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ZINSSER ANALYTIC
by Gardner Denver

Highly Flexible Automation Solution for Synthesis Workup and Solid Phase Extraction

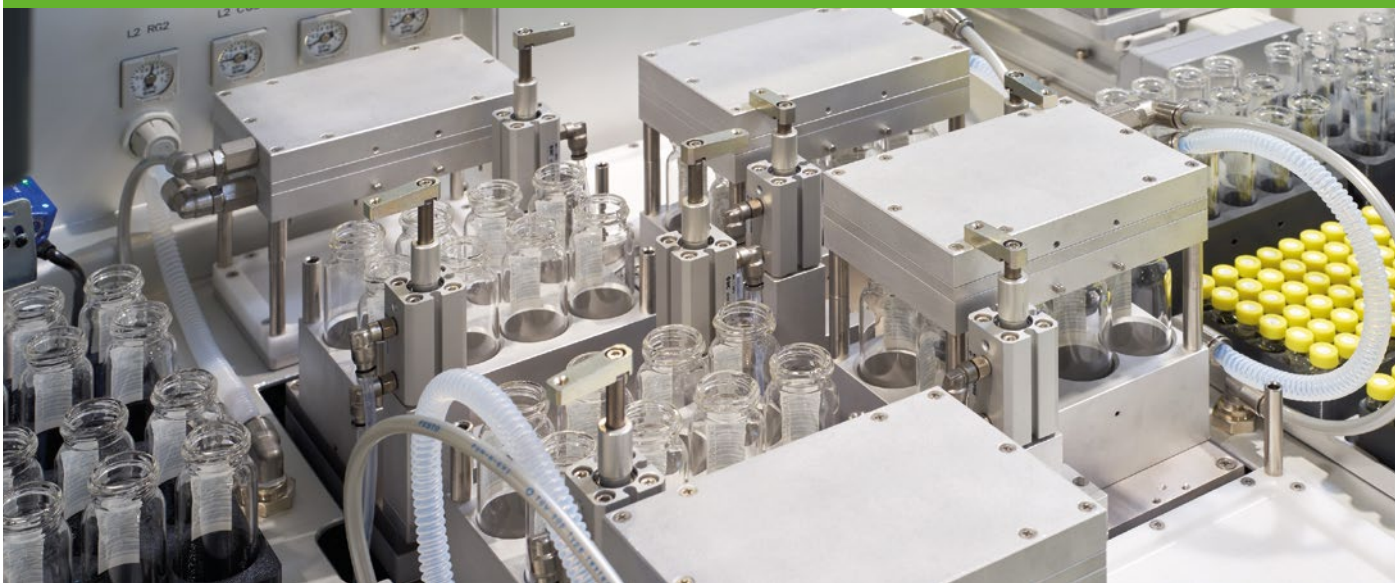
Fast, efficient and flexible synthesis workup with innovative and precise SPE modules.

Fully Customized Automated Solution

Zinsser Analytic and Eli Lilly and Company ("Lilly") designed, developed and successfully implemented a fully automated platform to automate Solid Phase Extraction (SPE) for sample pre-purification. SPE, the first step in their high-throughput purification strategy, has proven to be of great success in terms of both, efficiency and cost-effectiveness (e.g. single preparative LC/MS injection per sample and lack of system downtime due to the high quality of the SPE isolated material).

Solid Phase Extraction (SPE) in chemistry research laboratories is usually performed in semi-automated or even manual mode due to the lack of fully automated solutions capable of handling the amount of material generated at the working scales of Drug Discovery. Although SPE work can be efficiently performed, mostly if applying generic protocols, it still distracts chemists from more value-added tasks, such as molecule design. Lilly was looking for a platform able to perform the entire workflow in a fully automated manner. Zinsser Analytic was the only manufacturer with the engineering skills and flexibility willing to collaborate on the design and development of the customized SPE workup solution that could meet all the customer's specific requirements. This strong collaborative effort provided a unique approach in laboratory automation that is expected to push the boundaries of what is possible in the industry. The novel fully automated platform, equipped with modular tools to fit into the customer's process, moves materials from crude reaction mixtures to dried SPE collected fraction(s) without human intervention, with required labware made available to the system in an automated manner by an external robotic arm.

