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Sartorius Extractables Simulator: Simplifying E&L Through in-Silico Modeling

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Abstract

The biopharmaceutical industry uses increasingly complex single-use technologies in order to benefit from maximum flexibility on production capabilities and to react to short-term demands. Maintaining, scaling, and combining extractables data has become a crucial step. To facilitate the employment of single-use systems (SUS) in critical processing operations, the industry requires alternatives to a purely test-driven approach. It requires a software-supported environment for a reliable data prediction. Sartorius has implemented specialized algorithms for the scaling and combination phases based on physical principles rather than intuitive and empirical procedures. We describe the conceptualization of a database and software application, the Extractables Simulator (ExSim). ExSim enables broad insight into device-related extractables under customer process conditions. We outline how this methodology will allow the industry to predict reasonable extractables data that are required as exposure data in risk assessments, even for the numerous, very complex modular systems on the market.

Introduction

With the successful deployment of single-use technologies (SUT), the importance of a good understanding of process equipment-related leachables (PERLs) has become a crucial aspect for biopharmaceutical manufacturers.[1,2] They must demonstrate that no compounds migrating from plastics into production or ultimately into medical products compromise patient safety.[3,4]

Two essential requirements for a comprehensive understanding of PERLs are fully elucidated extractables profiles of single-use (SU) devices and comprehensive Extractables & Leachables (E&L) qualification.[5,6] In addition, the BioPhorum Operations Group (BPOG) is driving an additional request of harmonized extractables investigation protocols across all SU suppliers with near-process, worst-case conditions[7]. At Sartorius, we decided that BPOG's recommendations were a good starting point but were not enough to create fully elucidated extractable profiles. That is why we go a step further and take a more in-depth approach to optimize component characterization:

The Standardized Extractables' Approach by Sartorius.[5]

Since 1996, we aim to simplify the use of single-use systems (SUS) for our customers by providing comprehensive solutions and providing our E&L expertise to support them in qualification (DQ|IQ) or process validation.

With this support, we fulfill the customers' need for E&L validation. Our experts determine the exposure data important for assessing patient safety. For this, the extractables data will be scaled to the customer process conditions and put into the patient context. Scaling is straightforward for homogeneous materials, such as a single piece of tubing. For devices made of different materials, such as sterilization filters, or even complex assemblies consisting of multiple subcomponents as shown in Fig. 1, correct scaling becomes much more complex.

We understand that, for lack of better alternatives, intuitive and worst-case approaches to safety evaluations have been taken in the past. That is why we are moving away from pure empiricism to simulation and prediction. With our proprietary Extractables Simulator (ExSim) software, we combine extractables, substance, plastics, and toxicological data with intelligent algorithms so that we can perform process-customized extractables scaling with a click.

There are no more concerns about how to master extractable scaling – even for complex assemblies.

Figure 1: Examples showing the variety of SUS: top, modular system of a bio-reactor, mixing tanks and crossflow cassette. Lower left, filter assembly for high throughput. Lower right, filters in different sizes connected with tubing and sterile connectors.

Methodology and Algorithm

Extractables studies for SUS are conducted based on standardized extraction protocols.[5,7,8] ExSim provides highly flexible functionality to use data from all available standardized protocols. A summary of the key extraction parameters can be found in Table 1.

	Sartorius Approach	BPOG	USP <665> (draft)
Extraction Temperature	40°C	40°C	40°C
Extraction Solvents	Aqueous, high and low pH, pure organic	Aqueous, high and low pH, 50% organic	High and low pH, 50% organic
Defined Short-Term Extraction			
Time Points	1, 7 days	1, 7 days	1, 7 days
SA_p/V_l ratio*	1:1 (cm^2/ml)	1:1 (cm^2/ml)	1:1 (cm^2/ml)
Defined Long-Term Extraction			
Time Points	21, 70 days	21, 70 days	21, 70 days
SA_p/V_l ratio*	6:1 (cm^2/ml)	6:1 (cm^2/ml)	6:1 (cm^2/ml)

*Ratio of component surface area (SA_p) to extraction volume (V_l)

