Characterisation of impurity standards: **How good is good enough?**

1 The background

In contrast to the detailed guidance available for reference standards for active pharmaceutical ingredients (as outlined in Ph. Eur. Chapter 5.12.[1]), there is a notable lack of clear guidance on how to characterise impurity reference standards (IRSs).

The ICH guidelines[2] only require that impurities "should be evaluated and characterized according to their intended uses." Additionally, ICH Q3A allows flexibility, permitting either the accurate quantification of impurities or the use of "the drug substance," combined with a correction factor, to "estimate the levels of impurities."

2 The intended analytical use

The intended analytical use is the major factor which should determine the extent of analytical characterization of the IRS.

There are two main types of analytical uses: qualitative and quantitative

Possible qualitative uses could be:

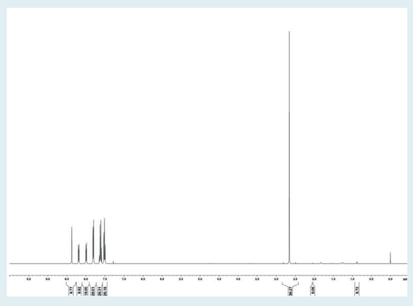
- System suitability test, e.g. resolution check
- Peak identification
- Validation of specificity parameters

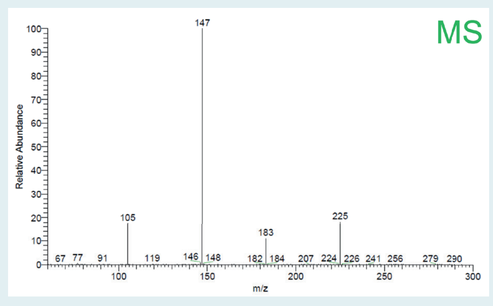
Possible quantitative uses are:

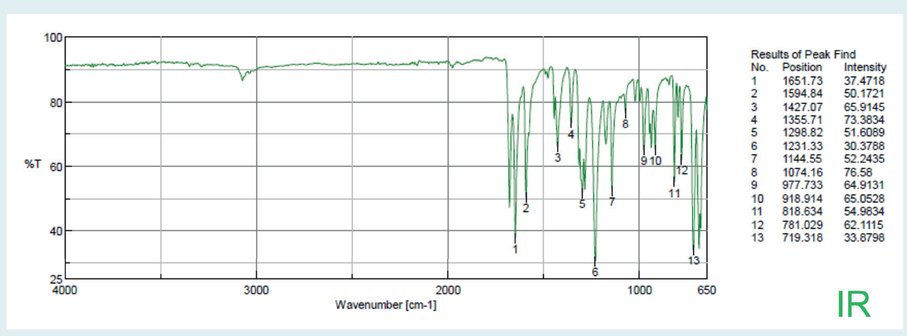
- Limit test (semi-quantitative)
- Quantification of an impurity with the direct use of the IRS
- Quantification of an impurity via relative response factors (determined with IRS)
- Validation of accuracy parameters

3 The methods

For qualitative use, we suggest the full confirmation of identity, at least with the following methods:







We also recommend CHN (elemental) analysis, as it provides valuable data, such as distinguishing between free base and salt forms. When the impurity is specified as an enantiomer, chiral methods, including optical rotation, should also be considered.

During interpretation, no signal or result should conflict with the assumed chemical structure of the IRS. The minimum purity should be 85-90%; otherwise, interpreting NMR and IR data can become challenging[4].

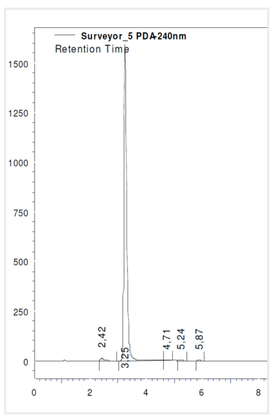
For semi-quantitative one-sided upper limit tests no assay value is needed, however the IRS should be assumed to have a 100% assay[4]. This approach will result in an overestimation of the impurity, ensuring that safety and compliance are maintained.

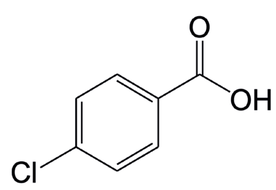
For quantitative use, both purity and assay should be clearly defined. Purity should be assessed using a sufficiently specific separation technique, such as HPLC or GC. Additionally, water content and residual solvents should always be determined to accurately calculate the assay value using the equation provided below.

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

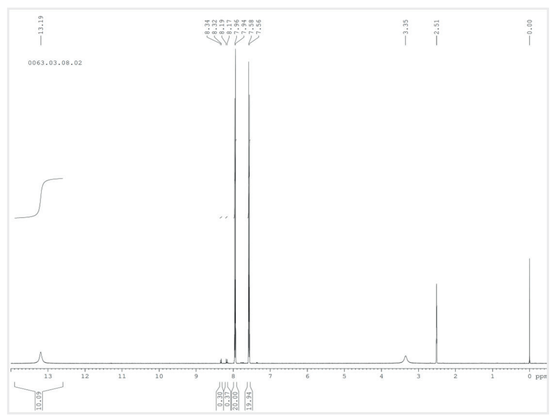
4 The power of consistency

Checking for consistency between different results is a powerful tool for ensuring correct identity and assay.





4-Chlorobenzoic acid (MM0063.03), bezafibrate impurity A (EP), with traces of hydroxy derivate



5 The final question

Can I use a qualitative IRS for quantitative purposes?

Possible, but think twice:

- Avoid underestimation of impurities: Calculate with 100%!
- The resulting overestimation of the impurity is accepted by authorities, but may lead to unnecessary OOS results.
- Once Relative Response Factors (RRFs) are validated, impurity quantification can be accomplished in routine testing based on the % area of the reference peak (typically the API). Additionally, qualitative standards can be used to confirm retention time, ensuring accurate peak identification.