- ✔ End-to-End Solution
- ✔ Reproducible and Reliable Results
- ✔ Continuous Processing of Samples Arriving at Different Times on the Platform
- ✔ Customized Graphical Software Interface
- ✔ Meets the Needs of a Broad Range of Working Scales and Chemistries
- ✔ Efficient Sample Pre-Purification or Even Purification Depending on Intended Use of Isolated Material



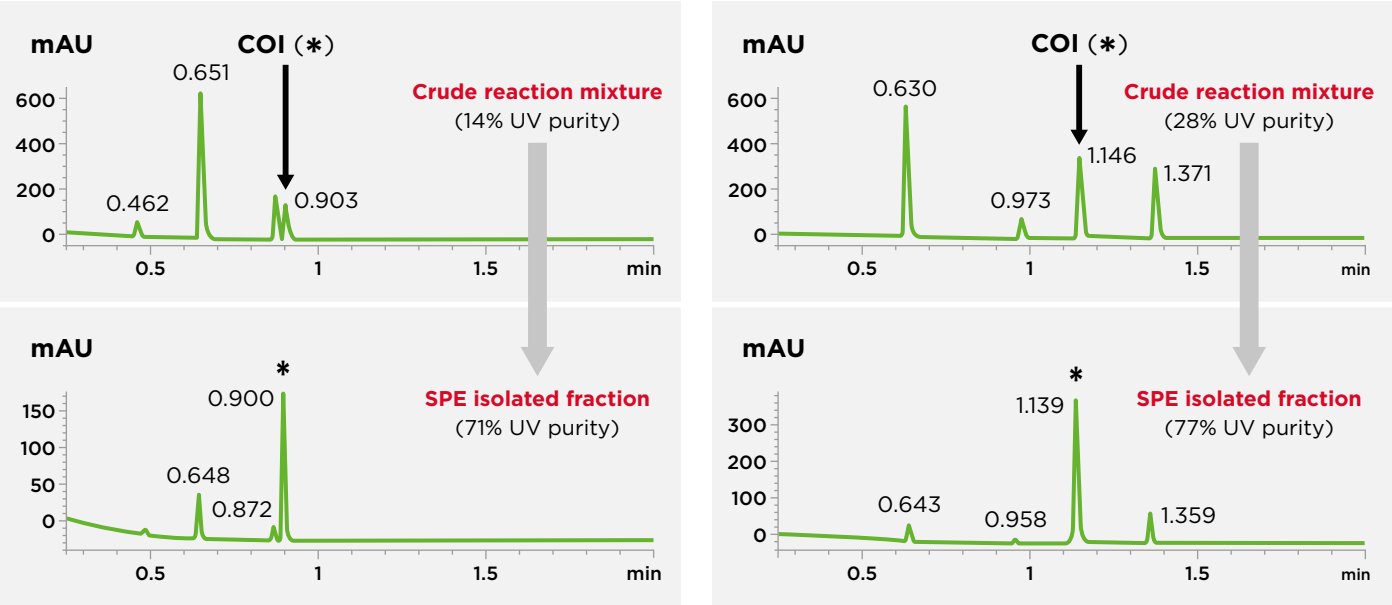
PROCESSES OF SAMPLE WORKUP

INPUT	• Single or multiple vials containing crude reaction mixture(s).
PROCESS	• Evaporate residual solvent from synthesis step.
	• Reconstitute in specified volume of solvent compatible with SPE protocol assigned to sample.
	• Vortex the resulting homogeneous or heterogeneous solution.
	• Sonicate to ensure maximum solubility even after vortexing.
	• Centrifuge for separation of the supernatant and precipitate.
	• Condition SPE cartridge as detailed in the assigned SPE protocol (step run under minimal positive pressure).
	• Transfer supernatant – expected to contain the dissolved compound of interest (COI) – onto the SPE cartridge.
	• Allow for proper retention of supernatant on the cartridge (by gravity load).
