Development of a Standardized Extractables Approach for Single-Use Components

General Considerations and Practical Aspects — A Manufacturer's Perspective

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The subject of extractables for single-use bioprocess contact materials has been a subject of heated debate since roughly the summer of 2012, when the first ISPE paper was published issuing a call to action to develop a standardized extractables protocol for the industry (**1**). As a supplier that pioneered the science of extractables (**2–11**) and has published extractables data for our products for over 20 years, Sartorius Stedim Biotech (SSB) took the opportunity to look back, take stock, rationalize, and define a new internal procedure for extractable analysis of single-use components. The existing approach to support biopharmaceutical clients with extractables data and services for implementation of single-use products already evolved over many years at both Sartorius and Stedim before they merged into SSB in 2007.

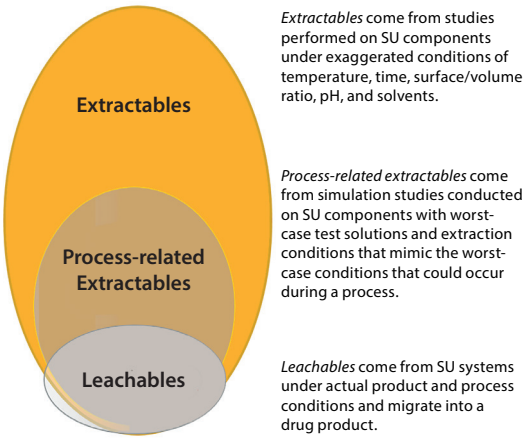
The decision was made to define a new SSB approach unconstrained by decisions of the past and supported by the best science currently available. We additionally decided that if a strong scientific rationale did not exist for a given decision, then scientific research would be conducted to provide such rationale.

We quickly determined that to define our new internal approach, we needed to ask and answer several questions relating to study intent, extraction solutions, conditions of extraction, and analytical methods. Other considerations included the number of lots to be extracted, definition of reporting limits, and third-party components.

Intent of Study

The root of all differences in extractables approaches stems from the stated intent of a study and follow-on use of data generated by it. For example, consider the discussion regarding which specific extraction solutions should be used for an extractables study: If the intent is to

Figure 1: Venn diagram shows the accordance between extractables, process related extractables, and leachables.



generate data to simulate bioprocess conditions, then real-world solutions (e.g., buffers) might be the right extraction solutions. If a study is intended to characterize a component chemically, however, then more aggressive solutions with higher propensity to extract might be more appropriate. This same logic drives many decisions made during definition of a new extractables approach.

No presentation on extractables and leachables is complete without some version of a Venn diagram showing leachables to be a subset of extractables. In Figure 1, we include an intermediate category for process-related extractables.

As we defined our internal procedure, we decided that the largest part of that Venn diagram was the responsibility of the supplier. We need to define the universe of potential extractables that characterizes our components and to assist in material selection, early toxicological risk assessment, and change control. This intent drives the definition of our entire approach.

Table 1: Parameters considered in the risk assessment

Risk Factor (RF)	Classes*	Risk Value
Temperature	–80 °C to +15 °C	1
	15–37 °C	5
	>37°C	10
Surface area to volume ratio (SA/V)	<0.05 cm^2/mL	1
	0.05–2.00 cm^2/mL	5
	>2.00 cm^2/mL	10
Contact time	0–24 hours	1
	1–30 days	5
	>30 days	10
Patient proximity	Upstream	1
	Downstream	5
	Formulation, filling	10

* Class levels are oriented on ISO 10993-1 if applicable

Risk Assessment and Classification of SU Components

SSB performed a risk assessment of the extraction of chemical entities that potentially remain within process fluid to end up in an active pharmaceutical ingredient (API). The assessment was performed with respect to the industry and authority view published by Merseburger et al. (**12, 13**). Risk factors such as temperature, ratio of surface area to volume, contact time, and proximity to patients were defined because they influence the extractables concentration of the SU component within a biopharmaceutical process. The patient-proximity factor takes into account purification steps that potentially dilute, concentrate, or remove leachables within a process stream. The influence of an extraction solvent is not part of this risk assessment. The intention of the extractables study is to seek for comprehensive information. Therefore, SSB performed a deep exercise for appropriate solvent selection (**6**).

