weighed value R within the weighing range.

Expressed in absolute terms, this therefore results in uncertainties between

$U_{gl}(0) = 0.00024\ g + 3.88 \cdot 10^{-6} \cdot 0\ g = 0.00024\ g$

and

$U_{gl}(Max) = 0.00024\ g + 3.88 \cdot 10^{-6} \cdot 220\ g = 0.0011\ g.$

Expressed in relative terms, this uncertainty is negligible again at high loads (at Max: 0.0011 g/220 g = 0.0005 %), but increases at small loads (at the minimal load d = 0.0001 g: 0.00024 g/0.0001 g = 240 %).

The concept of the minimum sample weight as per EURAMET cg-18 now provides that the user sets the maximum relative measurement uncertainty – for example, 1 %. With a relatively simple calculation it can then be seen that the sample weight must always be at least 0.0242 g (also see the dotted lines in fig. 3) – at this load, the relative measurement uncertainty is exactly the required 1 %; at higher loads, the relative measurement uncertainty is lower, and at smaller loads it is higher.

In many application areas, it is further common practice to include an additional safety factor (SF) that is used to multiply the measurement uncertainty. If the user selects, for example, a safety factor of SF = 2, this corresponds to a multiplication of the above equation for $U_{gl}(W)$ by 2.

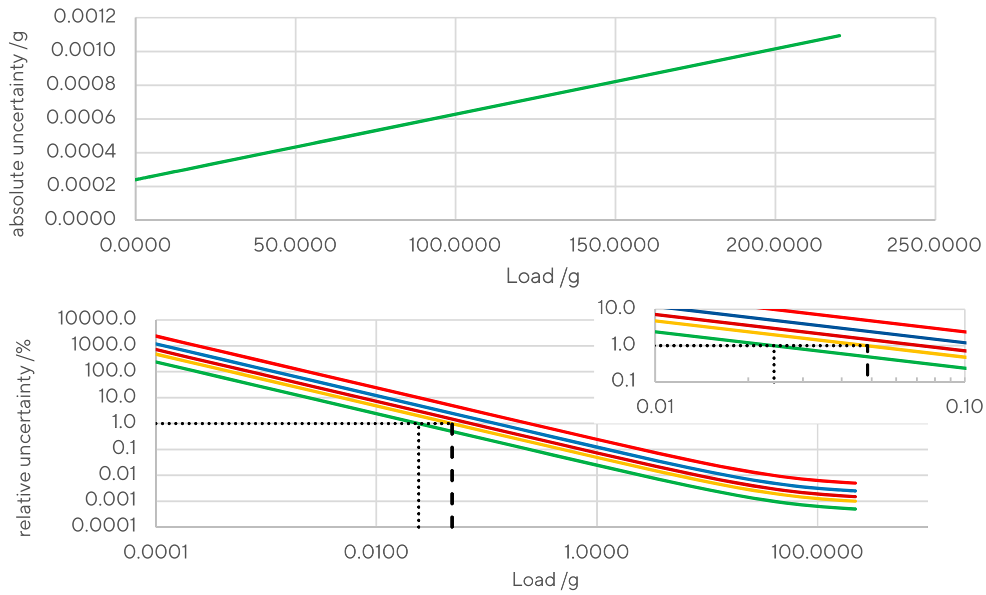

Figure 3: Example of absolute (top) and corresponding relative (bottom, green line) uncertainty according to EURAMET cg-18 for a laboratory balance Secura224-1S. In the diagram below, additional lines are entered, which result from multiplication with a safety factor of 2 (orange), 3 (dark red), 5 (blue) or 10 (light red). The determination of a minimum sample weight described in the text is represented by black lines. The additional small diagram is an enlarged section.

The relative measurement uncertainty multiplied by such a safety factor is then generally referred to as the process accuracy. According to the safety factor, more must be weighed to always remain above the required accuracy. In the example of a required process accuracy of 1 % with a safety factor of 2, namely 0.0485 g (dotted line in fig. 3). Please note: Even if in this example, the safety factor of 2 almost exactly doubles the value for the minimum sample weight, it is not always the case that the safety factor is directly proportional.

Remark: As with the minimum sample weight as per USP, chapter <41> for the minimum sample weight according to EURAMET cg-18, we also recommend setting the actual minimum sample weight for your processes somewhat higher. If in the example above (1 %, SF = 1, Min_{cg18} = 0.0242 g = 24.2 mg) it is set to 25 mg, for example, there would be the risk that this is higher the next time the minimum sample weight is determined according to EURAMET cg-18, for example due to somewhat poorer measurement results.