	• Run elution step(s) as detailed in the assigned SPE protocol (with specified positive pressure).
	• Take aliquots from each collected fraction and dilute in the appropriate solvent for running LC/MS analysis.
	• Identify the fraction(s) containing the COI by LC/MS data analysis.
	• If COI is not found in any of the SPE collected fractions, process the precipitate in the receiving vial under new conditions, repeat LC/MS analysis on collected fraction(s) to determine if COI has now been extracted.
	• Concentrate or fully evaporate the SPE collected fractions.
OUTPUT	• Single or Multiple vials (e.g. if COI elutes in >1 fraction or if multiple COIs are selectively isolated in separated fractions) containing pre-purified samples.

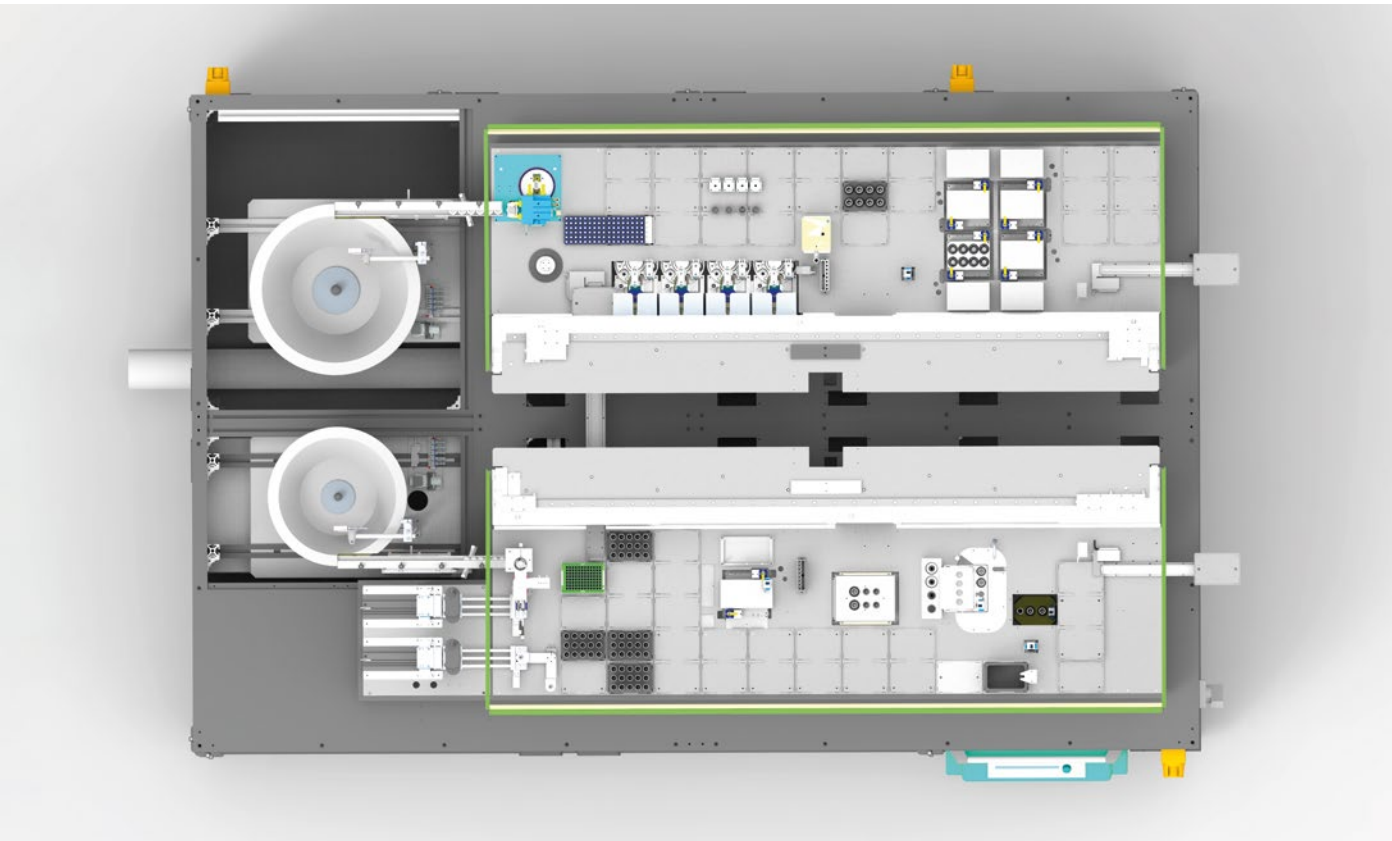
The time required to complete a sample depends on reaction scale, both the number and volume of SPE conditioning and elution steps, etc. The time can also depend on the number of samples being processed simultaneously in the platform (continuous process where multiple samples can be run at the same time, each at a different step, but in case of those steps that can be run in parallel such as evaporation or SPE itself).

