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Residual Solvents to USP <467> and <1467>

Changes to USP <467> and Introduction of USP <1467>

At Butterworth Laboratories Ltd we understand the importance of keeping up with changes in the Pharmacopoeias and ensuring their implementation. A revision of USP <467>, Residual Solvents. The revision clarified verification and validation requirements for use of the monograph for Class 1, 2, and 3 residual solvent determination in compendial materials. In addition as part of the revision, USP <1467> was introduced to delineate verification and validation requirements. Both became effective from 1st March 2019.

What were the changes that required adoption of a new approach?

a. Introduction of <1467> in place of <1225> for Verification of Residual Solvent Methods, which requires all sample matrices have to be verified for the procedure. No matter what path you choose to follow

b. Analysis no longer driven mainly on solubility of sample but rather whether known solvents Likely To Be Present (LTBP) or not. Decisions taken then follow based on this answer

So 18 months on, how have Butterworth been able to adapt to these changes?

a. Before USP <1467> Residual Solvents – Verification of Compendial Procedures and Validation of Alternative Procedures, the USP relied upon the more general procedure <1226> Verification of Compendial Procedures which the company had already adopted for performing numerous other pharmacopoeia monograph tests. This further references Table 2 in USP <1225> Validation of Compendial procedures had again been used in producing our own internal Method Validation Procedures. The new General Chapter offers more clearly defined verification and validation parameters which include limit and quantitative approaches. In addition, where the USP<467> method requires modifications, this new chapter provides the validation requirements for alternative methods. The overall impression is that this addition has brought clarification to the process of validating and verifying Residual Solvent methods.

b. The decision tree presented in the USP monograph, provides a flow chart of the decision making process that needs to be followed upon analysis. The simplest part of the chapter revision to understand is when solvents LTBP are not known. We have adopted the following process:

   - Solvent Screen as per Procedure A following the old style parameters and preparation (Analysis requires preparation of Class 1, Class 1 SST, Class 2A, Class 2B when required)

   - Matrix verification takes place within the sequence with extra Class 2A and Class 2B spikes per sample

- Verification requirements as per <1467> for compendial limit test methods, which are:

  - ❖ Specificity: Blanks free from significant interference & Acetonitrile/DCM resolution NLT 1.0
  - ❖ Detection limits: S/N enhancements for each solvent in each Class 1, 2A, 2B preparation (spikes - samples) NLT 3
  - ❖ Solution stability: Detection limits met throughout timeline of test (start & end of sequence)

Where solvents LTBP are known. We have adopted the following process:

- Limit Tests, which we have found to be the most commonly requested route, following the USP monograph text and using only standards containing solvents of interest. These semi quantitative analyses are performed while noting the following:
  - Verification takes place within sequence (Detection limits, and specificity which are incorporated into system suitability)
  - Result of <limit reported e.g. <600 ppm OR <limit with a calculated value for information only
- Quantitative Tests under 'Procedure C' where if full quantitation is required, a validation plan under the requirements of <1467> needs to be produced in conjunction with the client, unless this has become a routine test. These quantitative tests can be tailored to suit compendial USP monograph preparations or alternate preparations depending on solvent and validation path followed under <1467>.

In conclusion we have had to make some minor changes to our approach as a result of this revision, but we have only found them to benefit, both ourselves and our clients. Where feasible we have continued to combine the verification and sample analysis process in a single analytical run to save our client costs and time.

Author Biography

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After gaining analytical experience in a QC lab post university, Emmanuel joined Butterworth in 2016 as Analytical Chemist. A role that has continued to date.

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John started at Butterworth in 1987 as an Analytical Chemist and has had various roles including Quality Assurance Manager and Business Development Manager before becoming Associate Director of Business Operations in 2018.