Table 1: Comparison of three standardized extraction protocols

It is noteworthy that all published standardized experimental protocols have a high degree of overlap. All approaches contain two distinct temporal static extraction conditions, which can be characterized as follows:

- Short-time extractables experiments (1 to 7 days) that are diffusion-controlled.[9-11]
- Long-time extractables experiments (21 to 70 days) that are controlled by phase equilibrium.[10,12]

Scaling and Combination Algorithm for Extractables in Short-Contact-Time Experiments

The scaling and combination algorithm used in ExSim are derived from the principles of migration calculations. Migration calculations are describing the mass transfer of PERLs by diffusion inside the polymer and by partitioning of the PERLs between polymer and liquid phase. Migration calculations and associated modelling approaches are approved methods in the context of food-contact notifications in Europe.[13,14] The mathematical background for the diffusion-controlled mass transfer can be found in Crank.[9] Applications of migration calculations are published by Piringer and Baner.[10]

For short-term extractions, the release of extractables is a diffusion-controlled process, which can be described by Ficks' first law of diffusion. It relates the flux of PERLs through a surface element (F), with a diffusion constant (D) and a concentration gradient (dc) along the diffusion distance (dz):

$$F = -D\frac{dc}{dz} \qquad [\mu g/cm^2 * sec] \qquad \text{Eq. 1}$$

Surface related analytical extractables data are nothing else than temporary fluxes ($\hat{F}$), obtained over a certain extraction time (t_{ext}):

$$\hat{F} = F * t_{ext} \qquad [\mu g/cm^2] \qquad \text{Eq. 2}$$

The concentration (c_l) in the liquid phase can be calculated from the temporal flux by using the exposed polymer surface area (SA_p) and extraction volume (V_l):

$$c_l = \hat{F} * SA_p/V_l \qquad [\mu g/cm^3] \qquad \text{Eq. 3}$$

Considering that the fluxes of extractables from the different components is independent, the general equation for the scaling of extractables data for multiple combined SU devices (with components i = 1 ... n) can be given. The total extractables concentration in the solvent (c_l) is a function of the polymer surface areas ($SA_{p,i}$) and the surface-area-related extractables results of each component ($\hat{F}_i$):

$$c_l = \sum_{i=1}^{n}(\hat{F}_i * SA_{p,i})/V_l \qquad [\mu g/cm^3] \qquad \text{Eq. 4}$$

Justifications and the experimental proof of the correctness of the equations 3 and 4 are published elsewhere.[15]

Scaling and Combination Algorithm for Extractables in Long-Contact-Time Experiments

For long extraction times, the system is running into equilibrium, and the net flux F becomes zero. The contact surface area has no influence on the extractables concentration during long-contact extraction. The solvent's extractables concentration (c_l) at equilibrium conditions is a function of polymer and extraction volume (V_p and V_l), the partition coefficient ($K_{p/l}=c_p/c_l$), and the total mass of extractables (m_{tot}):[10,12]

$$c_l = \frac{m_{tot}}{V_l + K_{p/l} * V_p} \quad [\mu g/cm^3] \quad \text{Eq. 5}$$

Extractables originate initially from the plastic phase only, i.e., $c_{p,0}=m_{tot}/V_p$, and, therefore, Eq 5 becomes:

$$c_l = \frac{c_{p,0}}{V_l/V_p + K_{p/l}} \quad [\mu g/cm^3] \quad \text{Eq. 6}$$

This algorithm can be extended to *n* different components with different sizes. Herein, the total mass of extractables in all components is given by $\sum_{i=1}^{n}(m_i)=m_{tot}$. The individual partition coefficients between component i and the extraction solution are $K_{i/n}$, and V_i are the volumes of the different components. By convention, the extractables concentration in the solution is assigned to the n^{th} component ($c_l=m_n/V_n$). This leads to:

$$c_l = \frac{\sum_{i=1}^{n-1}(m_i)}{\sum_{i=1}^{n-1}(K_{i/n} * V_i) + V_n} \quad [\mu g/cm^3] \quad \text{Eq. 7}$$

