



# The Value of Pharmacopeial Reference Standards

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**The US Pharmacopeia and other major pharmacopoeias have established that only the combination of documentary standards and pharmacopeial reference standards (RS) is conclusive and determines compliance to their official quality requirements. Therefore, the use of non-pharmacopeial RS with pharmacopeial methods is inconclusive, and the user takes responsibility at their own risk. Secondary RS are often used for qualitative and quantitative purposes. This article provides an overview of the key risks that can be associated with the use of secondary RS based on the measurement uncertainties that are intrinsically connected to the approach, and information that might help mitigate these risks to some extent. Case study examples are included to illustrate scientific challenges associated when transitioning from pharmacopeial RS to secondary RS. The guard band principle is discussed as an evocative way to visualize risk.**

To ensure the safety and efficacy of APIs and their finished dosage forms, these pharmaceutical articles need to be of a certain quality. The US Pharmacopeia (USP) and other pharmacopoeias establish public compendial standards to ensure quality requirements. Such compendial standards and their revisions are established in a transparent process. These standards are of high relevance, as they help facilitate access to affordable medicines (1), and they almost always have official status. At the same time, they are of high value to the pharmaceutical industry because they also decrease the development effort of pharmaceutical articles (2). The value of compendial standards is also described in a recent white paper authored by the World Health Organization International Meeting of World Pharmacopoeias (3).

Typically, a compendial standard is a combination of a documentary standard, such as a monograph or general chapter, and an associated physical reference standard (RS). These pharmacopeial RS are primary RS and are established by a rugged collaborative testing approach; they have official status when connected to compendial documentary standards (4) and are, therefore, generally accepted by regulatory authorities without additional qualification by users. When assessing the compliance of a pharmaceutical article against the official compendial standard, only the combination of documentary standard and pharmacopeial RS is conclusive. For example, the *European Pharmacopoeia (Ph. Eur.)* general text 5.12 states that (5):

“A *Ph. Eur.* reference standard referred to in a monograph or general chapter represents the official standard that is alone authoritative in case of doubt or dispute.”

The *United States Pharmacopeia (USP)* General Notices under 5.80 points out that (6):

“Where *USP* or *NF [National Formulary]* tests or assays call for the use of a *USP* Reference Standard, only those results obtained using the specified *USP* Reference Standard are conclusive.”

Consequently, the use of other (i.e., unofficial) RS in combination with a documentary standard is not conclusive or authoritative. The release or compliance assessment of a pharmaceutical article based on such a combination is the responsibility of the users and is their risk alone, which would also

apply when secondary RS are used, even if they were derived by comparison with the corresponding pharmacopeial RS.

The purpose of this article is to provide case study examples to illustrate scientific challenges associated with transitioning from pharmacopeial RS to secondary RS. This topic is approached from the perspective of measurement uncertainties that are connected to reportable values obtained using compendial standards and how this might change when transitioning from pharmacopeial RS to secondary RS. Calculations for measurement uncertainties for the use of compendial standards are provided in the Methods section, and information on the challenges of transitioning from pharmacopeial to secondary RS are provided in the Discussion section. Only uncertainties for characterization of the pharmacopeial and secondary RS and assay result of substance tested will be discussed in this article. There are other contributions to uncertainties that may influence a measurement, such as contributions for the RS from homogeneity and long-term stability (7), but these are not considered in this paper.

The authors are aware that the calculations performed here are beyond most users for technical reasons. Uncertainties for pharmacopeial RS are not provided, as it is unnecessary for their official use in the monograph. Pharmacopeial RS are not tailored to assign assay values to secondary RS or to set up a traceability relation between them, as these are non-compendial applications. Therefore, it is difficult for users to assess the impact that the switch from pharmacopeial RS to secondary RS would have on the acceptance criteria. This limitation has been clearly pointed out to the pharmaceutical community (8). Nonetheless, the impact on acceptance and rejection zones can be visualized by this approach in an evocative way.

