



Mikromol™

External Reference Standards or Relative Response Factors: Considerations for Quantitation of Impurities in Pharmaceuticals

Dr. Bernard Olsen, Webinar Presentation, October 2, 2018



Before we start



Audio

Sound Check

Computer-Audio
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STUMMGESCHALTET

Mikrofonbuchse (IDT High Defi...
Lautsprecher / Kopfhörer (IDT H...

Fragen

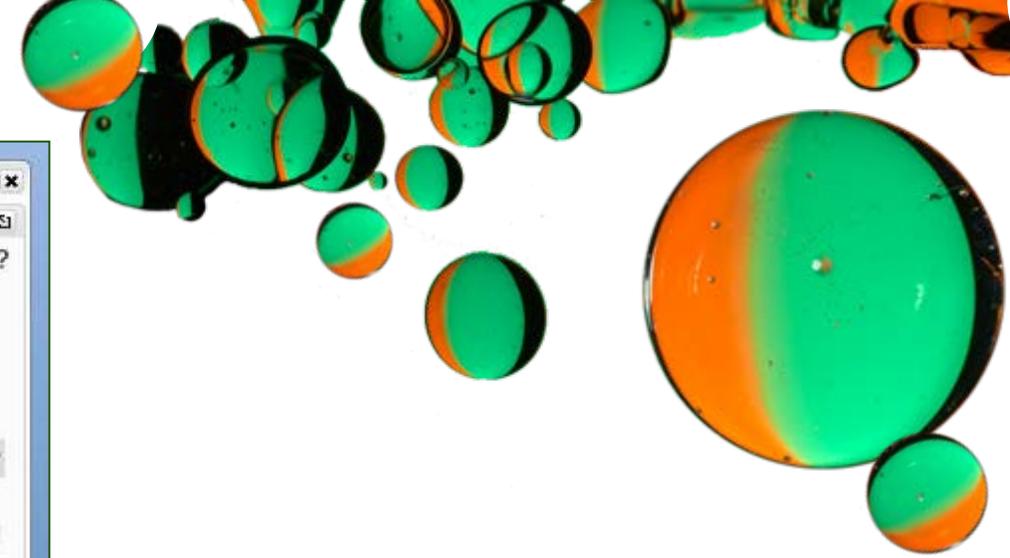
Welcome to our LGC webinar!