The derivation and detailed justification of equations 5 – 7 can be found in the recent publication from Hauk et al. 2021.[16]

Estimation of Partition Coefficients

The application of equations related to equilibrium-controlled extractables scaling (Eq. 5–7) requires the knowledge of the partition coefficients of the extractables in the given polymer | liquid system. A range of partition coefficients for standard plastics in contact with EtOH, but also alcohol | water mixtures, can be found in the scientific literature.[10] For various plastics in contact with pure ethanol commonly partition coefficient of 1 for typical organic extractables, like antioxidants and their degradation products are used.[10,14] Besides this approach, widely used in food contact migration modelling, methods to derive and | or estimate partition coefficients are described in the scientific literature.[16-21]

In case the extractables are organic acids, fatty acids, or phenols that can be deprotonated, the aqueous partition coefficient ($K_{p/l}$) for the neutral species needs to be adjusted to the pH value of the solution. A suitable equation for the adjustment of extractables partition coefficients to apparent partition coefficients ($K^{\#}_{p/l}$) for different pH values can be found in the literature:[12]

$$K^{\#}_{p/l} = \frac{K_{p/l}}{1 + 10^{(pH - pKa)}} \quad \text{Eq. 8}$$

For calculating ($K^{\#}_{p/l}$), the approximated default pKa values for all organic acids (pKa = 5) and all phenols (pKa = 10) are used.

Application Development

Sartorius developed an integrated system that aids in retrieval, scaling, and combining of extractables data. This consists of three main elements (cf. Fig. 2):

a. Database
b. Scaling and Combination Algorithms
c. Reporting Module

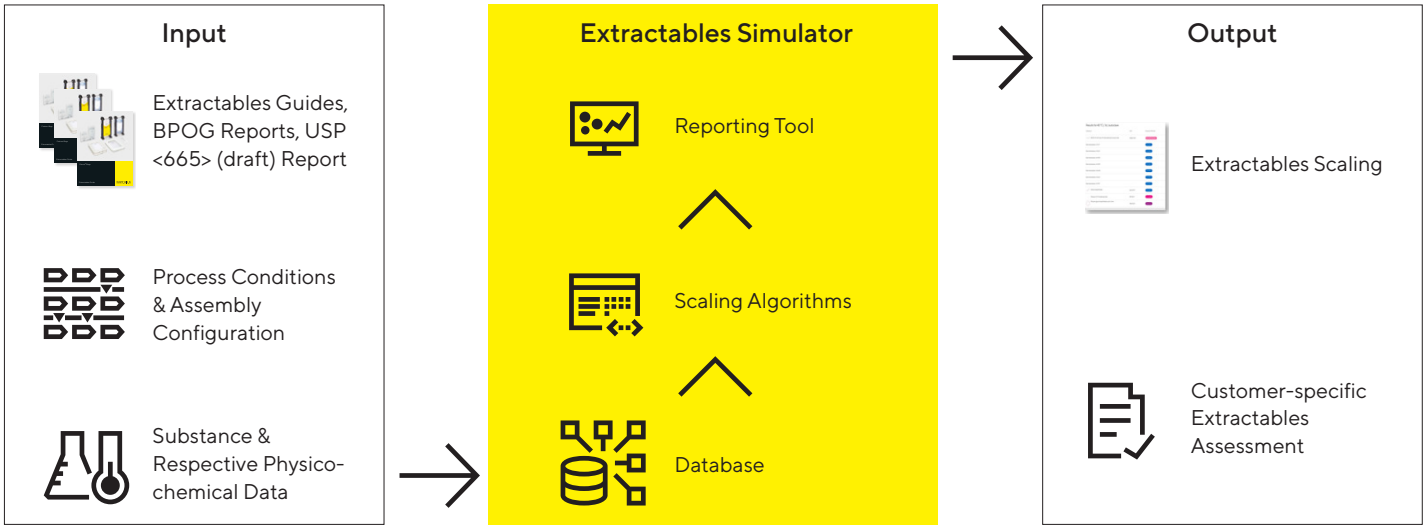


Figure 2: ExSim structure with schematic presentation of back-end (input); data-storage-container; retrieval, scaling, and combination algorithm, reporting tool, and front-end elements (output)

a) Database

The software includes the following categories stored in data objectives:

Analytical extractables results
The respective extractables data are taken from experiments conducted with the Sartorius extractables methodology, the BPOG protocol, and | or USP <665> (draft) protocol. This extractables data is currently available in 50 complete laboratory report data sets.