REAL EXAMPLES OF PRE-PURIFICATION RESULTS

Properly performed SPE simplifies the entire analytical purification workflow. In addition to a significant reduction of the amount and the complexity of the material to be purified by preparative LC/MS, SPE removes impurities that are either responsible of most LC/MS blockages / system downtime (e.g. catalysts) or demand a significant analytical LC/MS method development effort to find conditions for successful LC/MS scaleup (e.g. impurities eluting very close to COI). Using both the new platform and the appropriate SPE protocols, crude reaction mixtures can be pre-purified in fully automated fashion and with exceptional results: COI can be isolated at purity >98% with standard values ranging from 75 to >90% depending on the complexity of the crude reaction mixture.



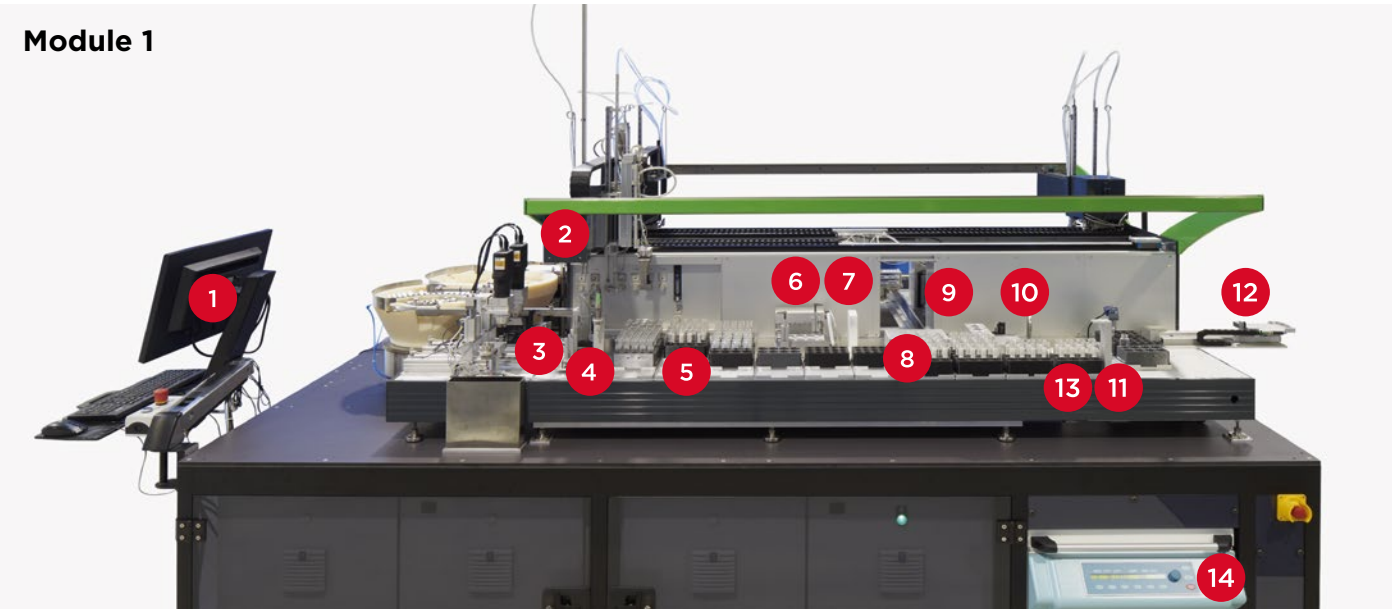
The platform was designed with the ability to contain some level of future proofing. As an example, disposable tip-based SPE hardware – tip adapter and dropping station – is already available in the unit for potential rapid integration either as a new workflow or as a new step into existing ones.