Here you can put in questions

Senden

Test (Christian Zeine)
Webinar-ID: 164-379-595

GoToWebinar





Our brand for pharmaceutical reference standards

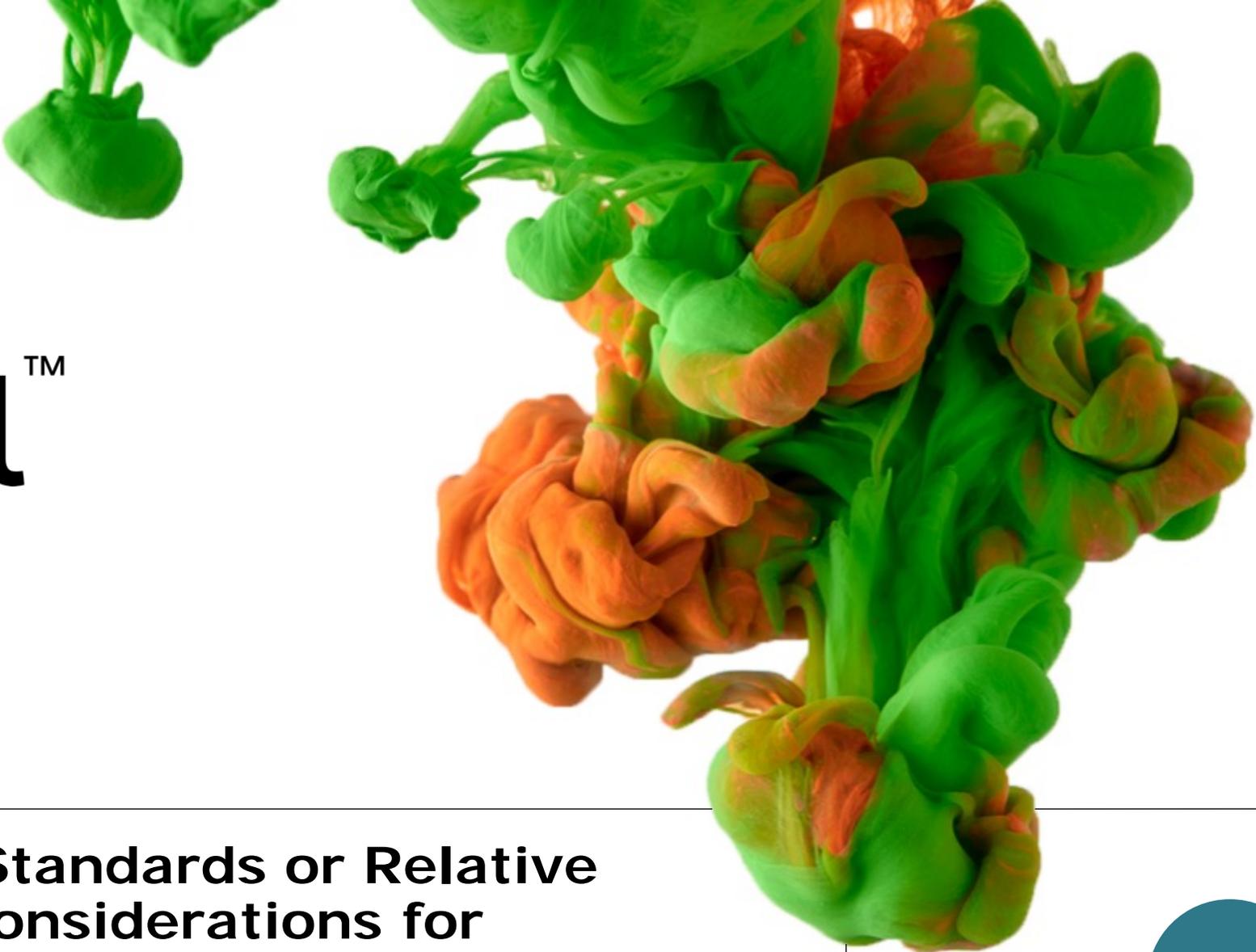
- Over 5,000 Impurity, Active Pharmaceutical Ingredient (API) and Excipient reference standards for more than 1,000 API families
- Suitable for qualitative and quantitative applications in method development, validation and routine quality control
 - For API, excipient and finished dosage form production
- Extensive Certificate of Analysis (COA)
 - Comprehensive, detailed COA for impurity standards
 - COA for API reference standards produced under ISO guide 17034
- Expert technical support
- Advice on technical applications for pharmacopoeial methods and internally developed protocols

5,000+
reference standards

4,000+
impurities for more than

1,000
API families

25 years' experience



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Impurity Quantitation



ICH Q3A: Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself.

The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated.

Relative Response Factor

$$\text{RRF} = \frac{(\text{Impurity response}/\text{Impurity concentration})}{(\text{API response}/\text{API concentration})}$$

USP: $F = \text{RRF}$, appears in denominator of calculations

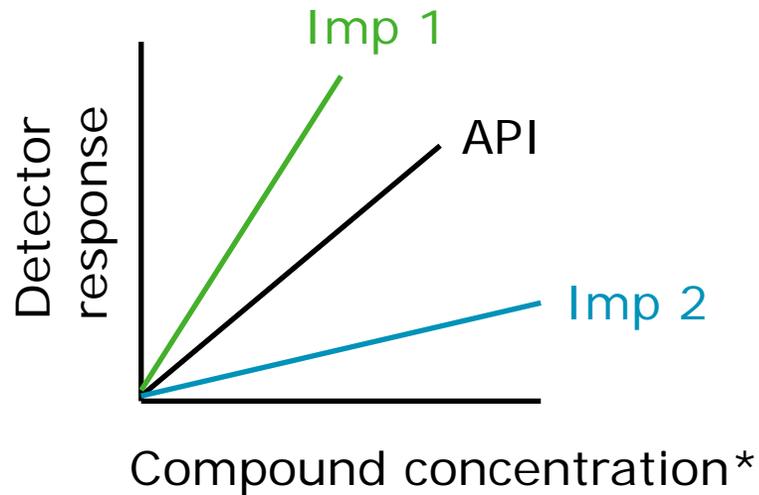
PhEur: $\text{CF} = 1/\text{RRF}$, appears in numerator of calculations