Determination of the process accuracy and the safety factor under Euramet cg-18

The freedom to be able to set the process accuracy and safety factor for determining the minimum sample weight makes some users unsure and has them ask what values are suitable. In general, users must decide this for themselves in line with the requirements of their processes. However, there are of course some basic recommendations for this that should be followed:

It should first be checked whether there are specifications in regulations, directives, etc. for the specific application. While a specific specification for balances is very rare, there are general specifications for process accuracies and safety factors for all types of measuring equipment in some directives.

In addition, the values for process accuracy and the safety factor should be adjusted to your own requirements and the specifications of the process and general logic. For example, it does not make sense to set a process accuracy of 0.1 % if work instructions specify that sample weights may deviate from the set point by up to 1 %. It also does not make sense to set such a strict process accuracy if, for example, the mass of a substance to be determined has a mass concentration in the sample which is only known with 5 % accuracy.

For the **safety factor** in particular, additional considerations can be made as to what exactly should be achieved with this additional safety:

For very special applications, uncertainty contributions may be relevant, which (cannot be) are not taken into consideration in the uncertainty in use determined as part of calibration as per cg-18 – for example creep and hysteresis effects can occur during very long weighing processes. If determining these contributions is very complex or is not possible, they can pragmatically be "covered" by a safety factor.

A safety factor >1 may also be useful for compensating for the fact that the balance may be operated in poorer conditions (e.g. rain when weighing outdoors, balances under fume cupboard...) than those under which it was calibrated. We generally recommend calibrating under "realistic" ambient conditions, but this is not always possible – even then, it also makes sense to "cover" these worse conditions with a safety factor.

Another way to sensibly determine the safety factor comes from the "confidence level": By convention, uncertainties are specified with a confidence level of 95.45 % – which means that the true value lies in the interval [measured value – uncertainty ... measured value + uncertainty] with a probability of 95.45 %. With a safety factor of 1.5, this confidence level can be increased to 99.73 % and even to 99.99 % with a safety factor of 2 – This is illustrated by fig. 4.

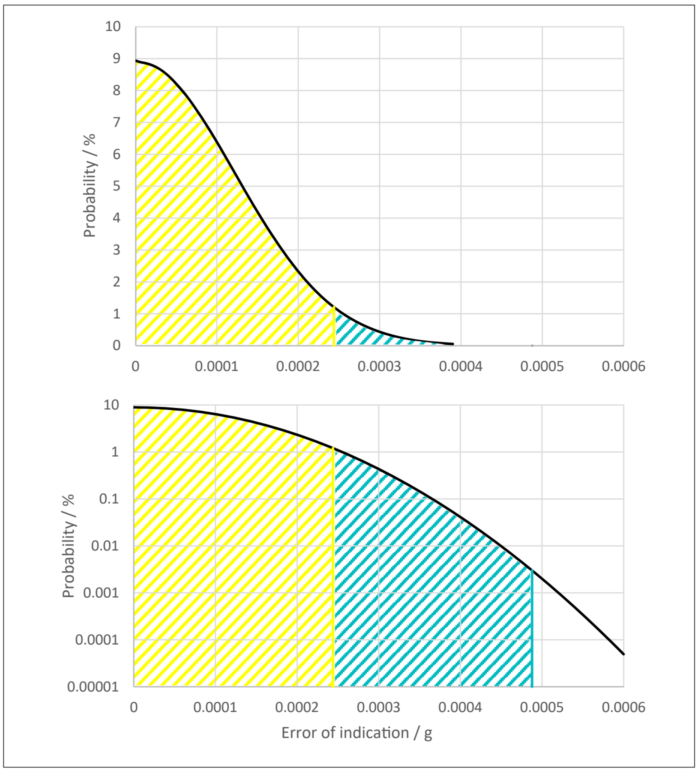

Figure 4: Probability for a determined error of indication, calculated for an example. If the specified expanded uncertainty is taken, "only" 95.45 % of all cases are covered (area shaded in yellow). If the specified uncertainty is multiplied by a safety factor of 2, 99.99 % of all cases are covered (area shaded in yellow + area shaded in cyan).

What does Sartorius offer with respect to the minimum sample weight?