HARDWARE DESIGN

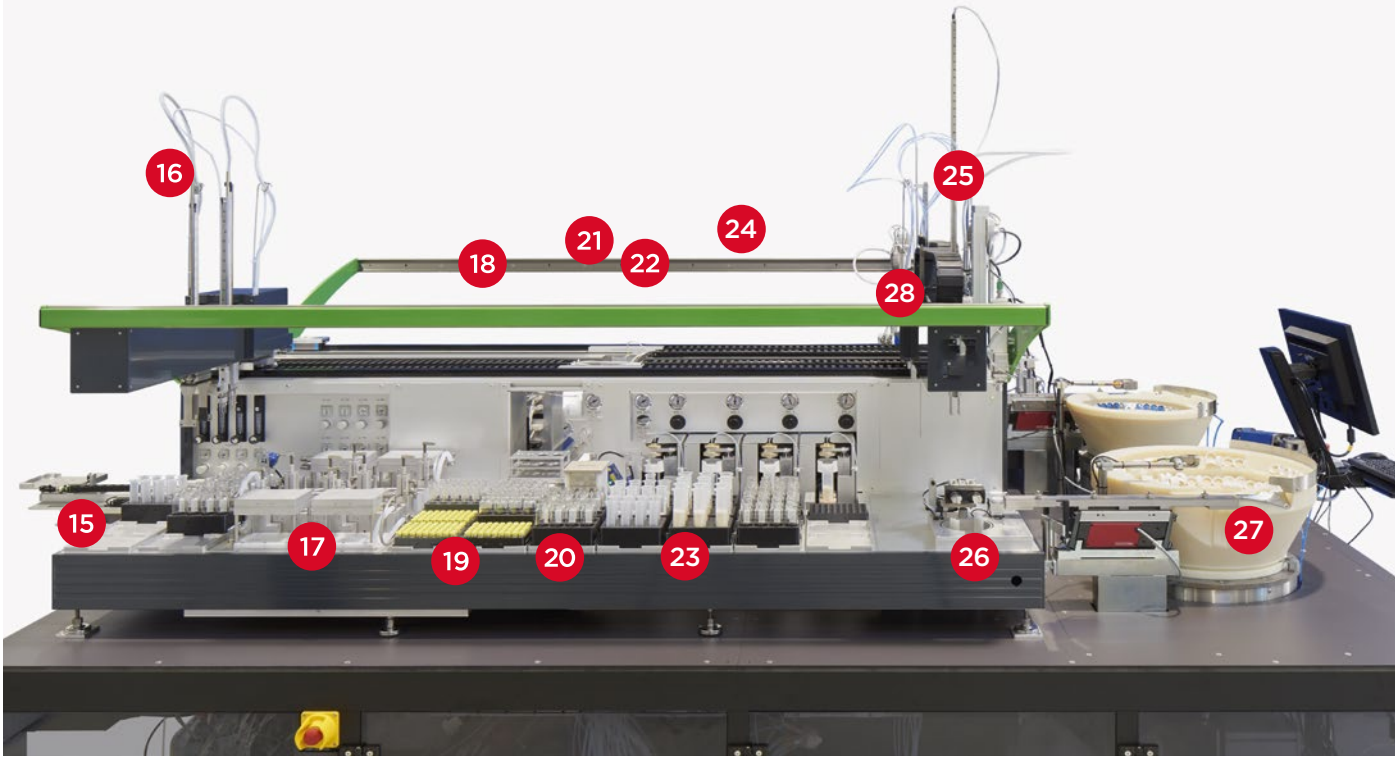
By using a back-to-back design with a connecting shuttle, two modules (1 and 2) have been combined in a single platform thus reducing footprint and enhancing efficiency by allowing continuous, parallel processing of work.