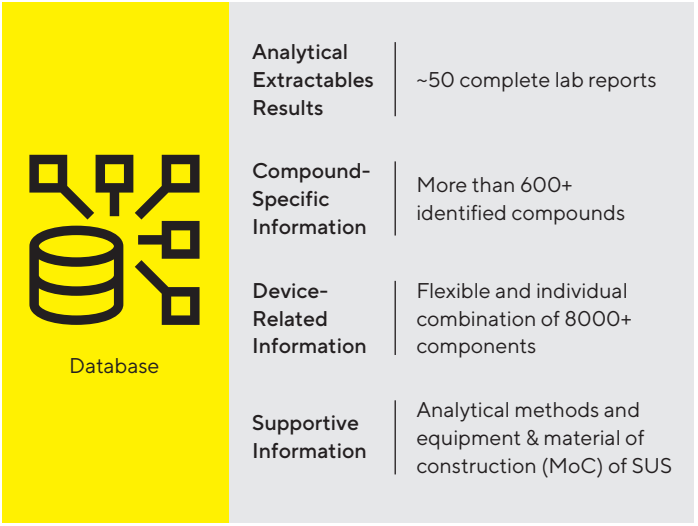
Compound-specific information
In this category the database summarizes all relevant substance information for 600+ identified compounds. This includes qualitative information, physical | chemical and toxicological properties as well as key parameters, such as: CAS number, chemical structure and molecular mass, and partition coefficients for various solvent compositions. In addition, a series of safety information, which can be used in toxicological assessments, are included.

Device-related information

More than 8,000 components are included in the ExSim. The relevant sizes and dimensions of each component are deposited and enable a flexible combination to configure individual SUS, assemblies, Configure-to-Order (CTO) or Engineer-to-Order (ETO) devices.

Supportive information

Additional information needed for writing reports and extractables guides is provided. This is, for example, the description of the analysis methods and analysis devices, including details on their operating conditions, as well as generic information on the tested devices such as the material of construction (MoC).



b) Scaling and Combination

For the scaling calculation, the Extractables Simulator correlates data from the database with information on process-related extraction conditions such as solvent, extraction time, and temperature. In detail, the scaling and combination of extractables data for assemblies, CTO, or ETO devices consists of the following phases:

Identification and retrieval of data for calculation

Physical and | or chemical parameters of the customer process can differ for each (sub-)component of the SUS device, i.e., the assumed contact times.

The software identifies the appropriate lab report in the database for every component and matches it with the process-related configuration.

Scaling and combining the quantities

For our extractables simulation, the system selects the appropriate algorithms to perform the analysis: either diffusion-controlled (short contact times) or equilibrium-controlled (long contact times) scaling. The following calculation modules (see Table 2) are available in the ExSim:

	Calculation Modules	Relevant Scaling Parameter	Contact Time*	Equation
1	Short contact time, one component	Surface Area	1, 7 days	Eq. 3
2	Short contact time, multiple components	Surface Area	1, 7 days	Eq. 4
3	Long contact time, one component	Polymer Volume	21, 70 days	Eq. 6
4	Long contact time, multiple components	Polymer Volume	21, 70 days	Eq. 7
5	Combination of short and long contact time, multiple components	Surface Area & Polymer Volume	1 – 70 days	Eq. 4, Eq. 6, Eq. 7

*According to the selected time points in the performed extractables tests of the respective standardized extractables protocols.

Table 2: Overview of available calculation modules in ExSim

Once the required data was identified and provided, the algorithm calculates the concentration of each compound across all analytical methods (i.e., GC-MS, HPLC-UV, LC-MS, etc.). It provides the highest cumulated concentration for the investigated device or assembly according to Eq. 4 or Eq. 7.