Minimum sample weight according to OIML R 76 for legal metrology
The minimum sample weight according to OIML R 76 is determined for each balance model; in other words, it is not dependent on ambient conditions or measurement results, and therefore is permanently printed on the identification plate or is permanently visible in or on the display.
However, users must ensure that the balance complies with the permissible error limits at any time, i.e. also between any legally prescribed (re)verifications. For this purpose, Sartorius Service offers corresponding reports in many countries, which document that the balance complies with the legally permissible error limits and that weighing down to the specified minimum load is also permitted.
For this purpose, also see the corresponding white paper of this series (8).

Minimum sample weight according to USP, chapter <41>
In many countries, Sartorius Service offers the minimum sample weight to be determined according to USP, chapter <41>, with a so-called "USP certificate" as corresponding professional documentation for the user's quality management documents.

For Sartorius Cubis® balances, there is still the "USP Advanced" Q-app, available via the corresponding app center, which allows the users themselves to determine the working range according to USP, chapter <41>. The optimal working range is automatically evaluated here. The documentation of the check can occur on a connected Sartorius printer and|or via the network based on Q-Web via HTML visualisation. For this purpose, also see the corresponding white paper of this series (9).

Minimum sample weight according to EURAMET Calibration Guide No. 18
When calibrating according to EURAMET cg-18, Sartorius Service offers an optional minimum sample weight certificate in addition to the calibration certificate. The minimum sample weights for different process accuracies and safety factors can be easily and clearly read from a table in this certificate. For this purpose, also see the corresponding white paper of this series (10).

SQmin function with Sartorius premium balances
The premium balance series from Sartorius (Cubis®, Secura®, Cubis® II etc.) have the SQmin function to monitor the compliance of a minimum sample weight in the weighing process. With this function, a Sartorius technician can store a value for a minimum sample weight in the scales, so that the user is visually informed when the function is activated if the weighed value is below this minimum sample weight. This function is primarily intended for a minimum sample weight according to chapter <41> of the USP – but, of course, at the request of the user, the service technician can also save a value for a minimum sample weight that has been otherwise determined.

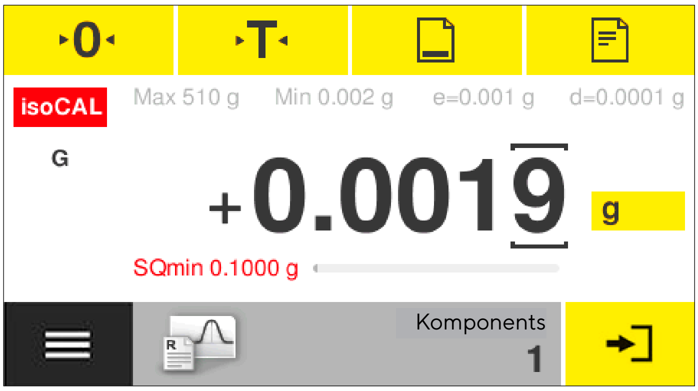

Figure 5: Display of a Secura524-1S with switched on SQmin function. If the value that has been determined based on the USP and stored by Sartorius Service of, in this case, 0.1 g is not reached, the indication of the minimum sample weight lights up in red. With a correspondingly set higher security level, the weighing result is also identified as "not valid" by the exclamation mark and | or the result cannot be expressed or printed.

Literature

1. United States Pharmacopeia and National Formulary (USP 43-NF 38); 2019.
2. OIML R 76-1 Edition 2006 (E). "Non-automatic weighing instruments. Part 1: Metrological and technical requirements – Tests".
3. EURAMET Calibration Guide No. 18, Version 4.0. "Guidelines on the Calibration of Non-Automatic Weighing Instruments" (11|2015).
4. Directive 2014/31/EU of the European Parliament and the Council from 26 February 2014 for harmonising the legal requirements of the member states regarding the provision of non-automatic weighing instruments on the market.
5. EN 45501:2016; Metrological aspects of non-automatic weighing instruments.
6. NIST Handbook 44 Specifications, Tolerances, and Other Technical Requirements for Weighing and Measuring Device, 2020.
7. GB/T 23111-2008 Non-automatic weighing instrument.
8. Sartorius white paper:
   Working in legal metrology (use and examination of laboratory balances in the legally regulated environment), 2020.
9. Sartorius white paper:
   Weighing in a pharmaceutically regulated environment (chapter <41> and <1251> of the US pharmacopeia as well as chapter 2.1.7 of the EU pharmacopeia), 2020 (planned).
10. Sartorius white paper:
   Calibration guideline EURAMET cg-18 for electronic, non-automatic balances (specifications, options and implementation of the guideline by Sartorius), 2020 (planned)

Sartorius recommendation

- Check which minimum sample weight concept applies to your balance | your application.
- If you have the minimum sample weight determined according to EURAMET cg-18, check whether specifications regarding process accuracy and the safety factor apply to your applications. Otherwise select these values according to the recommendations mentioned in the text.
- Determine a minimum sample weight that is also adhered to with the following provisions and have it checked regularly.