Module 1



1	Process control computer.
2	Robotic arm equipped with grippers for rack and vial transportation, liquid handling channels including 1 stainless steel tip and 1 disposable tip adapter, both for 3 mL syringes.
3	Crimping and decrimping stations for glass vials with crimp cap feeder.
4	Liquid level sensor.
5	Deck trays with positions for racks for pipetting and park positions.
6	Evaporation station.
7	Wash station for pipetting tips.
8	Vortexer with heating plate.
9	Connection shuttle between modules.
10	Ultrasonic bath with vial drying station.
11	Workbench-cutout for installation of vials into the centrifuge.
12	Connection shuttle for incoming and outgoing racks with 2D barcode reader for racks and vials, enabling integration with external robotic solutions for unattended loading of required labware.
13	Camera module for image recording.
14	Centrifuge (underneath workbench).

Module 2



15	Connection shuttle for incoming and outgoing racks with 2D barcode reader for racks and vials, enabling integration with external robotic solutions for unattended loading of required labware.
16	Robotic arm equipped with grippers for vials and racks.
17	Four evaporation stations with eight ports each.
18	Shuttle to move racks with vials between the two modules.
19	Resource racks for HPLC vials.
20	Resource racks for SPE fraction vials.
21	Ultrasonic bath for pipetting tip cleaning and wash station.
22	2D barcode reader for vials, racks and camera module installed into workbench.
23	Resource racks for SPE columns.
24	SPE stations with four elution vials each.
25	Robotic arm equipped with a filtration tip and grippers for vials and SPE cartridges.
26	Capping and decapping station for vials.
27	Screw cap stock and feeder.
28	Vortexing station.

PRECISION IN EVERY DETAIL

With the broad variety of devices included in the modules we are able to automate almost every process.

2 Arm Tools

- Multiple arms are available that include:
  - Grippers for different types of vials: HPLC, small / medium / large scale glass vials, in addition to SPE cartridges (20 and 35 cc) or racks.
  - An adapter for disposable tips.
  - A piercing pipetting tip with downholder.

3 Crimper / Decrimper (Module 1)

- Laser-controlled cap orientation of incoming caps from the feeder.
- Vial transport rails to place the vials safely with the arm gripping tool and ensure a smooth movement to the crimping and decrimping station.
- Waste box for removed crimp caps.

4 Liquid Level Sensor (Module 1)

- Level surface detection (supernatant in vial).
- Supernatant transferring tip going to “slightly below” solution level point, slowly aspirating total volume with level tracing and without getting into precipitate (minimized risk of blockage).

8 10 Vortex, Ultrasonic Bath and Centrifuge (Module 1)

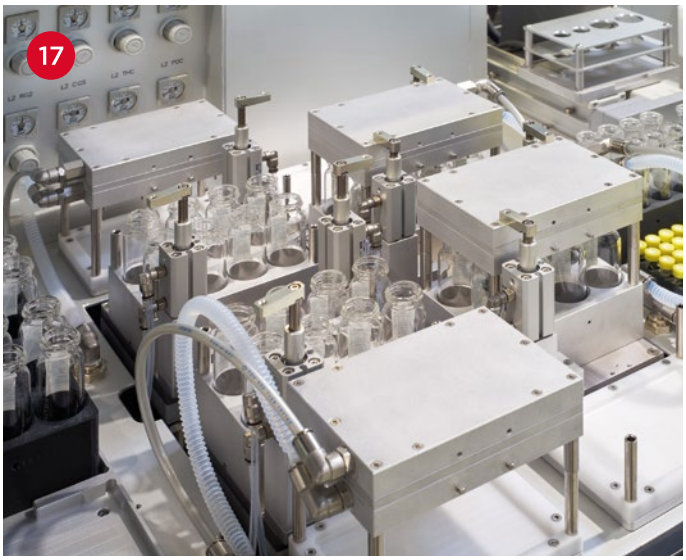
- Vial shaker with integrated hotplate tailored to customers’ specific vials.
- Ultrasonication in ultrasonic bath followed by vial drying on a separate station with help of compressed air. Continuous process, one by one in current design, four vials in parallel in the new design.
- Centrifugation of single (using dummy vials for balancing) or two same sized vials.