Traceability
The extractables quantities determined by the scaling and combination calculation may originate from multiple analytical methods or components. To ensure traceability of the results, the sources affecting the quantities and operations are recorded and kept in a log file. For each calculation, the complete calculation scheme is documented, including all coefficients used, as well as the calculation modules. This allows a complete reconstruction of all algorithmic decisions made in the scaling calculation. In addition, it ensures that the verifiability of predictions is not affected if the source information available in the database changes over time. The persisted resource preserves for the future critical information used in the calculations to provide a holistic understanding of the results.

Scaling and Combination

Identification and Retrieval of Data for Calculation	Matching of appropiate lab report to SU process component
Scaling and Combining the Quantities	Static extractables simulation for short and long contact times and multiple components
Traceability	Operation, calculation, quantities, and results are recorded and preserved for complete traceability

c) Reporting

The results of the scaling calculation are displayed in the web application as seen in Figure 3. Our reporting enables the user to read out the concentration of each compound regarding the device size, batch volume, and contact time according to the customer's process.

In addition, a download function enables further processing of the data. The data is provided in a tabular format and can be integrated into our Confidence® Extractables Assessments.

These assessments contain the similar information as an Extractables study performed in the laboratory. However, they are available within one week and at significantly decreased costs. Our assessments are qualified documents that can be used to support drug submissions to regulatory authorities.

Technical Implementation Overview

To provide accuracy and traceability of ExSim results, the back end is built based on the OpenJDK Java platform for strong typing and validation. The application is made accessible to educated users via an in-browser web application. In order to be able to guarantee qualified handling and results accuracy, users must be familiar with the deposited article number structure and the performed extractables experiments and also have a general understanding of extractables.

Our web application is a cloud-based, interactive system that enables optimal usability, low disruption, and reduced load times (thanks to a React user interface) while streaming data interactively over a web socket connection for smooth operation. This approach allows live collaboration of multiple users and fosters integration of the Sartorius internal extractables and leachables laboratories with other expert departments. It also provides an interface for integrating verified third-party extract data, for example, from a BPOG protocol.