## METHODS

The authors examined several USP RS and their relevant data for the calculation of the assigned value. The following exemplary cases illustrate the differences between two types of models used for the calculation of the assay value of the primary RS:

- Type 1 follows a model where all impurities were determined on a percent weight-per-weight (w/w) basis and simply subtracted from 100%(w/w).
- Type 2 follows a model where the chromatographic impurities were considered as relative percentages. Every other contribution (e.g., water, residue on ignition [ROI]) was considered as w/w percentages, to be subtracted from 100%(w/w) before multiplying with the chromatographic purity.

A real compendial RS was selected to represent each type. For confidentiality reasons, they are referred to in this paper as Surrogatine Hydrochloride (HCl) RS for type 1 and Replaceam RS for type 2.

The assay value of the substance tested (ST) is calculated as shown in **Equation 1** and has two components:

$$ST = R \times P \quad [\text{Eq.1}]$$

The first is a ratio (R) often of areas, response factors, or a relative potency comparing the substance tested to the primary reference material. The second comprises the multiplication of the ratio by the value assigned to the primary (P) RS, in this case the pharmacopeial RS, which establishes the reportable value for the substance tested. Both components contribute to the uncertainty of the value assigned to the substance tested, but only the magnitude of the former is within the control of the company developing or adopting the analytical method (9).

As described in Section 8.2.2 of the *Eurachem Guide on Quantifying Uncertainty in Analytical Measurement (QUAM)* (10), the general relationship between the combined standard uncertainty  $u_c(y)$  of a value  $y$  and the uncertainty of the independent parameters  $x_1, x_2, \dots, x_n$  on which it depends is shown in **Equation 2**:

$$u_c(y(x_1, x_2, \dots)) = \sqrt{\sum_{i=1, n} c_i^2 u(x_i)^2} \quad [\text{Eq.2}]$$

Here,  $y(x_1, x_2, \dots)$  is a function of several parameters  $x_1, x_2, \dots$ , and  $c_i$  is a sensitivity coefficient evaluated as  $c_i = \partial y / \partial x_i$ , the partial differential of  $y$  with respect to  $x_i$ . Applied to **Equation 1**, the combined standard uncertainty of the measurement result for the substance tested can be calculated using **Equation 3** (9):

$$u_c(ST(R, P)) = \sqrt{P^2 u_R^2 + R^2 u_P^2} \quad [\text{Eq.3}]$$

For **Equation 3**, the uncertainties for the ratio,  $u_R$ , and for the assay value of the primary RS,  $u_P$ , need to be determined. The assay value  $P$  can be taken from the information provided from the supplier of the RS or from calculations from other sources. For the purpose of this article, the value for the ratio  $R$  can be set to 1, as typically peak areas of similar size are compared.

For the pharmacopeial RS shown in the following sections, all measurements relevant for the calculation of the final assay value were determined in three different laboratories (i.e., standard deviations were obtained on the [precision] level of reproducibility). Uncertainty was calculated using the (relative) standard deviations of these measurements.

**Uncertainty calculation for assay value of pharmacopeial RS, case type 1.** **Table 1** shows the exemplary data for Surrogatine HCl RS, including test results of the collaborating laboratories for the tests relevant for the calculation of the assay value. All organic and inorganic impurities (residue on ignition [ROI]), residual solvents [ReS], water by Karl Fischer [KF], organic impurities [I]) were determined as w/w percentages.

**Table I.** Surrogate Hydrochloride reference standard and test results of the collaborating laboratories.

Surrogate Hydrochloride reference standard	Lab 1	Lab 2	Lab 3	Mean	Standard deviation
Residue on ignition, %(w/w)	0.01	0.03	0.01	0.02	0.01
Residual solvents, %(w/w)	0	0	0	0.00	0.00
Water content (Karl Fischer), %(w/w)	4.00	3.43	3.82	3.75	0.29
Organic impurities, %(w/w)	0.037	0.04	0.045	0.04	0.00404
Assigned value, %(w/w)	95.95	96.50	96.13	96.19	

Therefore, this RS's assigned value (P) was calculated using **Equation 4**, subtracting all single impurity contributions from 100%(w/w).

$$\begin{aligned}
 P &= 100 \text{ \%}(w/w) - (ROI + ReS + KF + I) \text{ \%}(w/w) \\
 &= 100 \text{ \%}(w/w) - (0.02 + 0 + 3.75 + 0.04) \text{ \%}(w/w) \\
 &= 96.19 \text{ \%}(w/w)
 \end{aligned}$$