To set the risk value (Table 1) for each factor, we considered using one SU component through the whole bioprocess. A risk score for each SU component is calculated by multiplying each risk value by 1, 5, or 10. Finally, risk is scored into

Table 2: Risk evaluation for SU components

Component	$RF_{temperature}$	$RF_{SA/V}$	$RF_{contact\ time}$	$RF_{patient\ proximity}$	Risk Value	Risk Classification
Storage bags	5	10	10	10	5,000	High
Mixing bags (storage bags, mixing parts, sensors, and valves)	5	5	5	10	1,250	High
Bioreactors	5	10	5	1	250	Medium
Tubing	5	10	5	5*	1,250	High
Tubing connector	5	5	5	5	625	Medium
Sterile connectors	5	5	5	5	625	Medium
Sterilizing-grade filters/process filters	5	10	1	5*	250	Medium
Crossflow filtration cassettes	5	5	1	5	125	Medium
Sensors (and valves)	5	5	5	5	625	Medium
Membrane adsorbers	5	10	1	5	250	Medium
Filling needles	5	1	1*	10	50	Low

Risk Scores: 1–50 low risk, 100–625 medium risk, 1,000–10,000 high risk

* For certain applications (e.g., fill–finish), the factor could be 10; nevertheless, it will not change the risk classification or derived actions.

three classes: low risk (L), medium risk (M), and high risk (H) (Table 2).

Different risk classifications were identified for SU components within process applications (Table 2). Those risk levels were taken into account to set up the parameters for the extractables study. From the risk evaluation, the following extraction times were defined:

- For low- and medium-risk SU components, one short contact time (1, 7, or 21 days) for e.g., sterilizing-grade filters and sterile connectors
- For high-risk SU components two time points of longer-term contact (21 or 70 days) for e.g., storage bags and tubing.

Extraction Solutions

The goal was to define a minimum number of extraction solutions that would yield a comprehensive number and quantity of extractables without dissolving the base polymer of the components and while respecting the intended use of a given SU item. Although SSB had performed literally thousands of studies for different purposes, no single study sought to define the minimum extraction solutions to define the universe of potential extractables under biopharmaceutical process use.

For extractables studies, Dorey et al. (6) selected pure ethanol and pure water, which do not dissolve polymers at 40 °C. Pure ethanol shows a strong extraction capability, which is necessary for material characterization, and pure water shows good extraction capabilities for hydrophilic compounds and can be applied to each analytical method. 1 M NaOH and 1 M HCl acid can increase the polarity of small, targeted organic

Table 3: Repeatability and intermediate precision for analytical methods according to ISO 5725-1 and ISO 3534-1

Analytical Method	Repeatability/Intermediate Precision
HPLC-UV	Repeatability for BHT* is 0.5% (10 ppm, 10 x repetition); intermediate precision for BHT is 5.7% analyzed over six months (10 ppm)
GC-MS	Intermediate precision is <25% when analyzing representative extractable compounds** over weeks; repeatability for BHT is 4.0% (10 ppm, 10× repetition); intermediate precision for BHT is 6.2% analyzed over five months (10 ppm)
TOC	Repeatability is 0.4% (three samples, 500 ppb); intermediate precision is 5.2% on different days (500 ppb)

* BHT: Butylhydroxy toluene

** e.g., 1,3 di-*tert*-butyl benzene, caprolactam, Tris(2,4-di-*tert*-butylphenyl) phosphite

Table 4: Repeatability and interseries precision of typical extractables (extraction of PESU filter capsules at 40 °C after seven days contact time) determined from GC-MS analysis

	Repeatability (Three Samples)	Intermediate Precision (Four Samples)
Dodecane	1.2%	5.6%
1,3 di-*tert*-butyl-benzene	1.5%	4.0%
2,4 di-*tert*-butyl-phenol	6.5%	7.7%
Total sum (eight compounds)	1.0%	4.4%

Figure 2: Kinetic experiment — total extractables amount measured by HPLC-UV analysis of film ethanol extract (with fitted curves)

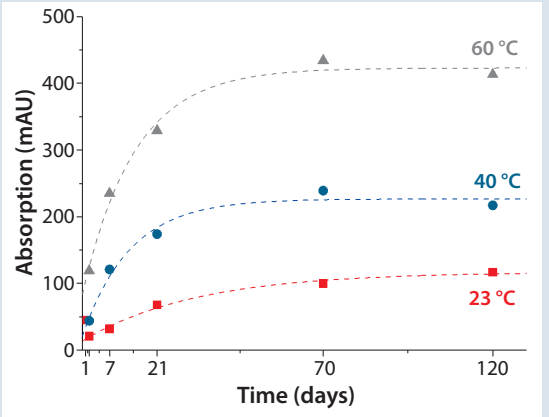
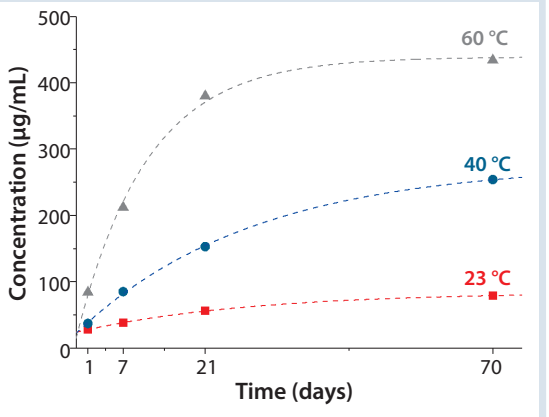


