

Residual Solvents: Alternate Validated Methods

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Since the USP General Chapter <467> on Residual Solvents became effective on July 1, 2008, Lancaster Laboratories has seen a multitude of requests for many different solvent and sample matrix combinations. The new General Chapter applies to both monographed and non-monographed items, including all drug substances, excipients and products “subject to relevant controls.” So a number of manufacturers have turned to Lancaster Laboratories for assistance. The methodology provided in the General Chapter can be utilized for many of these requests (Class 1 and Class 2, Mix A and B compounds). However, the Class 2, Mix C compounds (Table 1), all of the Class 3 compounds (Table 2) and any other unlisted solvents used in manufacturing, cannot be tested by the General Chapter’s GC method. In these cases, an alternate method may need to be developed and validated. Due to the different properties of the Class 2, Mix C solvents and the Class 3 solvents, several different techniques may be necessary for sample analysis as shown in Tables 1 and 2.

One approach Lancaster Laboratories analysts have been utilizing is a technique referred to as a self-validating method. This particular approach is a possible alternative to the traditional method development and validation

project. The self-validating method parallels the USP General Chapter <467> methodology but takes it a step further by using a minimum of a three point calibration curve rather than the single point method of additions indicated by the General Chapter.

Prior to performing the self-validating method, feasibility would be performed to determine an

appropriate solvent that provides acceptable sample solubility. Chromatographic conditions would also be evaluated and optimized for the compounds being analyzed. Once this evaluation has been performed, the sample matrix (unfortified) would be tested along with direct fortification of the sample matrix at a minimum of three levels. These three levels will bracket the limit concentration and would typically be made

Table 1. USP Class 2 Residual Solvents – Mix C

Solvent	USP Limit Concentration (ppm)	Recommended Methodology
N,N-Dimethylacetamide	1090	Direct Injection GC/FID (Provided the sample is water soluble. For samples that are not water soluble, additional evaluation may be necessary.)
N,N-Dimethylformamide	880	
2-Ethoxyethanol	160	
Ethylene glycol	620	
Formamide	220	
2-Methoxyethanol	50	
N-Methylpyrrolidone	530	
Sulfolane	160	

Table 2. USP Class 3 Residual Solvents

Solvent	USP Limit Concentration (ppm)	Recommended Methodology
Acetic acid	5000	HPLC with UV detection
Acetone	5000	Headspace GC/FID
Anisole	5000	Headspace GC/FID
1-Butanol	5000	Headspace GC/FID
2-Butanol	5000	Headspace GC/FID
Butyl acetate	5000	Headspace GC/FID
tert-Butylmethyl ether	5000	Headspace GC/FID
Cumene	5000	Direct Injection GC/FID
Dimethyl sulfoxide	5000	Direct Injection GC/FID
Ethanol	5000	Headspace GC/FID
Ethyl acetate	5000	Headspace GC/FID
Ethyl ether	5000	Headspace GC/FID
Ethyl formate	5000	Headspace GC/FID
Formic acid	5000	HPLC with UV detection
Heptane	5000	Headspace GC/FID
Isobutyl acetate	5000	Headspace GC/FID
Isopropyl acetate	5000	Headspace GC/FID
Methyl acetate	5000	Headspace GC/FID
3-Methyl-1-butanol	5000	Headspace GC/FID
Methylethylketone	5000	Headspace GC/FID
Methylisobutylketone	5000	Headspace GC/FID
2-Methyl-1-Propanol	5000	Headspace GC/FID
Pentane	5000	Headspace GC/FID
1-Pentanol	5000	Headspace GC/FID
1-Propanol	5000	Headspace GC/FID
2-Propanol	5000	Headspace GC/FID
Propyl acetate	5000	Headspace GC/FID

at a tenth of the limit, the limit and two times the limit concentration. In addition, system suitability injections are made to ensure the system is precise and accurate by performing multiple injections of a standard prepared at the limit concentration along with evaluating the recovery of a second working standard preparation. Linear regression analysis of the curve that is generated from the fortified sample preparations yields the compounds concentration and may be considered a quantitative result provided the determined coefficient of determination is acceptable ($r^2 = 0.99$) and the value falls within the range evaluated. Due to the method of additions approach utilized with the self-validating method, many of the tests performed in a traditional method validation are evaluated with each analysis. Linearity is directly determined at the actual time of analysis by evaluating the linear regression data available from the different fortification levels. Specificity can be determined by evaluation of a blank injection and the unfortified sample injections made during the analysis. If significant interference is observed, an alternate approach would be attempted. Accuracy, range and precision are determined by evaluating the agreement of data from the different fortification levels in the presence of sample matrix. Quantitation will not be performed if the result is below the lowest fortification level and the results will be reported as less than lowest level. The result is only reported as an estimate if the result exceeds the highest fortification level. Finally, the self-validating method



evaluates a practical working limit of quantitation based on the concentration of the lowest fortification level. Although the actual LOQ may be significantly lower, this is beyond the scope of interest for quantitative evaluation of residual solvents around a much higher limit concentration.

Lancaster Laboratories has had success performing the self-validating method approach using headspace GC/FID, direct injection GC/FID and HPLC analysis with UV detection. Although Tables 1 and 2 suggest recommended types of methodology for these solvents, changes may be necessary due to different sample matrices or due to the different solvents expected in a sample.

The benefits to this self-validating method approach include a faster timeline when compared to the traditional method development

and validation project. This approach is more cost effective than the traditional approach for clients having a short term or infrequent need for testing. Additionally, the approach parallels the USP General Chapter <467>, while taking it a step further by utilizing multiple fortification levels. For samples that contain multiple solvents (five or more) or for samples in which testing will be performed frequently, the traditional method development and validation approach may prove to be a more cost effective analysis. Clients are encouraged to consult their internal SOPs regarding validation requirements since the self-validating method does not perform validation in the traditional sense.

For more information on residual solvent testing and the self-validating method approach, contact Lancaster Laboratories' Pharmaceutical Business Development at 717-656-2300.

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