[Eq.4]

The determination of the combined standard uncertainty for the USP RS follows Rule 1 as explained in Section 8.2.6 of *Eurachem QUAM* (10). This rule is used for calculations involving only sums or differences. **Equation 5** shows Rule 1, applied to the specific case, using the standard deviations as uncertainty contributions.

$$\begin{aligned}
 u_p &= \sqrt{u_{ROI}^2 + u_{ReS}^2 + u_{KF}^2 + u_I^2} \\
 &= \sqrt{0.01^2 + 0^2 + 0.29^2 + 0.00404^2} \text{ \%}(w/w) \\
 &\approx 0.29 \text{ \%}(w/w)
 \end{aligned}$$

[Eq.5]

**Uncertainty calculation for assay value of pharmacopeial RS, case type 2.**

In this example, the impurities that are undetectable by the chromatographic purity method (i.e., water by KF, ROI, ReS, related compound H by gas chromatography [GC], Replacepam R-isomer, and others detectable by capillary electrophoresis [CE]) were determined as w/w percentages; however, the organic purity was determined as relative percentage (see **Table II**). The RS's assigned value (P) was calculated using **Equation 6**, subtracting all w/w contributions from 100% and then multiplying with the chromatographic (organic) purity.

$$\begin{aligned}
 P &= ((100 - (KF + ROI + ReS + GC + CE)) \text{ \%}(w/w)) \times ((100 - I) \div 100) \\
 &= ((100 - (0.14 + 0.04 + 0.05 + 0 + 0.03)) \text{ \%}(w/w)) \times ((100 - 0.09) \div 100) \\
 &= 99.65 \text{ \%}(w/w)
 \end{aligned}$$

[Eq.6]

**Equation 6** contains both sum/difference and product/quotient parts. As recommended in Section 8.2.7 of *Eurachem QUAM* (10), the determination of the combined standard uncertainty follows a combination of the Rules 1 and 2. Therefore, the interim uncertainty for the first part of the product, “(100-(KF+ROI+ReS+GC+CE)) %(w/w)”, will be derived separately using Rule 1. For the second part, “(100-I)÷100”, only the uncertainty for the organic impurities (I) needs to be considered. These interim uncertainties will then be linked together to the combined standard uncertainty for the USP RS assay value. **Equation 7** shows the calculation for interim uncertainty  $u_{Int}$  by Rule 1, for the specific part “(100-(KF+ROI+ReS+GC+CE)) %(w/w)”:

$$\begin{aligned}
 u_{Int} &= \sqrt{u_{KF}^2 + u_{ROI}^2 + u_{ReS}^2 + u_{GC}^2 + u_{CE}^2} \\
 &= \sqrt{(0.04^2 + 0.02^2 + 0.01^2 + 0 + 0.06^2)} \text{ \%}(w/w) \\
 &\approx 0.074 \text{ \%}(w/w)
 \end{aligned}$$

[Eq. 7]

**Equation 8** then combines both  $u_{Int}$  and uncertainty for the organic impurities  $u_p$ , following Rule 2 from Section 8.2.6 of *Eurachem QUAM* (10):

$$\begin{aligned}
 u_p &= P \sqrt{\left(\frac{u_{Int}}{Int}\right)^2 + \left(\frac{u_I}{I}\right)^2} = \\
 99.65 \text{ \%}(w/w) &\sqrt{\left(\frac{0.074}{99.74}\right)^2 + \left(\frac{0.11}{99.91}\right)^2} \approx 0.13 \text{ \%}(w/w)
 \end{aligned}$$

[Eq.8]

**Table II.** USP Replacepam reference standard and test results of the collaborating laboratories.

USP Replacepam reference standard	Lab 1	Lab 2	Lab 3	Mean	Standard deviation
Water determination (Karl Fischer), %(w/w)	0.11	0.12	0.19	0.14	0.04
Residue on ignition, %(w/w)	0.04	0.05	0.02	0.04	0.02
Residual solvents, %(w/w)	0.05	0.06	0.05	0.05	0.01
Replacepam Related Compound H, %(w/w)	0	0	0	0.00	0.00
Replacepam R-Isomer and other, %(w/w)	0	0	0.1	0.03	0.06
Organic Impurities (high performance liquid chromatography), % total detected area	0.21	0.02	0.03	0.09	0.11
Assigned value, %(w/w)	99.59	99.75	99.61	99.65	

To calculate test results and their expanded uncertainties, the assigned values and their uncertainties from **Equations 4, 5, 6, and 8** will be used.