Figure 3: Kinetic experiment — total extractables amount measured by GC-MS analysis of filter capsule ethanol extract (with fitted curves)



chemicals, raising their solubility and improving their detectability.

The chosen extraction solutions are considered to be worst-case compared with use of acidic and caustic solutions (such as buffers) during production of API, and they can cover storage applications of concentrated acidic and basic solutions as well. With this selected set of solvents, the extraction of all potential extractables from SU components in bioprocess applications can be achieved. Because filling needles generally see only neutral pH solutions in real-world applications, they are tested only with pure water and pure EtOH.

Conditions of Extraction

The stated intent of our study demands conditions of extraction that significantly exaggerate the conditions of actual use while still being practicable in laboratory studies.

Surface Area/Volume ratio (SA/V): USP <661> requires a SA/V of 6 cm^2/mL of component to be extracted for every milliliter of extraction solution (**14**). Although the rationale for this ratio is undocumented, it does represent a significant exaggeration of expected SA/V in real-world applications, and it has proven to be close to the maximum SA/V that is practicable in laboratory settings. For filters, the accepted SA/V is 1 cm^2/mL, which also is exaggerated but practicable (**15**).

Therefore, we defined the SA/V as 1 cm^2/mL for filters, crossflow devices, and membrane adsorbers and 6 cm^2/mL for all other components. We want to emphasize that SA/V ratio influences the concentration of extractables depending on contact time and the physical property of a given compound (**16**). In short-term extractions of up to seven days, the release of extractable compounds is controlled by the diffusion within the polymer (Figures 2 and 3). Thus, for short-term extraction, the concentration of extractables will be governed by the ratio of SA/V. For long-term contact extraction, the concentration in equilibrium is no longer controlled by diffusion, but by the partition between polymer and solvent. The concentration becomes independent from the SA/V ratio in compounds with large partition coefficient ($K_{p/l}$) values (**16**).

Extraction Temperature: Extraction temperature should allow a comprehensive extraction of compounds without compromising the physical and chemical integrity of the component.

First Rationale: The chosen temperature is a temperature to accelerate extraction (**17, 18**).

Second Rationale: The worst-case temperature is determined by the maximum working temperature of a component without compromising its integrity (**19**).

Low extraction temperatures (e.g., 23 °C) lead to low (down to immeasurable) extractables concentrations. By contrast, with higher extraction temperatures (e.g., 60 °C) and longer extraction times (>70 days), the extractables yields rose for most compounds. During kinetic studies — results not presented here are based on qualitative evaluation of peak intensities of high-performance liquid chromatography with ultraviolet-detection and gas chromatography with mass spectrometry (GC-MS) analysis — it came out that in few cases the concentrations decreased over long periods (70 days). Specifically, kinetic studies on films of storage bags (Figure 2) and filter capsules (Figure 3) revealed clear dependency of the concentration on temperature and contact time. GC-MS data (Figure 3) showed that after 70 days extraction time, a plateau of the sum of the concentration of all detected compounds was reached for all temperatures tested (23 °C, 40 °C, and 60 °C). A broad spectrum of chemical species was detected and identified by GC-MS screening.

Extraction at 60 °C turned out to be impractical because of leakages during extraction of the filter capsules. For all extraction time points, an effective acceleration in extraction efficiency by a factor of ~2 can be seen between 20 °C and 40 °C (Figures 2 and 3). Based on the results and our rationale, the extraction temperature was set at 40 °C.

Time of Extraction: Contact time is relevant to ensure interaction between the material of the component and the extraction solvent to yield high extractable concentrations for analysis (**17, 18**). From kinetic studies (Figures 2 and 3) performed with storage-bag film material, we observed that longer contact times yielded higher extractables levels. Knowing the intended use of each component and expected in-process contact times, we could define extraction times that exaggerate real-world use times. Additionally for films, the kinetic studies show that the extraction at 40 °C for 21 days and/or 70 days allows detection of a high number of extractables (detailed data not shown). Most extractables reached the equilibrium concentration after about 70 days at 40 °C. Table 7 shows the extraction times for each category of component.