13 22 Camera (Modules 1 & 2)

- Polarization filter and back light unit / light box.
- Software for imaging recording and archiving.
- Possible Image Analysis (detection of gray values).

17 Evaporation Stations (Module 1 & 2)

- Nitrogen / air stream and moderate shaking while heating to speed up evaporation process.
- Removed solvent continuously diverted to a highly efficient centralized exhaust.
- Single station (15 positions) in module 1 and four stations (8 positions each) in module 2 for increased throughput.



21 Vortexer, Sonication Bath and Wash Station (Module 2)

- Single vial shaker to ensure solution homogeneity if not evaporating collected fraction(s) to dryness and/or in case a new solvent is added for reconstitution (e.g. for further injection in preparative HPLC/MS).
- Ultrasonic bath and wash station for tip clean-up to prevent cross-contamination and/or to recover from undesired blockages.

24 SPE Stations (Module 2)

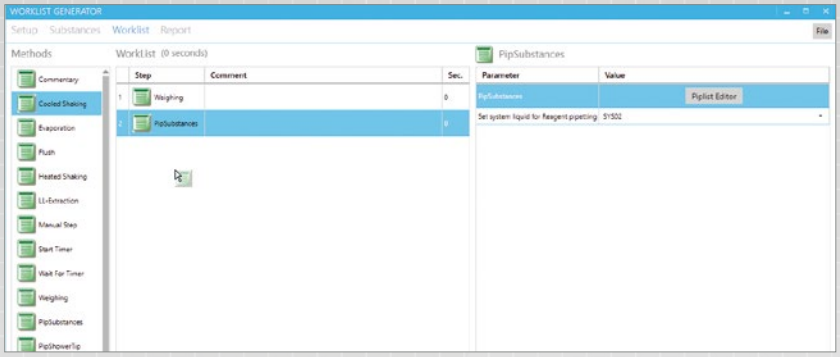
- Continuous processing on four independent manifolds enabeling up to four samples in parallel.
- Commercial 20 and 35 cc cartridge sizes, available from multiple vendors.
- Carousel with four elution vessels, there will be six positions in the new design.
- Conditioning of SPE column independent from arm pipetting tools.
- Sample loading with filtration pipetting tip.
- Integrated management of wash and waste solutions.
- Pressure tool to run SPE steps as described in assigned protocol.
- Independent operation of SPE manifolds that allows for running different protocols (different solvents, cartridge sizes, resin types, etc.) either sequentially and/or in parallel.

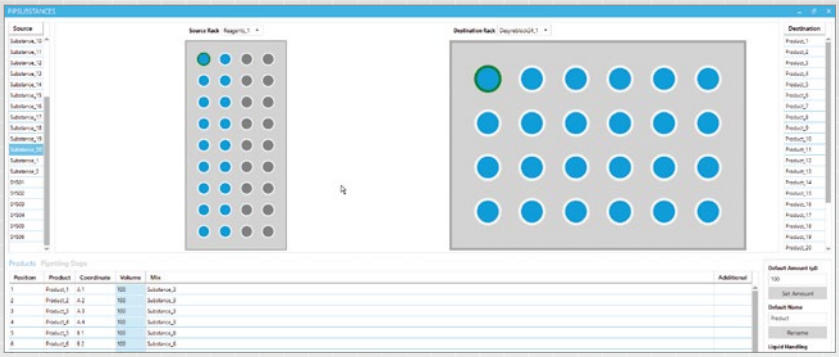
SOFTWARE SOLUTION FOR YOUR SPECIFIC PROCESS

Our software solution has a simple to use interface making it easy for your staff to configurate or change process steps by themselves. Every process step is designed modularly to help to set up a variety of individual processes depending on different samples, chemicals and solvents. This way you can easily set up the sample workup and solid phase extraction system according to your requirements and processes. Detailed Information about Zinsser Analytic's software solution are available in a separate note.