**Calculation of test results and expanded uncertainties.** The calculation of test results and uncertainties follows **Equations 1 and 3**, respectively. In **Equation 3**, the uncertainty of the ratio  $u_r$  is the last factor to be considered.

Ratio R is determined from peak areas, response factors, or a relative potency comparing the unknown sample (ST) to the primary RS (P) (9). For the cases presented here, the ratio is determined by the comparison of the peak areas of both ST and P and, for simplicity, can be set in first approximation to 1 (**Equation 9**), as typically peak areas of similar size are compared.

$$R = 1 = \frac{\text{area}(ST)}{\text{area}(P)} \quad [\text{Eq.9}]$$

The uncertainty  $u_r$  of the ratio can then be calculated following the previously described Rule 2 (**Equation 10**). The terms under the root square are the relative standard deviations (RSD) of the chromatographic method used to determine the areas of the main peaks, see also Section 8.2.6 of *Eurachem QUAM* (10). The authors assume a value of 0.2% for the RSD of the method, for both the Surrogatine HCl and the Replacepam, described previously. The actual method's RSD should be used, but RSDs are typically approximately that size, depending on the precision regime (i.e., repeatability, intermediate precision, reproducibility) used to determine the RSD (see **Table III**).

$$u_r = 1 \sqrt{\left(\frac{u_{\text{area}(ST)}}{\text{area}(ST)}\right)^2 + \left(\frac{u_{\text{area}(P)}}{\text{area}(P)}\right)^2} = 1 \sqrt{\left(\frac{0.2}{100}\right)^2 + \left(\frac{0.2}{100}\right)^2} \approx 0.0028 \quad [\text{Eq.10}]$$

All data are now available to calculate the uncertainty for an assay result using **Equation 3** to determine the combined standard uncertainty of a Surrogatine HCl (**Equation 11**) and of a Replacepam substance (**Equation 12**).

**Table III.** Dependency of guard bands from reference standard type used and measurement relative standard deviation (RSD) realized.

Widths of guard bands (expanded uncertainties) for reportable values of Surrogatine Hydrochloride, depending on reference standard used and measurement RSD assumed, in % (w/w)	RSD 0.2%	RSD 0.3%	RSD 0.4%	RSD 0.5%
Pharmacopeial reference standard	0.80	1.00	1.23	1.48
Secondary reference standard	0.96	1.29	1.65	2.01

$$u_c(ST(R, P)) = \sqrt{P^2 u_R^2 + R^2 u_P^2} = \sqrt{96.19^2 \times 0.0028^2 + 1^2 \times 0.29^2} \approx 0.40 \% (w/w) \quad [\text{Eq.11}]$$

$$u_c(ST(R, P)) = \sqrt{P^2 u_R^2 + R^2 u_P^2} = \sqrt{99.65^2 \times 0.0028^2 + 1^2 \times 0.13^2} \approx 0.31 \% (w/w) \quad [\text{Eq.12}]$$

These combined standard uncertainties are normally reported as expanded uncertainties by multiplying them with a coverage factor (k) of 2 to reflect a confidence level (CL) of 95%, as described in Section 8.3.3 of *Eurachem QUAM* (10). The assay values for substances tested with a pharmacopeial RS, as discussed previously, would be reported as follows:

- For Surrogatine HCl with an expanded uncertainty of  $\pm 0.80\% (w/w)$  (k=2, 95% CL)
- For Replacepam with an expanded uncertainty of  $\pm 0.62\% (w/w)$  (k=2, 95% CL).

These expanded uncertainties are of utmost relevance in the following discussion, which introduces the concept of guard bands.

