

TriPlus 500 Headspace Autosampler with TRACE 1310 GC and Q Exactive GC-MS/MS system enhances productivity and reliability in pharmaceutical laboratories



Thermo Scientific™ TriPlus™ 500 GC Headspace (HS) Autosampler coupled to the Thermo Scientific™ TRACE™ 1310 Gas Chromatograph and Thermo Scientific™ Q Exactive™ Orbitrap™ GC-MS/MS system

“As a contract lab we must deliver high-quality results within a very short timeframe to meet client timelines to get products to market, so we want a system that is very robust and reliable. We definitely recommend the Thermo Scientific solution to our colleagues for E&L and residual solvent applications.”

— Dr. Dujuan Lu, Technical Client Manger/Global Lead, Extractable and Leachable (E&L) Testing,

SGS

## Introduction: extractables and leachables and residual solvent testing

Headspace (HS) sampling coupled to gas chromatography (GC) is commonly used in the pharmaceutical industry to provide fast and convenient analysis of volatile impurities impacting the quality and safety of the pharmaceutical processes and products. Used or created during the production of drugs and pharmaceutical additives, residual solvents are volatile impurities that manufacturers must ensure are not present at toxicologically significant levels as laid out in the United States Pharmacopeia (USP) general chapter <467> Residual Solvents. Additionally, pharmaceutical products come into contact with a wide range of materials on their journey from production to patients. Materials such as plastics can contain a wide range of extractable and leachable (E&L) organic compounds that are derived from additives and storage aids such as antioxidants, plasticizers, emulsifiers and colorants. The volatile fraction of E&L can be conveniently analyzed with simple sample preparation, thanks to the HS sampling technique, which extracts the volatiles leaving behind heavier non-volatile matrix compounds, preventing possible contamination of the analytical system.

Contract laboratories performing E&L and residual solvents tests are usually under pressure to turn around client projects quickly, because the results must be supplied to regulatory agencies prior to bringing pharmaceutical products and medical devices to market. Therefore, robust and reliable instrumentation, particularly for unattended operation, is imperative when choosing analytical systems. For the analysis of volatile organic compounds where HS coupled to GC or GC-MS is the technique of choice, solvent carryover is an additional challenge, which may require several cleaning blank runs between test samples. Another challenge for E&L analysis is unknown identification; both the testing laboratory and the client may not know what is present in the samples.

These are among the concerns of the Extractable and Leachable (E&L) Testing laboratory of SGS, a laboratory chartered with performing comprehensive testing for extractables in container materials, medical devices and single-use systems, as well as leachables in final products. Using the Thermo Scientific™ TriPlus™ 500 Headspace (HS) Autosampler coupled to the Thermo Scientific™ TRACE™ 1310 GC and Q Exactive™ GC Orbitrap™ GC-MS/MS system, the laboratory is realizing the benefits of enhanced productivity and increased confidence in test results for targeted and untargeted compounds identification and quantitation. In their evaluation of the TriPlus 500 HS autosampler with flame ionization detection (FID) for routine residual solvent testing for USP <467> compliance, the laboratory has developed a robust analytical workflow and high sample throughput capabilities.



TriPlus 500 GC HS Autosampler coupled to the TRACE 1310 Gas Chromatograph



Photo courtesy of SGS

“With a 120-vial capacity and TraceFinder software, it is easy to run a large sequence of many samples for longer unattended operations. We set up the method and go. This will increase our throughput for both E&L and residual solvent testing substantially.”

— Mr. Xiaoteng (Shelton) Gong

### Designed for reliable automation

To deliver client results in a timely manner, reliable automation is essential. Instruments must be able to dependably run a large number of samples, unattended overnight. With the highest sample capacity for a valve-and-loop system, and 12 positions for simultaneous incubation, the TriPlus 500 HS autosampler offers the highest overlapping capability for long unattended sequences.

According to Lu, “with a 120-vial capacity and TraceFinder software, it’s easy to run a long sequence with a lot of samples, which helps us achieve higher throughput. And we have the flexibility to run either 10 or 20 mL vials in the sequence. With our previous headspace system we had to manually change the configuration to accommodate different vial sizes, which took about five minutes, and even then the vials of different sizes could not be run in one sequence.” “TraceFinder software offers a very simple workflow, making it easy to set up and run a large sequence,” added Mr. Xiaoteng (Shelton) Gong, Instrumentation Chemist, Extractable and Leachable (E&L) Testing, SGS.

### Easy method transfer and flexible sequencing

Like the other HS systems in the laboratory, the TriPlus 500 HS autosampler is loop-based, allowing staff to port methods between systems easily, avoiding time-consuming re-validation procedures and re-optimization of methods to get the same or better results. The TriPlus 500 HS autosampler provides control of three

pressures — vial pressure, loop pressure and inlet pressure — compared to the limited parameter control of the other HS systems used in the lab. However, choosing optimum settings for these additional method parameters is straightforward. “For these pressures, it is very easy to determine the correct parameter, so in general it is easy to transfer a method and obtain the expected results” said Gong.

