

# Identification of an Unknown Leachable Species from BFS Vials

## CATALENT BIOLOGICS

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## BACKGROUND

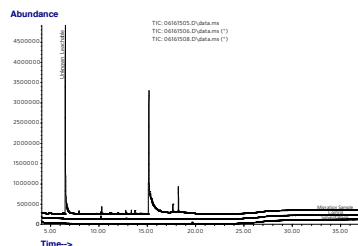
An unknown leachable species was detected by GC-MS analysis of an alkaline drug product (pH approximately 10.5) that was packaged in a novel self-contained plastic Blow Fill Seal (BFS) vial. Due to the high pH of the drug product formulation, it could not be stored in untreated glass vials. Treated glass vials are more expensive and are prone to delamination and particulate formation.

The unknown leachable was not easily identified using mass spectral databases or by manual identification. Furthermore, it was not a known additive of the resin formulation or a typical degradant of the known additives. A study was conducted to determine the identity and the origin of the unknown leachable compound.



## OBSERVATION OF THE SPECIES

The unknown species was observed as a leachable during a migration study where filled BFS vials were stored at 75°C for 4 weeks to simulate 36 months of long term storage at 25°C.



STUDY	EXTRACTION SOLVENT	EXTRACTION CONDITIONS	CONCENTRATION OF THE UNKNOWN (MG/VIAL)
CHARACTERIZATION	WATER	REFLUX, 0.5 h	2.11
	SALINE	REFLUX, 0.5 h	1.89
	ISOPROPANOL	REFLUX, 4 h	ND
MIGRATION	DRUG PRODUCT	75 °C, 4 wks	1.95

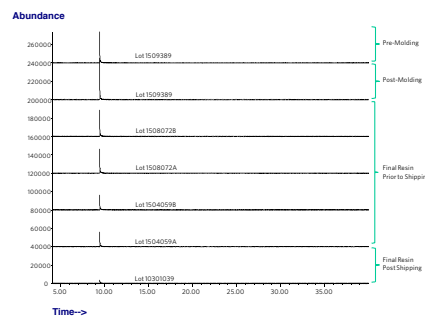
Typically, higher levels of extractables are observed when harsher extraction conditions are employed; however, the opposite trend was observed in this study. This was due to the formulation (pH ~10.5) having a direct impact on the level of leaching.

This highlights the importance of selecting the appropriate extraction conditions during the characterization. Extraction solvents should be chosen that mimic the extraction propensity of the drug product medium and its excipients.

## DETERMINATION OF THE UNKNOWN SOURCE

Samples of the raw resin from which the BFS system was produced were obtained and subjected to extraction in dilute sodium hydroxide solution (pH 10-11) at elevated temperatures. The intent was to determine if the compound of interest was present prior to the molding process, which would eliminate the possibility that the compound was a contaminant introduced during or after molding or an additive used by the molder in the finished resin and/or BFS extrusion process.

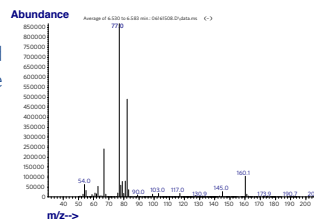
Examination of several resin samples taken prior to the resin supplier molding process indicated that the compound of interest was indeed present.



## DETERMINATION OF STRUCTURAL INFORMATION

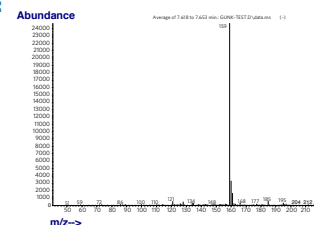
### Electron Ionization Mass Spectrum:

The fragmentation pattern observed in EI-MS provides clues to the structure of the compound.



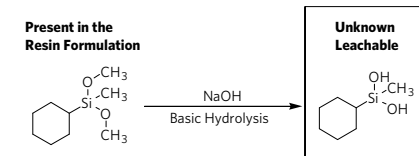
### Chemical Ionization Mass Spectrum:

CI-MS was employed to verify the molecular weight of the unknown compound. The molecular weight was determined to be 160 amu, which helped to rule out higher molecular-weight compounds. The spectrum also indicated that the compound was polar and could be deprotonated.



## IDENTIFICATION OF THE COMPOUND OF INTEREST

One compound in the resin formulation was determined to be a likely precursor: 1-cyclohexyl-1-methyl-1,1-dimethoxysilane.

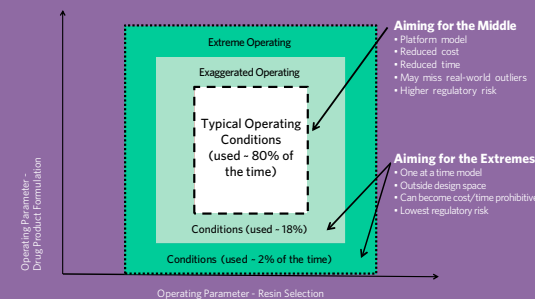


This species is commonly used within the industry as a catalyst during the synthesis of resin base powder. These compounds are known to hydrolyze to silanediols under basic conditions. The identification of the unknown leachable was confirmed by subjecting the catalyst to hydrolysis and observing the unknown leachable in the resulting sample.

## CONCLUSION

The unknown leachable was identified through structural elucidation as 1-cyclohexyl-1-methyl silanediol and verified by synthesis and mass spectral confirmation. The source of the confirmed leachable species was determined to be based on catalyzed hydrolysis of the resin processing catalyst in the presence of the alkaline drug product formulation.

This is an example of a transformative leachable species. This leachable was not directly related to the known resin additives, but a formation product of a known additive and the drug product/excipient.



The results of this study were outside of the "80%" extractables design space. This highlights the utility of migration studies to understand and expand your knowledge space (extractables) in support of identifying your desired control space (leachables), which results in more robust leachable control methods and greater protection of patient health.