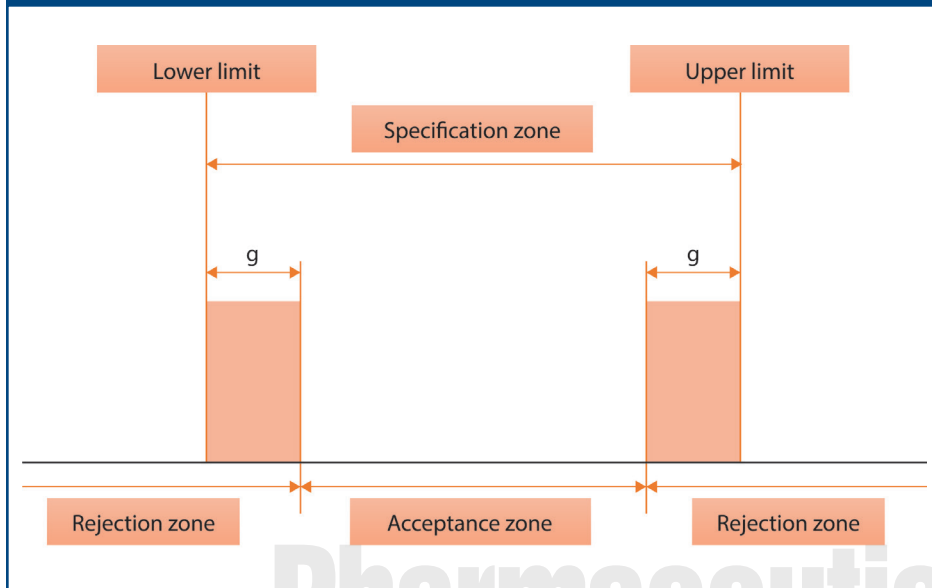
## DISCUSSION

The principle of guard bands is commonly used in compliance testing. It considers the expanded uncertainties of analytical methods including the RS used, as outlined and calculated in the Methods section. The principle also considers possible risks of false acceptance or rejection, and the desired level of probability for the correct/false acceptance or rejection. From these considerations, decision rules are derived. Guard bands were also suggested for use in pharmaceutical quality control (release testing) (11, 12).

Basically, decisions for correct acceptance/rejection are made on reportable values that have a certain distance from the original specification limits. **Figure 1** shows the general concept of guard bands; more detailed information is available elsewhere (13). Ideally, they should be chosen to be as wide as the expanded uncertainty of the measurement to make sure the risk of a false acceptance/rejection stays considerably low. Furthermore, depending on the criticality of the true value being within the specifications, the guard bands can be either positioned inside the specification zone (stringent acceptance zone, see **Figure 1**) or outside of the original specification zone (relaxed acceptance zone) (14). Results within the acceptance zone would lead to the release of the pharmaceutical article; results outside of the acceptance zone would lead to an initial rejection. In case of initial rejection, two events could be distinguished by using the following decision rules, depending on the laboratory's risk management:

- Results within the guard bands could be considered outside of expectation (OOE) and would trigger a

**Figure 1.** Schematic acceptance and rejection zones for simultaneous upper and lower limits. The guard band (g) is usually as wide as the expanded uncertainty for the measurement result.



**Guard bands for Surrogate HCl with a secondary RS.** The scenario would change if a secondary RS is used, compared to the pharmacopeial RS for its assigned value (Figure 3). Adding that additional measurement step results in a larger uncertainty for the secondary RS. Consequently, the expanded uncertainty for the overall measurement increases as well. The outcome is an extension of the guard band (i.e., a narrowing of the acceptance zone). Again, this narrowing is usually not known to the user. However, as per definition, only results obtained with the original pharmacopeial RS are conclusive; there is a real risk of obtaining an OOS result without realizing it when working with an