This white paper is part of the white paper series "Best Practice Guide: Lab Weighing". To be able to dynamically add updates and corrections and at the same time giving users as clear a reference as possible, for example in their QM documentation, versions are provided.

Version history

Version	Date	Changes
1.0	July 2020	Initial version

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Smallest possible, typical and recommended values for minimum net weights according to OIML R76 I USP <41> I EURAMET cg-18

Smallest possible and typical values for minimum net weights for some models of the Cubis® II series.
The values can be used as good approximations for models of other series as well, when they comprise the same metrological characteristics (Max and *d*).

The following table is functional - in the pdf version, values for the process accuracy and the safety factor can be entered and the respective values in the table will change accordingly.

	Min$_{R76}$	Min$_{USP41}$			Min$_{cg18}$ (Process accuracy: 1.0 %; Safety factor: 3.0)		
		smallest possible	typical**	recommended***	smallest possible	typical**	recommended***
MCA2.7S	10 µg*	82 µg	300 µg	1 mg	24 µg	143 µg	309 µg
MCA3.6P	100 µg*	820 µg	1 mg	2.5 mg	240 µg	484 µg	928 µg
MCA6.6S	100 µg*	820 µg	1 mg	2.5 mg	240 µg	546 µg	1237 µg
MCA125P	1 mg*	8.2 mg	13 mg	20 mg	2.4 mg	5.1 mg	9.1 mg
MCA125S	1 mg*	8.2 mg	13 mg	20 mg	2.4 mg	5.6 mg	12.0 mg
MCA225P	1 mg*	8.2 mg	13 mg	20 mg	2.4 mg	4.7 mg	9.0 mg
MCA225S	1 mg*	8.2 mg	13 mg	20 mg	2.4 mg	6.7 mg	18.1 mg
MCA124S	10 mg*	82 mg	100 mg	300 mg	24 mg	38 mg	60 mg
MCA224S	10 mg*	82 mg	100 mg	300 mg	24 mg	38 mg	60 mg
MCA324P	10 mg*	82 mg	100 mg	300 mg	24 mg	39 mg	60 mg
MCA324S	10 mg*	82 mg	100 mg	300 mg	24 mg	41 mg	60 mg
MCA524P	10 mg*	82 mg	100 mg	300 mg	24 mg	39 mg	60 mg
MCA524S	10 mg*	82 mg	100 mg	300 mg	24 mg	41 mg	60 mg
MCA1203S	0.1 g*	820 mg	1 g	3 g	240 mg	385 mg	604 mg
MCA2203P	0.1 g*	820 mg	1 g	3 g	240 mg	437 mg	607 mg
MCA2203S	0.1 g*	820 mg	1 g	3 g	240 mg	391 mg	603 mg
MCA3203S	0.1 g*	820 mg	1 g	3 g	240 mg	406 mg	602 mg
MCA5203P	0.1 g*	820 mg	1 g	3 g	240 mg	391 mg	602 mg
MCA5203S	0.1 g*	820 mg	1 g	3 g	240 mg	454 mg	602 mg
MCA5202S	1 g*	8.2 g	8.2 g	15 g	2 g	4 g	6 g
MCA10202S	1 g*	8.2 g	8.2 g	15 g	2 g	4 g	6 g
MCA14202P	1 g*	8.2 g	8.2 g	15 g	2 g	4 g	5 g
MCA14202S	1 g*	8.2 g	8.2 g	15 g	2 g	4 g	8 g

*Note: The minimum net weight according to OIML R76 is only defined for devices that are approved for legal applications - for all other devices, this value is neither defined nor relevant.

**The typical values do not represent a guarantee of properties. They correspond to the mean value from a sufficiently large number of measurements.

***The recommended values do not represent a guarantee of properties. They correspond to the value that is met in 90 % of a sufficiently large number of measurements.