For laboratories performing research and development (R&D) with substantial method development, Thermo Scientific™ TraceFinder™ software offers increased flexibility and an array of capabilities for performing both routine quantitation and unknown analysis with Orbitrap mass spectrometer generated high-resolution accurate-mass (HRAM) GC-MS data. For those laboratories, TraceFinder software provides valuable tools like intelligent sequencing, which can be used to make real-time decisions that prevent manual review and re-analysis of suspect samples. Intelligent sequencing can be configured to trigger actions on flagged results for real-time rejection of samples, insertion of blanks, and to halt sample sequences in which data has fallen outside of predefined criteria. “Intelligent sequencing has more options,” noted Gong. “For R&D and method development projects, we want more flexibility to change and monitor methods — we need to set up five, six or even ten methods per sequence, while for routine testing we need higher throughput. Having the option to do both helps us to address both types of projects,” added Lu.



Photo courtesy of SGS.

“A challenge with headspace GC-based testing is carryover of residual organic solvents. It does take time or effort to deal with carryover. We found that the TriPlus 500 GC headspace autosampler fully addresses the carryover problem.”

— Dr. Dujuan Lu

### Unique direct-connect design eliminates carryover

For HS-GC testing, the injector can hold onto residual solvent, causing carryover risks to sample integrity. Carryover can interfere with subsequent injections because the residual compound can remain in the system for a long time or until it is manually cleaned or the system baked. Method optimization to reduce these risks is time consuming and may not fully eliminate the problem. The TriPlus 500 HS autosampler addresses this concern with a unique design that delivers the highest possible sample integrity while eliminating carryover (Figure 1).

According to Lu, “Based on our studies, the TriPlus 500 HS autosampler is able to remove all the residual solvent between injections. Directly after an organic solvent

injection, we can run a blank and see no carryover, which is excellent. By bypassing the GC injector and directly connecting the headspace system with the GC column, the TriPlus 500 HS autosampler eliminates any carryover issues. We haven’t seen this type of performance in any previous headspace instruments we’ve used.”

Effective purging and a short sample path ensure minimal-to-no carryover when the TriPlus 500 HS autosampler is used. Instead of a long transfer line connecting the HS to the GC column, the TriPlus 500 HS autosampler features a direct connection from the valve manifold to the GC column. This creates a shorter sample path that eliminates cold or hot spots and increases system inertness, assuring sample integrity during transfer into the column. The overall result is better chromatographic peak shape and high repeatability.

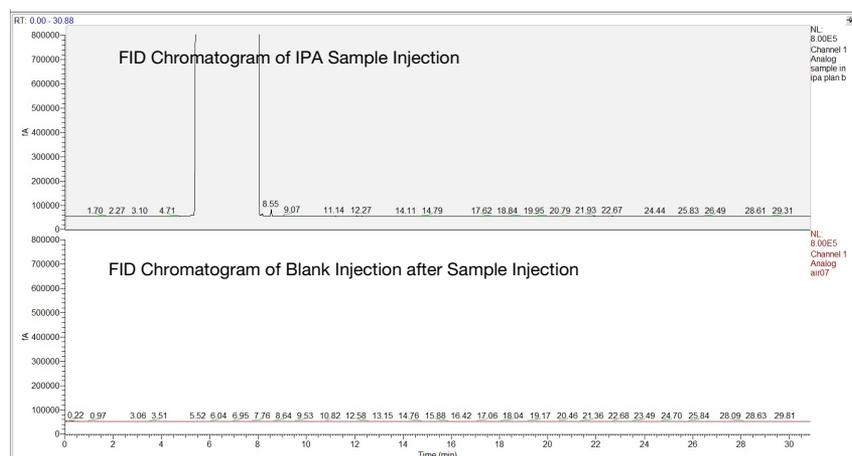


Figure 1. The TriPlus 500 HS autosampler GC-FID chromatogram of a blank injection (bottom) immediately following injection of pure Isopropanol Alcohol (IPA) (top) shows virtually no carryover. Chromatograms courtesy of SGS.

“For our extractable and leachable testing, one of the challenges we have is unknown identification. The Q Exactive mass spectrometer with its high-resolution accurate-mass capability helps us a lot with ID and structural elucidation of unknown compounds.”

— Dr. Dujuan Lu

### High-resolution accurate-mass data facilitates unknown identification

The potential for unknown E&L compounds in testing workflows is on the rise. Determining the identity of these compounds can be a complex challenge, requiring a significant amount of analytical detective work. To assist in this work, the Q Exactive GC Orbitrap GC-MS/MS mass spectrometer produces HRAM MS and MS/MS data for high-confidence unknown identification (Figures 2 and 3).