Determination of RRF



Often done by comparing slopes of linearity plots



$$\text{RRF} = \text{slope Imp} / \text{slope API}$$

$$\text{RRF}_{\text{Imp 1}} > 1$$

$$\text{RRF}_{\text{Imp 2}} < 1$$

*For accurate RRF determination, the concentration of API and impurity solutions must be known accurately

Rationale for using RRFs



Comparison to a standard of a given impurity is the most accurate and robust means of impurity quantitation, but:

- Impurity standards may be difficult to isolate or synthesize in sufficient quantities for routine use
 - Nonetheless: Think about procuring a standard – commercial costs and availability have improved over the years!
 - Standards must be characterized
 - However, this must also be done with the impurity samples used to determine RRFs!
 - In fact, best would be to use impurity standards for RRF determination
- Preparing standard solutions for analysis can impact laboratory efficiency
- Complex impurity profiles may cause difficulty using standards for each impurity – give priority to specified impurities

Potential Errors in Sample Assay used for RRF Determination



Components of impurity sample not accounted for:

- Impurity salt form
- Moisture levels
- Solvent levels
- Other impurities

$$\text{Assay (\%)} = (100 \% - \text{KF} - \text{RES}) * \frac{\text{Purity HPLC (\%)}}{100 \%}$$

Salt form issues from some suppliers



Wanted: *1-(3-Chlorophenyl)piperazine Hydrochloride*

Literature data:

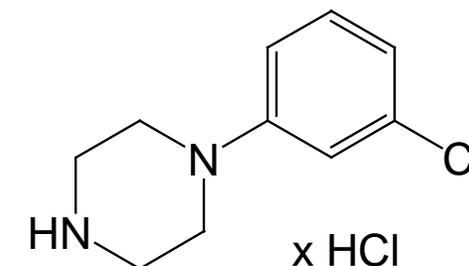
Free base
M=196.68
CAS 6640-24-0
liquid

84.4%

Hydrochloride
M=233.14
CAS 65369-76-8
mp=210-214°C

73.0%

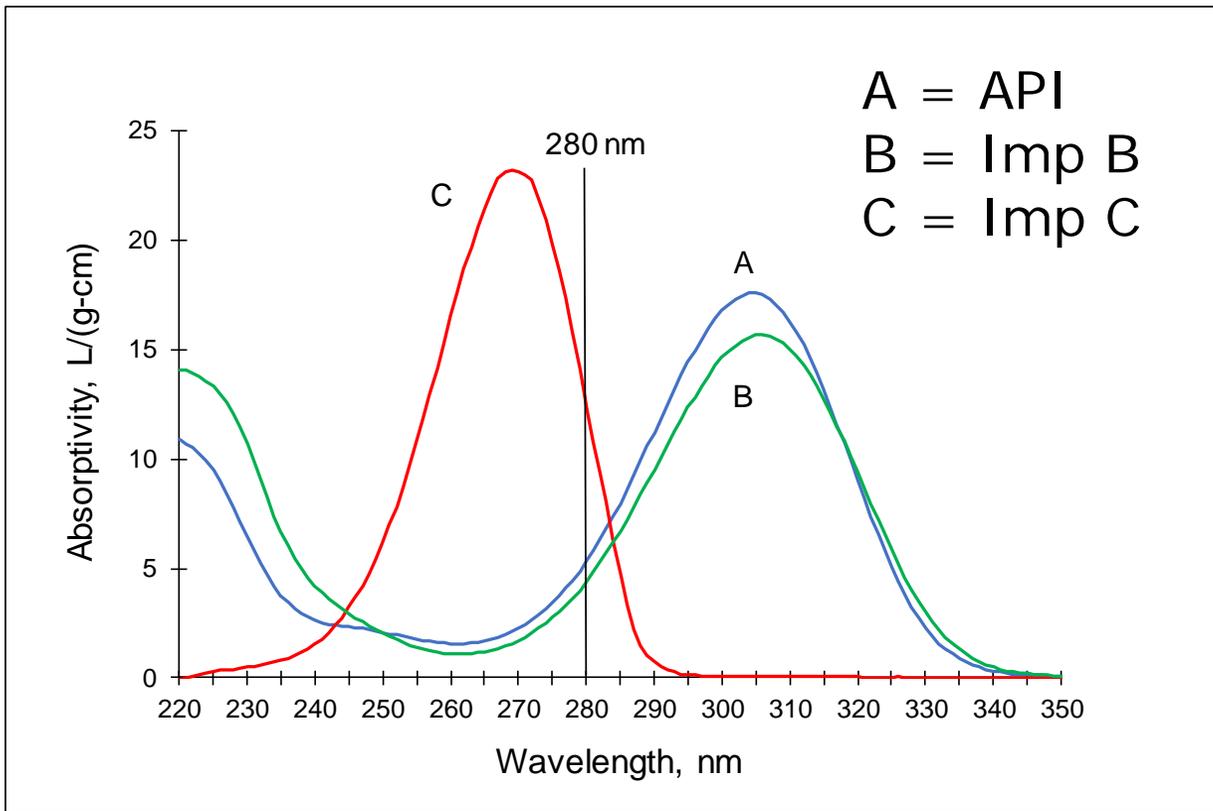
Dihydrochloride
M=269.60
CAS 51639-49-7
mp=189-191°C