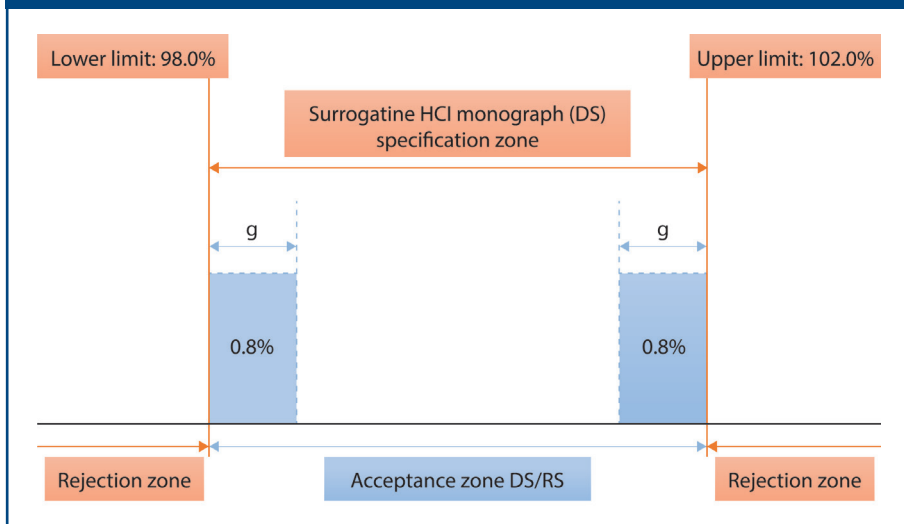
predefined OOE retesting routine. This is also known as transition decision rule (14).

- Results outside the limits could be considered out of specification (OOS) and would trigger a stringent investigation, according to the predefined OOS routine.

**Guard bands for Surrogate HCl.** For the example of Surrogate HCl, expanded uncertainties for the assigned value of the substance tested were described as calculated in the Methods section; however, for monograph purposes they are usually not known to the user and therefore not considered. This situation is illustrated in the Surrogate HCl monograph example (Figure 2) by showing the uncertainties as guard bands in dotted lines within the monograph’s specification zone. The acceptance zone in this case (i.e., when combining the monograph as documentary standard [DS] and the pharmacopeial RS) would be identical with the specification zone of the monograph. Any result outside the acceptance zone would be OOS. However, in practice (and not considered here), laboratories would probably allow a slightly stricter acceptance zone, in particular regarding the lower limit, because they need to make sure that the pharmaceutical article fulfills the monograph specification over its whole lifecycle.

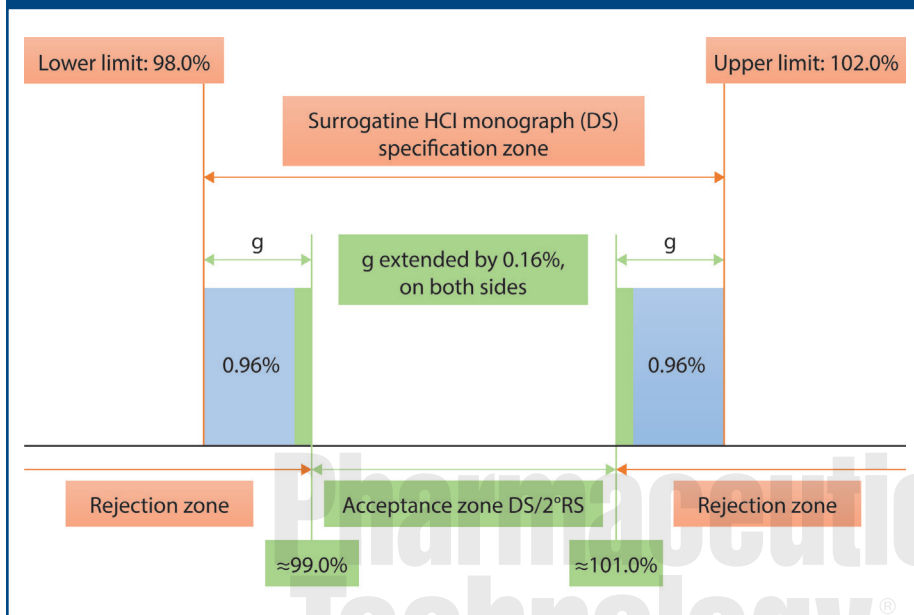
unchanged acceptance zone. To illustrate that risk, the additional measurement uncertainty has been added, reaching further into the acceptance zone (see Figure 3). Moreover, the full guard band should be considered now for narrowing the acceptance zone, as only the combination of documentary and pharmacopeial RS allows—theoretically—for a congruent specification and acceptance zone. For the user, however, it is not possible to estimate how much narrowing of the acceptance zone is necessary.