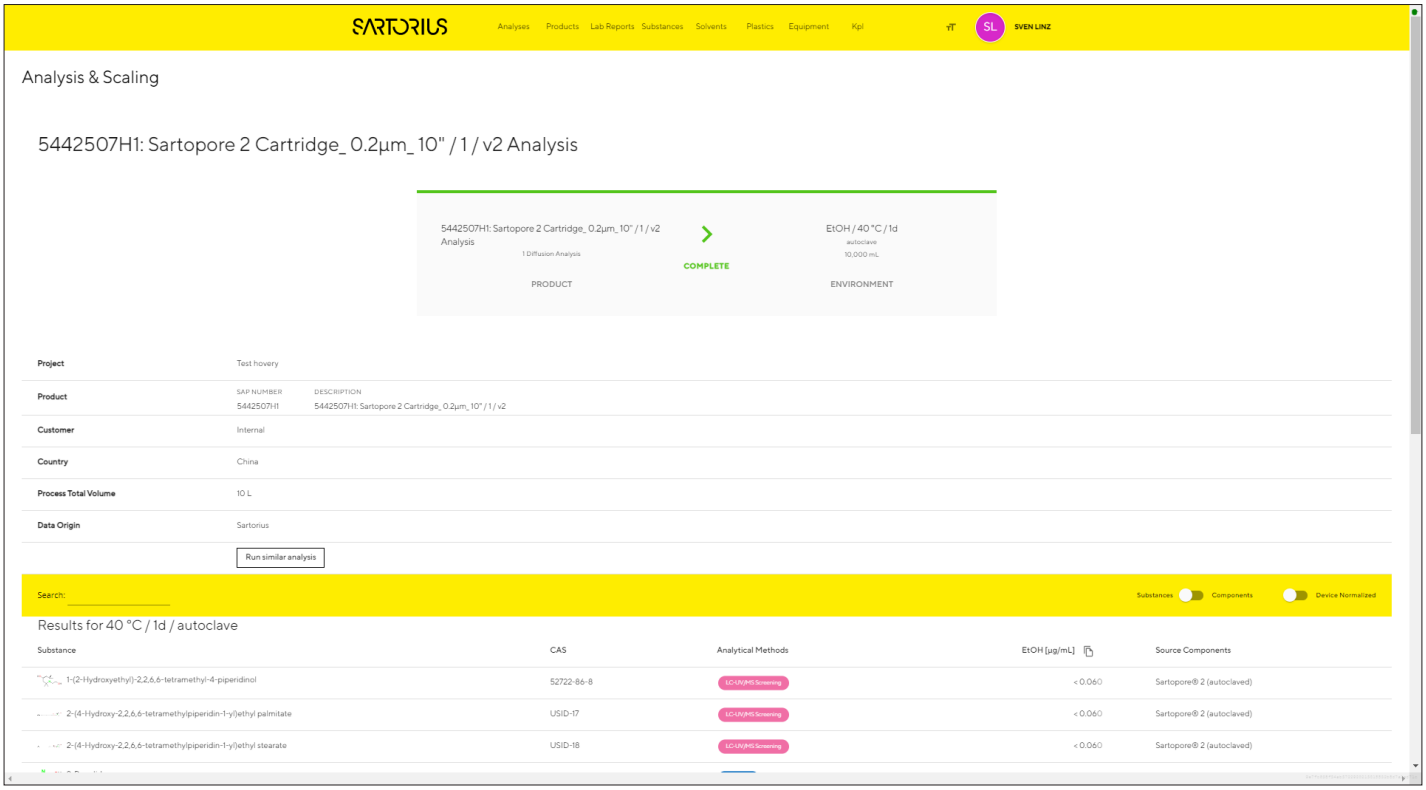


Figure 3: ExSim interface: extractables analysis calculation

Operational Qualification of the Extractables Simulator

The application was developed under controlled processes. For this purpose, during and after development, accompanying tests were performed for data integrity and algorithms. In addition, access to the database and programming are defined by access permissions. In use, it is ensured that all calculations are traceable via audit trails (access and data history as well as log files).

The result of operational qualification is that ExSim calculates concentrations correctly by retrieving the correct input data from laboratory reports and selecting the correct algorithms.

Examples of Extractables Calculations

Following, we show three examples of typical scaling and combination exercises, which can be made with ExSim using model extractables as shown in Table 3. Pure ethanol was assumed as the extraction solvent and a contact time of one day for components with short contact times and 21 days for those with long contact times.

Two equations are key to the scaling algorithms used for the flexible prediction of the potential extractables risk with the Extractables Simulator:

$$c_l = \sum_{i=1}^{n} (\hat{F}_i * SA_{p,i}) / V_l \quad [\mu g/cm^3] \qquad \text{Eq. 4}$$

$$c_l = \frac{\sum_{i=1}^{n-1} (m_i)}{\sum_{i=1}^{n-1} (K_{i/n} * V_i) + V_n} \quad [\mu g/cm^3] \qquad \text{Eq. 7}$$

Scaling a sterile filter cartridge
The basis for all scaling calculations is extractable data generated experimentally with a small laboratory test sample. Eq. 4 is used to calculate the process-specific concentration for short contact times, taking into account the effective membrane area (SA_p) and filtration volume (V_i). In real processes, a lower concentration is expected (see Table 3). This is due to a reduced surface-to-volume ratio, which in our examples decreases from 1 cm²/mL, worst-case laboratory application, to 0.6 cm²/mL.

Scaling a storage bag
Extractables data are available for bags for contact times of 21 or 70 days and a higher S/V ratio compared to filters of 6 cm²/mL. In our second example calculation, we have assumed a liquid volume (V_l) of 45 L for 21 days at 40°C. In addition to the liquid volume, the polymer volume (V_p) and individual $K_{p/l}$ values are considered in Eq. 7 to calculated process-specific extractables data.