Order from commercial sources:

	Molecular mass	CAS	Melting point	Supply of...
Supplier 1	M=196.68 (free base)	65369-76-8	210-214°C (lit.)	Dihydrochloride
Supplier 2	M=233.14	65369-76-8	210°C	Dihydrochloride
Supplier 3	M=233.14	51639-49-7	189-191°C	Hydrochloride

Potential robustness issues with RRFs: UV spectra differences



RRF for impurity C changes by about **30%** with a ± 2 nm change in wavelength from 280 nm

RRF for impurity B remains constant with small wavelength changes because of similarity of Imp B and API UV spectra

Other factors to consider

- Detector bandwidth?
- Variable λ vs diode array?

Points to consider regarding determination of RRFs



Can I use a qualitative impurity standard (research material) to determine an RRF

- Depending on your perspective: You can, but think twice!
- If purity indicated as, for example, ">80%" or similar, what value should I use for calculation of RRF: 80%? 90%? 100%? No idea?
 - Do not calculate with the minimum value (i.e. 80%)!
 - Material probably purer than that value, risk of RRF overestimation
 - If at all: assume 100%! Risk of RRF underestimation "only"!

RRF overestimation causes underestimation of impurity content

RRF underestimation causes overestimation of impurity content

Points to consider regarding determination of RRFs



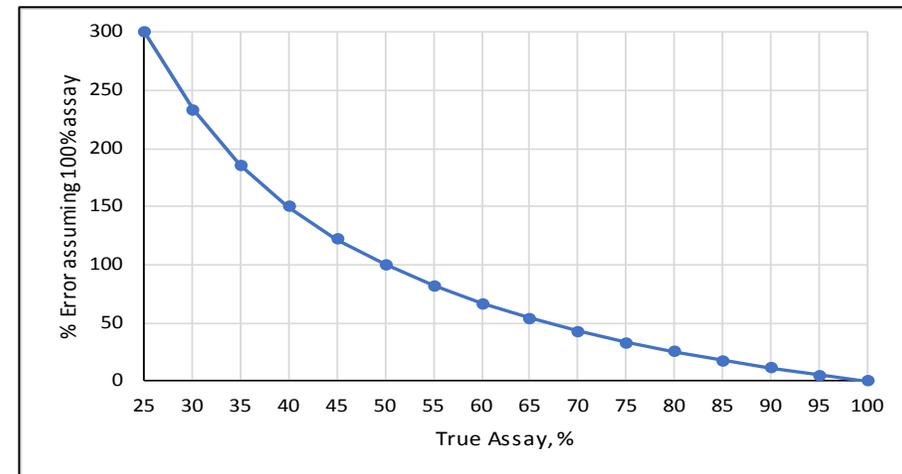
Can I use a qualitative impurity standard (research material) for determination of RRF?

