

## Customer information

### Determination of water according to the volumetric Karl Fischer method under GMP

It is generally standard for complex product-specific methods (e.g. HPLC, spectrometry, etc.) to be validated for GMP analyses. The authorities are increasingly demanding that general methods (e.g. general pharmacopeia methods) must also be validated or at the very least verified for use under GMP [1, 2]. This also includes the determination of water according to the volumetric (titrimetric) Karl Fischer method.

The latest 6<sup>th</sup> edition of the European Pharmacopoeia specifies that for the general test [3], which describes the Karl Fischer method and is also referenced in the monographs, a verification of the method is mandatory for each test substance (the accuracy of the determination ... must be verified for each substance to be determined). The procedure is illustrated by way of examples and consists essentially of the repeated sequential addition of water to the test substance and subsequent measuring of the water content. Variables using the parameters of linearity, accuracy and reproducibility are derived from the results.

The matrix-specific verification of the Karl Fischer method is necessary and expedient from an analytical point of view to validate the results, as the Karl Fischer method is always susceptible to matrix effects. Based on these effects, the Karl Fischer method cannot be counted as one of the "basic compendial procedures" [2] and must therefore be verified.

For the verification of methods, Solvias conforms to the specifications of the general test from the European Pharmacopoeia [3]. This applies to the direct application of the general Ph. Eur. method [3] and the general USP method [4] (there are currently no special instructions for carrying out the verification) and to variations of the volumetric (titrimetric) Karl Fischer method according to Solvias procedures, such as microdetermination and/or the gas extraction method (oven method).

According to the specifications of the pharmacopeias, since the start of 2008 we have consistently carried out verification on each test substance (matrix) for **GMP** orders for determining the water content according to the volumetric Karl Fischer method, unless there is already a product-specific and validated test procedure or a verification for the relevant test substance. The procedure complies with the current conditions specified by the authorities. Solvias is in constant contact with the responsible regulatory bodies, and if there are any changes, we will inform you immediately.

A generic verification is carried out once for each test substance (matrix). The additional verification costs are therefore only incurred once per test substance (matrix) and are added to the price of the sample analysis. If there is already a corresponding verification from an earlier analysis, only the net analysis costs for the water determination will be charged for subsequent orders. For optimum order processing, we request that you reference the order number of the verification on subsequent orders. For GMP orders without prior verification, this is done automatically in order to comply with official requirements.

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| [1] | EU GMP guidelines: Part II, Chapter 12.8 Validation of test procedures |
| [2] | USP - NF <1226> Verification of compendial procedures                  |
| [3] | Ph. Eur. 2.5.12. Water: Semi-micro determination                       |
| [4] | USP - NF <921> Water determination                                     |