Worklist Generator

Drag and drop the needed methods to the desired positions of the worklist. Dynamic scheduling as well as continuous workflows with samples arriving at different times at the platform are easily feasible.



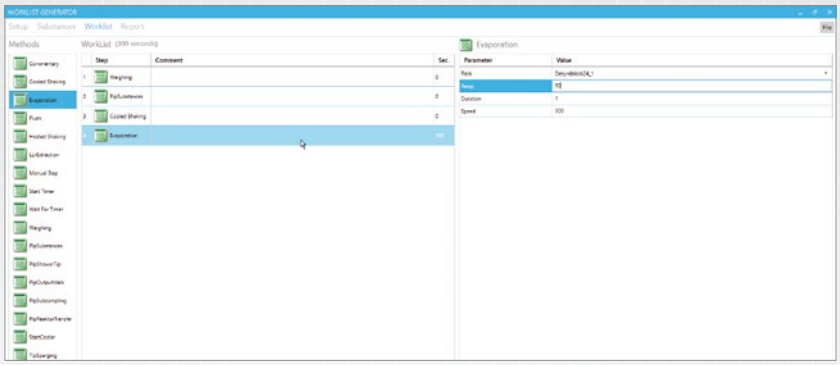


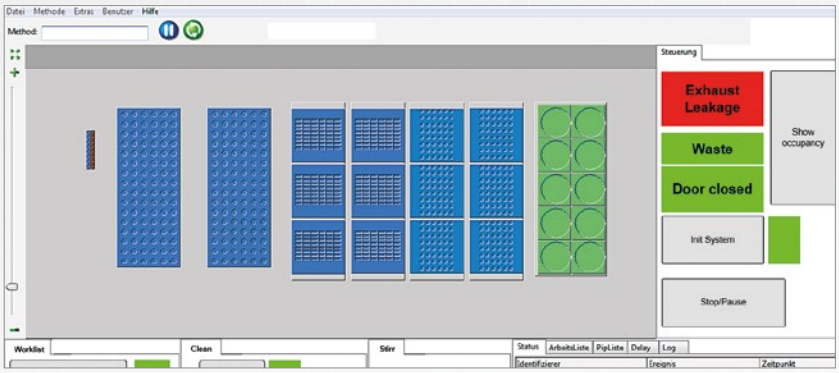
Pipetting Editor

For pipetting steps, the Pipetting-Editor is opened for the definition of racks and number of pipetting steps. Every filled position is indicated blue and the selected positions are highlighted green.

Method Definition

Input the desired time or anything the method requires, while you are defining the process. Each sample is tracked throughout the whole process, which enables easy and efficient workflow adaptions.





WinLissy®-Software

With our WinLissy®-software every prepared worklist of the Worklist-Generator is executable. Communication with customer specific databases or LIMS is easily conceivable.

GENERAL CONTACT

EMEA
Zinsser Analytic GmbH
Schwalbacher Str. 62
65760 Eschborn
Germany

Tel: +49 6196 58693 0
Fax: +49 6196 58693 80
info.zinsser-analytic@gardnerdenver.com

AMERICAS
Zinsser NA, Inc.
19145 Parthenia Street
Suite C
Northridge, CA 91324
USA

Tel: +1 818 341 2906
Fax: +1 818 341 2927
info@zinsserna.com

ASIA PACIFIC
Zinsser Analytic GmbH
Schwalbacher Str. 62
65760 Eschborn
Germany

Tel: +49 6196 58693 0
Fax: +49 6196 58693 80
info.zinsser-analytic@gardnerdenver.com

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