Scaling an assembly
The third example considers an assembly of a filter capsule, tube, and a bag system with the following typical application scenario. The filter capsule is used shortly to fill the bag, and the filtrate is stored for 21 days in the bag after the filter is disconnected from the liquid phase.
The contact time with the filter capsule is less than one day and, consequently, the extractables obtained from the filter cartridge and capsule housing are calculated with Eq. 4. The amount of the extractables from the filter capsule scaling exercise are added to the total mass of extractables (m_{tot}) of the bag and tubing system. Thereafter, an equilibrium calculation with Eq. 7 is started for the components that are in long contact with the liquid phase (bag and tube).

All three examples will return scaled and combined extractables data, as if one had performed a static extractables experiment.

Extractables	Input Data	Concentration Extractables Guide	Concentration Scaled by ExSim
Scaling of a Sartopore® 2 basic filter	A = 2,000 cm² V_l = 45,000 ml		
1,3-Di-*tert*-butylbenzene		0.75 µg/ml	0.033 µg/ml
2- Pyrrolidone		0.85 µg/ml	0.037 µg/ml
4-Methylbenzaldehyde		0.25 µg/ml	0.011 µg/ml
Scaling of a 50 L Flexsafe® storage bag	V_p = 358.8 ml V_l = 45,000 ml		
1,3-Di-*tert*-butylbenzene	$K_{p/l}$ = 1	1.8 µg/ml	0.073 µg/ml
2,4-Di-*tert*-butylphenol	$K_{p/l}$ = 1	3.1 µg/ml	0.13 µg/ml
Dodecane	$K_{p/l}$ = 1	2.1 µg/ml	0.085 µg/ml
Scaling of an Assembly (Sartopore® 2, TuFlux SiL, 50 L Flexsafe® Bag)	A_{Filter} = 2,000 cm² $A_{Housing}$ = 350 cm² $V_{p\ Bag}$ = 358.8 ml $V_{p\ Tube}$ = 11.88 ml V_l = 45,000 ml		
1,3-Di-*tert*-butylbenzene	$K_{p/l}$ = 1	0.75 µg/ml (filter) 0.32 µg/ml (housing) 1.8 µg/ml (bag) 0.66 µg/ml (tubing)	0.11 µg/ml
2- Pyrrolidone	$K_{p/l}$ = 1	0.85 µg/ml (filter)	0.037 µg/ml
2,4-Di-*tert*-butylphenol	$K_{p/l}$ = 1	3.1 µg/ml (bag) 0.88 µg/ml (tubing)	0.13 µg/ml
4-Methylbenzaldehyde	$K_{p/l}$ = 1	0.25 µg/ml (filter)	0.011 µg/ml
Octadecamethylnonasiloxanediol	$K_{p/l}$ = 1	90 µg/ml (tubing)	0.035 µg/ml

Table 3: Example of scaling calculation for representative extractables of three device designs: filter, bag, and assembly

Conclusion

Sartorius has developed the first software of its kind in the field of extractables and leachables to lead the way from a purely test-driven to a software-supported approach.

The Extractables Simulator database acts as a single point of truth for extractables, substances, and toxicological data. Combined with the scaling algorithms based on either diffusion-controlled or equilibrium-controlled calculation, prediction of scaled extractables data becomes a reality. Fast retrieval of process-specific, worst-case extractable data, individualized to the customer's use case, for more than 8,000 single-use components and component combinations is now possible.

The ExSim enables unprecedented flexibility in the scaling and combination of extractables to cope with increasing SUS complexity. Not only extractables data generated using the Sartorius approach, but also those based on BPOG or the USP <665> (draft) protocol is suitable for this purpose, since the extraction parameters overlap to a large extent.

An additional novelty enabled by the Extractables Simulator is the creation of virtual extractables calculation for devices under development or as a "feasibility proof" before material changes in real processes.

The next step to further advance the accurate prediction of extractables and leachables will be the development of a tool that will allow not only the aggregation of extractable data, but also the in-silico prediction of potential process equipment-related leachables (PERLs). Based on input data from ExSim, this software tool will calculate PERLs in the dynamic environment of an upstream or downstream operation, appropriately accounting for sources and sinks and, in addition, flow and residence times of process fluids.

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