Test-Sample Preparation: Higher doses of gamma irradiation have a known effect on increased levels of extractables (**20**). Based on the ISO 11137 (**21**), a minimal dose of 25 kGy was applied to sterilize our SU systems, with a typical maximum irradiation dose of 45 kGy. We therefore require a target dose for preconditioning of components for extraction of 50 kGy, and we apply a maximum time gap of up to six weeks after gamma irradiation of the SU component and the start of extraction.

Number of Lots: The next evaluation — to set the number of items for the study — was to assess the variability of extractable results from different filter and film lots (intermediate precision) and within one lot (repeatability). The most important parameters influencing variability of the whole extraction study are the extraction process, the sample preparation, and the process of analysis (including the analytical method). It is possible to detect lot-to-lot variation among SU components in extraction studies if the repeatability of the analytical method used is better than the lot-to-lot

Table 5: Analytical methods

	Pure Water	Pure Ethanol	1 M HCl	1 M NaOH
HPLC-UV/VIS	×	×	×	×
LC-MS-UV/VIS	×	×	×	×
Headspace GC-MS*	×	NA	×	×
GC-MS*	×	×	×	×
ICP-MS/OES	×	×	×	×
IC**	×	×	×	×
TOC	×	NA	NA	NA
NVR	×	×	NA	NA
pH	×	NA	×	×
Conductivity	×	NA	NA	NA
FTIR	×	×	NA	NA

* FID can be used in parallel to the MS detector.
** Ion chromatography
NA = not applied

Table 6: Reporting limits for analytical techniques

	Reporting Limit
HS GC-MS	0.1 µg/mL
GC-MS	0.1 µg/mL
HPLC-UV/Vis	0.3 µg/mL
LC-MS	0.1 µg/mL
ICP-MS	0.1 µg/mL

repeatability within the extraction study. In this study, HPLC/UV, GC-MS, and total organic carbon (TOC) analyses are used to determine lot-to-lot variations. The experimental data of repeatability and intermediate precision for these analytical techniques are below 10% (Table 3). Nevertheless, it has to be pointed out that for some compounds analyzed with GC-MS, the intermediate precision value could be up to 25%.

As an example, the data from GC-MS analysis of three common extractable compounds reported by Menzel et al. (**5**) showed that the repeatability and intermediate precision are on the same level (for dodecane 1.2% and 5.6%, respectively) and below 10% (Table 4). Even between single compounds, the repeatability within one lot is on the same level (dodecane at 1.2 % and 2,4 di-*tert*-butyl phenol at 6.5%) as the intermediate precision (dodecane at 5.6% and 2,4 di-*tert*-butyl phenol at 7.7%). Repeatability of the analytical system is equivalent to the lot-to-lot variation of the filters. Therefore, the analytical method does not reveal any lot to lot variation. Based on these data, there is no relevant need to test several batches when carrying out an extractables study. The same conclusion is made from TOC and HPLC-UV results. The repeatability and intermediate precision show the same level. No lot-to-lot variations from the filter capsules were detected. The conclusion drawn from these data is to test one lot of SU component for extractable studies. Extracts from multiple lots can be pooled for analysis.

Extraction Conditions and Handling of Extracts: Extraction of SU components is performed by either immersing or filling them (bags or tubes). Rigid SU components, such as filters and housings, are completely wetted by shaking to reduce the interface resistance between SU component and solvent and to make the surface accessible to the solvent. The SU component is used as an integral part whenever it is possible to reach the desired SA/V ratio. No manipulation such as shredding is performed. The component is treated according to its intended use: For components that may be irradiated and autoclaved before use, data for each pretreatment step are provided. Liquids for preservation of SU components are rinsed according to their instruction manuals (e.g., crossflow cassettes, membrane adsorbers). Extraction is performed with cleaned equipment. Blank sample, sample preparation, and measurement details are given in