“Accurate mass helps with unknown ID and structural elucidation for unknown extractables and leachables, one of our big challenges. With accurate mass, you can

get to the chemical composition, and sometimes we run MS/MS to get structural information that helps us to structurally elucidate unknowns when needed. I highly recommend the Q Exactive mass spectrometer for unknown identification,” commented Lu. “The 1-ppm mass accuracy is impressive.”

Gong added, “In addition to the exact mass, which can give us enough information to determine the formula of the compound, the Q Exactive mass spectrometer should help us detect low-concentration components in our samples and standards, which will also help us to quantify and identify compounds.”

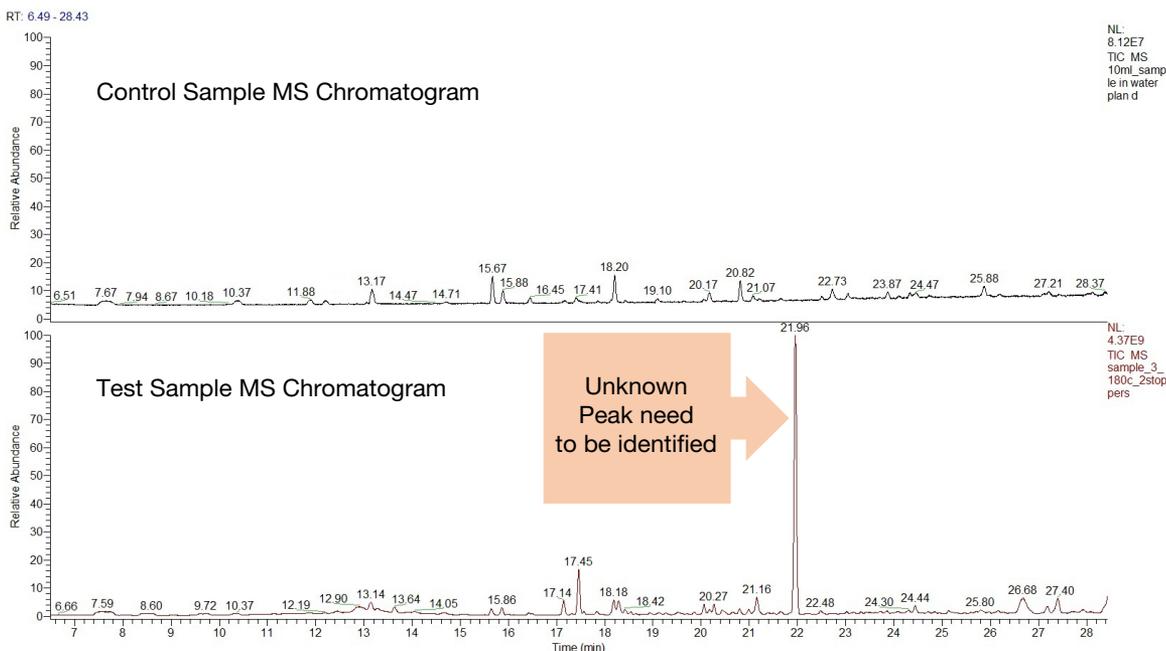
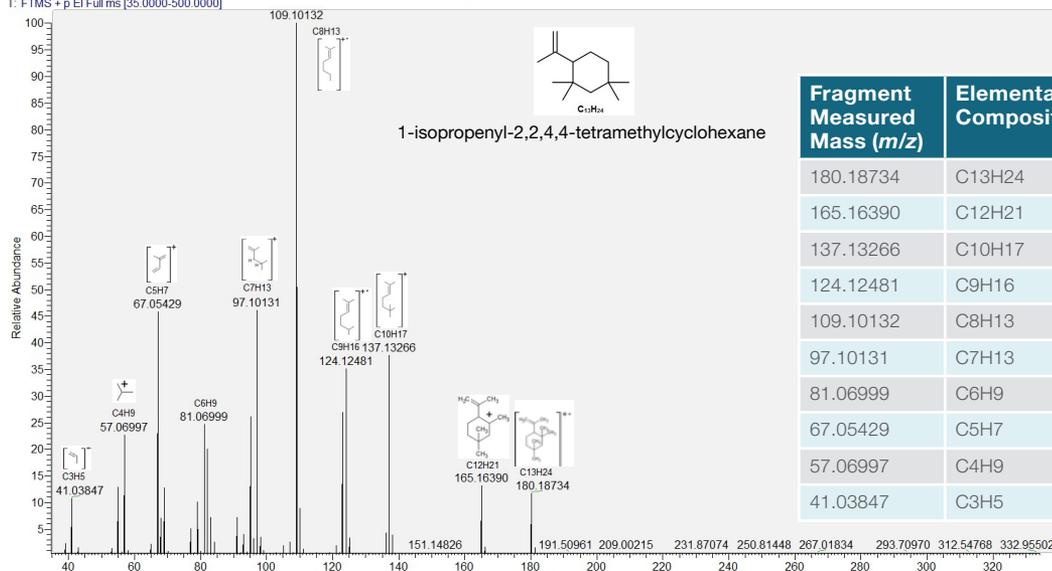


Figure 2. TriPlus 500 HS autosampler-Q Exactive Orbitrap GC-MS/MS mass spectrometer analysis of a negative control sample in which E&L are not present (top) and a test sample (bottom) showing an unknown peak in the MS chromatogram. Chromatograms courtesy of SGS.