- Risk of overestimation of impurity level
 - Normally no regulatory issue, as patients not at risk to receive medicines with impurities **really** out of specs
 - Economic risk, however, for pharmaceutical manufacturer
 - False positive OOS results for imps = unnecessary investigations!
 - During development and consideration of ICH Q3A/B: risk of exceeding qualification threshold, leading to unnecessary and expensive qualification studies (e.g., animal tox studies)

Impact of incorrect RRF



- Overestimation of impurity level caused by assuming 100% assay of an impurity used to determine RRF
- If impurity was only 70% pure, but taken as 100% for RRF determination, an error of 43% in impurity quantitation would result
- Would mean you report a 0.12% impurity as being 0.17%
- Above ICH qualification limit of 0.15%
→ unnecessary, expensive toxicity studies



Other RRF considerations



Is there a limit for the use of RRFs?

- EDQM recommendation is not to use RRF values below 0.2* for impurity quantitation
- Low RRFs can introduce large errors or variability in quantitative results because integration and chromatographic variability become magnified

*EDQM, *Technical Guide for the Elaboration of Monographs*, 7th Ed., 2015

Other RRF considerations



Impact of inaccurate RRFs on product lifecycle:

- Difficulty in comparison of results when revised or new methods are considered
- Specification limits may be inappropriate if based on inaccurate RRFs

Conclusions



- Well-characterized impurity reference standards are desirable for accurate and robust quantitation of impurities
- RRFs can be used for impurity quantitation, but should be defined using an accurately characterized impurity sample
- Potential ruggedness issues for RRFs should be investigated
- Inaccurate RRFs lead to:
 - Inaccurate impurity quantitation
 - Underestimation – potential safety risks
 - Overestimation – economic risks
 - Difficulty in comparing results between methods

Thank you

To LGC for the opportunity to present this webinar

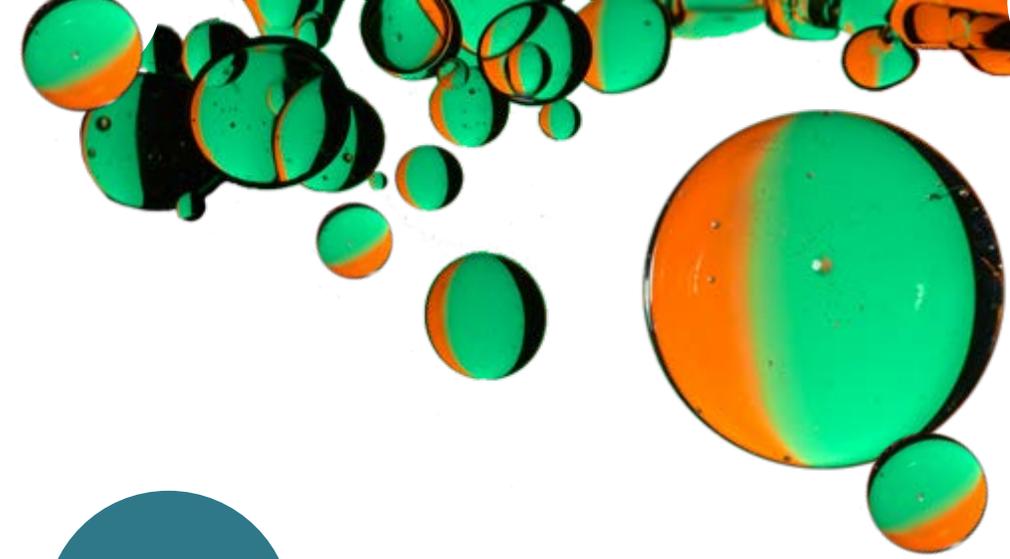
- Please download our corresponding white paper on RRFs under <https://bit.ly/2QndxAd>

To Dr. Andreas Sieg and Katrin Tänzler for the slide on salt form issues

And of course to you for your attention!



QUESTIONS?



Also via email to
christian.zeine@lgcgroup.com