Table 7: The SSB extraction scheme for SU components

Test Article (at 40 °C)	100% Water (cm²/mL) 1 day	7 days	21 days	70 days	100% Ethanol (cm²/mL) 1 day	7 days	21 days	70 days	1M NaOH, 1M HCl 70 days
Storage and mixing bags ♦	—	—	6	6	—	—	6	6	6
Tubing ♦	—	—	6	6	—	—	6	6	6
Bioreactors ♦	—	—	6	—	—	—	6	—	—
Tubing connectors/disconnectors ♦	—	—	6	—	—	—	6	—	—
Aseptic connectors/disconnectors ♦	—	6	—	—	—	6	—	—	—
Sterilizing-grade filters* ♦	1	—	—	—	1	—	—	—	—
Virus filters* (Sartobind) ♦	1	—	—	—	1	—	—	—	—
Crossflow cassettes* ♦	1	—	—	—	1	—	—	—	—
Filling needles ♦	6	—	—	—	6	—	—	—	—

* nominal filter area for SA/V ♦ high-risk category ♦ medium-risk category ♦ low-risk category

Menzel et al. (**5**). Other advice can be found in literature about handling extracts according to basic principles in laboratory work (**18, 19, 22**).

Analytical Methods

A combination of state-of-the-art orthogonal analytical techniques is used to detect, identify, and quantify volatile, semivolatile, and nonvolatile extractable-including elements. Little debate exists on this topic, and we have defined our analytical methods as listed in Table 5.

Definition of Reporting Limits: USP chapter <1663> mentions that "Characterization is the discovery, identification, and quantitation of each individual organic and inorganic chemical entity present in an extract above a specified level or threshold. Such thresholds can be based on patient safety considerations, materials considerations, the capabilities of analytical technology, etc." (**17**). Many publications describe applicable approaches for determining the limit of detection (LoD) and limit of quantitation (LoQ) for extractable compounds with different analytical methods (**23, 24**). Jenke et al. reported about 500 different potential extractables compounds from SU components (**25**). Due to the chemical diversity of polarity and volatility of the listed extractable compounds, LoD/LoQ values cannot be expected to be on an equal or even similar level. USP <1663> discusses qualitative extractables assessments and proposes having at least a concentration of one extractable compound of 5 µg/mL to perform structure elucidation.

In extractables studies, screening methods allow detection of potential extractable compounds present in the concentration range of parts per billion (ppb) to parts per million (ppm). To enable robust reporting of extractable results including identity and quantity, defining the reporting limits (RLs) for each individual analytical method is a practical step. Such limits are defined subjectively, can be higher than LoQs for single compounds, and can overcome interlaboratory LoQ differences. RLs can be derived from available LoQ data for single compounds for specific analytical techniques. This concept allows reporting of reproducible extractables information coming from

different laboratories. In the study, all detected peaks from extract samples are considered as extractable compounds if they exceed control peaks (blank) by ≥50% of the peak area. RLs are not fixed and represent the performance of the analytical equipment (Table 6). Further improvement and new robust analytical systems and techniques can lead to lower RLs.

The SSB Extraction Scheme for SU Components: Table 7 shows the extraction scheme applied to SU components. Sartorius Stedim Biotech uses a number of third-party components, including connectors and tubing, in its standard, configurable, and custom single-use assemblies. To support our customers with comprehensive extractables information for our SU systems, we have undertaken a comprehensive program to test a subset of our component library — including such third-party components — according to our new internal procedures.

A Pragmatic Approach to Extractables Studies

Sartorius Stedim Biotech has developed a pragmatic approach to perform extractables studies for the characterization of potential extractables of SU components used in biopharmaceutical processing. A testing program was set up to assess the influence of physical and chemical parameters during extractions and to deduce relevant conditions for the design of the extractables study for different SU components. Results were presented of the developed worst-case extraction study of SU components using standardized extraction parameters and state-of-the-art analytical methods to obtain comprehensive qualitative and quantitative extractables data.

The intention of extraction studies performed under worst-case conditions is to characterize the material of the SU component. The concentration of identified extractables in extraction studies are overestimated compared to real biopharmaceutical processes and are in the range of ppb to ppm for the presented extraction conditions. In this context, SSB regards extractables data to be basic information for the IQ process in industry. Users of SU technology can evaluate the material safety of SU components with extractables data and then plan further extractables/leachables (E/L) studies of their own. The data support the design of robust pharmaceutical processes and establish appropriate steps for removal or reduction of potential leachables within a process.

Extractables information represents the impurity profile of a SU component that can be screened for relevant potential leachable compounds under real process conditions. The advantage collecting substantial worst-case extractables data of single-use components is to build a database that can provide general information. Extraction studies limited to "typical process conditions" will reveal only a subset of potential extractables making extrapolations difficult. But such a database, in combination with appropriate methods and algorithms, allows extrapolation of extractables information to an unlimited combination of SU assemblies and allows the modeling of the fate of leachables in a downstream process.

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