**Figure 2.** Schematic acceptance and rejection zones for Surrogate Hydrochloride, a combination of its documentary standard (DS) and pharmacopeial reference standard (RS). Acceptance, specification, rejection, and guard band (g) zones are not true to scale; only uncertainties for characterization of the primary RS and assay result of substance tested have been considered.



FIGURES ARE COURTESY OF THE AUTHORS.

**Figure 3.** Schematic acceptance and rejection zones for Surrogatine HCl, combination of documentary standard (DS) and secondary reference standard (RS) compared to the pharmacopeial RS. Acceptance, specification, rejection, and guard band (g) zones are not true to scale; only uncertainties for characterization of the primary/secondary RS and assay result of substance tested have been considered.



To calculate the extension of the guard bands for a secondary RS, the candidate material for the secondary RS would first take the place of the substance tested and have an expanded uncertainty of 0.8%(w/w). Following the approaches outlined (see Methods) for Surrogatine HCl, and assuming an RSD of 0.2% for the method, an assay result of a substance tested with the secondary RS would then have a combined standard uncertainty of 0.48%(w/w), and an additional contribution of 0.08%(w/w) would be realized. In **Equation 13**, for simplicity, the assay value for S, the secondary RS, was assumed to be the same as for P in **Equation 11**. The guard bands would widen, from 0.80 to 0.96%(w/w), in agreement with the expanded uncertainties. Consequently, the acceptance zone should be narrowed down by 0.16%(w/w) on both sides.

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$$u_c(ST(R,S)) = \sqrt{S^2u_R^2 + R^2u_S^2} = \sqrt{96.19^2 \times 0.0028^2 + 1^2 \times 0.40^2} \approx 0.48\%(w/w)$$

[Eq.13]

Depending on the precision of the chromatographic methods used for the comparison, the scenario can change to the better or the worse. As mentioned above, an RSD of 0.2% is realistic, but larger RSD (and lower) are also possible. **Table III** shows guard bands as expanded uncertainty results for RSDs from 0.2 to 0.5% for Surrogatine HCl. Inevitably, the guard bands widen with transition from pharmacopeial to secondary RS; they also widen with increasing measurement RSD.

### CONCLUSION

As noted in the Discussion section, a significant change in the uncertainties of reportable values can clearly be seen between the pharmacopeial and secondary RS. The guard band principle illustrates this in an evocative way. When applying the principle on the topic of secondary RS in quality control (QC) release testing, the range of acceptance/rejection zones will change, as the use of the secondary RS introduces an additional measurement uncertainty.

Although the authors do not intend to take a position on the appropriateness of the use of secondary RS in individual circumstances, consider two important facts:

- Assigned values of secondary RS inherently carry a larger measurement uncertainty, compared to primary (pharmacopeial) RS, as an additional measurement step is taken (8). Consequently, measurements obtained with the secondary RS carry larger uncertainties as well, compared to measurements with the corresponding pharmacopeial RS.
- It is inappropriate to work with certain acceptance criteria when using documentary standard (monograph) and pharmacopeial RS, and to work with the same acceptance criteria when using a secondary RS derived from comparison with the pharmacopeial one. In fact, the users of secondary RS should narrow down the original acceptance zone to ensure they would still be within specification limits of the monograph for their acceptance decisions.

The authors understand that it is difficult for users to assess the impact that the switch from pharmacopeial RS to secondary RS would have on the acceptance criteria, because uncertainties for pharmacopeial RS are usually not provided, for the reasons discussed previously.

To address this issue, the pharmaceutical QC community could opt to:

- Work exclusively with pharmacopeial RS when compliance through combination of pharmacopeial documentary and RS is established
- Establish the identity of the secondary RS against pharmacopeial RS. The assay value and related measurement uncertainty should be determined independently for the

secondary RS, using mass balance calculation instead of assay against the pharmacopeial RS. Acceptance zones should be adapted according to the measurement uncertainties found. This approach is practiced in the pharmaceutical community (15) as suggested by a WHO expert committee (16). The results obtained with pharmacopeial and secondary RS should be compared; based on the comparison, the secondary RS can be released. Regular checks should be considered as to whether the relation is still valid, for example, during lot changes of the pharmacopeial RS.

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