Sample\_3\_180C\_2Stoppers#4869-4879 RT: 21.93-21.98 AV: 11 SB: 55 21.77-21.87, 22.08-22.22 NL: 5.94E8  
T: FTMS + p EI Full ms [35.0000-500.0000]



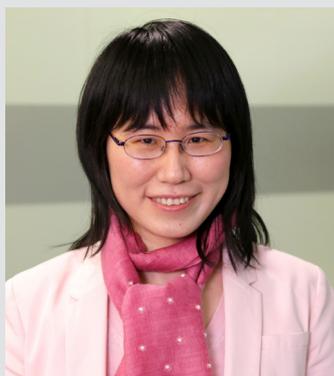
Fragment Measured Mass (m/z)	Elemental Composition	Fragment Theoretical Mass (m/z)	m/z error (ppm)
180.18734	C13H24	180.18725	0.49
165.16390	C12H21	165.16378	0.74
137.13266	C10H17	137.13248	1.33
124.12481	C9H16	124.12465	1.27
109.10132	C8H13	109.10118	1.31
97.10131	C7H13	97.10118	1.37
81.06999	C6H9	81.06988	1.40
67.05429	C5H7	67.05423	0.94
57.06997	C4H9	57.06988	1.63
41.03847	C3H5	41.03858	-2.6

**Figure 3.** Based on the high-resolution accurate-mass spectrum of the unknown peak provided by the Q Exactive GC Orbitrap GC-MS mass spectrometer, the formula of each fragment can be confirmed and the unknown compound structure elucidated. The table is reporting the 1-isopropenyl-2,2,4,4-tetramethylcyclohexane fragments information, showing exceptional high mass accuracy provided by the Orbitrap technology even for for low masses (< 100 m/z). Chromatogram courtesy of SGS.

## Conclusion

Powered by an innovative design, the TriPlus 500 GC HS autosampler maximizes productivity and confidence in results. Add seamless integration with TRACE 1310 GC, Q Exactive GC Orbitrap GC-MS/MS instrumentation and TraceFinder software, qualitative and quantitative determination of known and confident identification of

unknown volatile impurities are much more efficient and accurate. Together, these analytical solutions allow R&D analysts to cut through the complexity of E&L testing workflows and help QA/QC labs to boost sample throughput for residual solvents routine testing to ensure the safety and purity of pharmaceutical products.



## About Dr. Dujuan Lu

Dr. Dujuan Lu serves as the manager for the extractables and leachables (E&L) team at the SGS Fairfield facility as well as the global leader amongst the three centers of excellence for E&L testing. Before joining SGS, she was working at Fresenius Kabi, leading E&L projects to support transfusion and infusion medical device and parenteral products. She has extensive pharmaceutical industry experience with more than 300 E&L projects on a broad range of packaging systems, including process materials, pharmaceutical finished packaging, and medical device. As a well-recognized E&L subject matter expert in the field, she is frequently presenting at various conferences as invited speakers and technical session chairs. She holds her PhD in analytical chemistry from the University of Pittsburgh with more than 10 years of experience in pharmaceutical analysis by LC-MS and GC-MS.



### About Mr. Xiaoteng (Shelton) Gong

Xiaoteng Gong received his Master's degree from the Illinois Institute of Technology, and has worked on food contact materials at the National Center for Food Safety and Technology (NCFST) of the Food and Drug Administration (FDA). With extensive experience in analytical chemistry, he currently is an instrumentation chemist specializing in extractables and leachables (E&L) study for pharmaceutical packaging at SGS. Gong has more than five years of experience using Headspace (HS) gas chromatography (GC)/Mass Spectrometry (MS). In addition he is the project manager directly carrying out the TriPlus 500 GC HS autosampler application project.

### About SGS

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SGS contract laboratory services offer a range of capabilities along with the resources and know-how to help clients navigate complex bio/pharmaceutical and medical device markets. These laboratory services employ the latest technology and methodologies—so clients get the most accurate and reliable results possible. Expert staff is trained to the highest standards and has an in-depth knowledge of their fields and client business needs.



SGS, Fairfield, New Jersey. Photo courtesy of SGS.

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