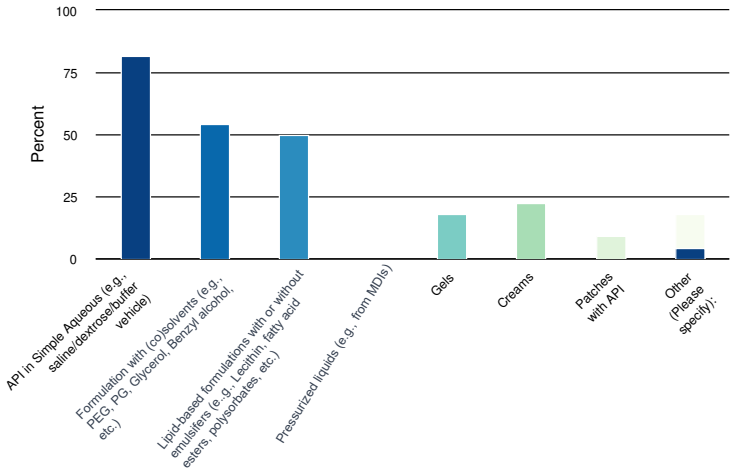
Report for ELSIE Survey: Low Analytical Evaluation Threshold (AET)

Response Counts

Completion Rate:	**100%**	
	Complete	23

Totals: 23

1. The matrix of a drug product can interfere when screening for leachables. The matrix can be very complex and is typically difficult to remove during sample preparation without loss of leachables. When injecting the DP sample for leachable screening on a detection system, this may result in low sensitivity, large number of peaks, and co-elution/peak overlap of matrix related peaks and leachables making it difficult to achieve the AET.Which of these matrices have you worked with when screening for leachables that had difficulties in achieving the AET? (check all that apply)



Value	Percent	Responses
API in Simple Aqueous (e.g., saline/dextrose/buffer vehicle)	81.8%	18
Formulation with (co)solvents (e.g., PEG, PG, Glycerol, Benzyl alcohol, etc.)	54.5%	12
Lipid-based formulations with or without emulsifiers (e.g., Lecithin, fatty acid esters, polysorbates, etc.)	50.0%	11
Pressurized liquids (e.g., from MDIs)	4.5%	1
Gels	18.2%	4
Creams	22.7%	5
Patches with API	9.1%	2
Other (Please specify):	18.2%	4
Other (Please specify):	4.5%	1

Other (Please specify):	Count
Implants	1
monoclonal antibody aqueous solution with 0.4% polysorbates	1
oil in water emulsion; high alcohol content	1
proteins in aqueous solutions, with amino acids, salts, sugars, surfactants	1
Totals	4

Other (Please specify):	Count
human derived blood plasma	1
Totals	1

2. The AET is calculated based on the dose-based threshold, e.g. the number of medical devices per day or the volume of the drug product per day. High dosing volumes, high dosing frequency and large dose amount requirements can result in a calculated AET which can’t be achieved because of limited sensitivity of detection systems. Complexity of the matrix results in interference in the detection system when screening for leachables.What product quality attribute represents the greatest challenge when screening for leachables in achieving low AET values in your studies? Please rank each with 1 being least difficult and 5 being most difficult (rank each option individually)

	1	2	3	4	5	Responses
Large Product/Dosing Volume Count Row %	2 8.7%	1 4.3%	3 13.0%	2 8.7%	15 65.2%	23
Complexity of the Matrix Count Row %	1 4.5%	4 18.2%	2 9.1%	8 36.4%	7 31.8%	22
Dosing frequency Count Row %	5 22.7%	3 13.6%	7 31.8%	3 13.6%	4 18.2%	22
Totals Total Responses						23

3. The AET is calculated based on the dose-based threshold, e.g. the number of medical devices per day or the volume of the drug product per day. High dosing volumes, high dosing frequency and large dose amount requirements can result in a calculated AET which can’t be achieved because of limited sensitivity of detection systems. Complexity of the matrix results in interference in the detection system when screening for leachables.What product quality attribute represents the greatest challenge when screening for leachables in achieving low AET values in your studies? Please rank each with 1 being least difficult and 5 being most difficult (rank each option individually) - comments

ResponseID	Response
	Large volume parenterals leads to very low AETs. Dose frequency leads to confusion because of different interpretations of AET.
	Dosing volume is most difficult.
	Typically we fins that large volume doses more commonly lead to low AETs tan do frequent dosing. ([redacted].)
	Rankings made under assumption that dosing frequency corresponds to tox thresholds. Unclear if question assumes dosing frequency is linked to dosing volume.

4. Different challenges may appear when an AET is set for leachable screening and interpretation of the data from the detection system. For example, due to the matrix many peaks appear in the chromatogram which can overlap/co-elute and make it challenging to distinguish between matrix/drug product related peaks and leachables. In addition, when screening at trace levels, contaminations from, e.g., solvents used in sample preparation or consumables could be detected and interfere with leachables or result in false positives.What is the greatest difficulty in leachable studies for screening that have low AETs? Please rank each with 1 being least difficult and 5 being most difficult (rank each option individually)

	1	2	3	4	5	Responses
Identification of unknowns						
Count	1	1	3	6	12	23
Row %	4.3%	4.3%	13.0%	26.1%	52.2%	
Dealing with a high number of leachable compounds						
Count	1	2	6	9	4	22
Row %	4.5%	9.1%	27.3%	40.9%	18.2%	
Ruling out (via appropriate controls) matrix/process related responses from true leachables.						
Count	7	3	4	0	9	23
Row %	30.4%	13.0%	17.4%	0.0%	39.1%	
Achieving the required level of enrichment via available sample preparation techniques (e.g., LLE, SPE)						
Count	4	5	5	8	1	23
Row %	17.4%	21.7%	21.7%	34.8%	4.3%	
Dealing with lab/preparation contamination						
Count	8	5	7	3	0	23
Row %	34.8%	21.7%	30.4%	13.0%	0.0%	
Defining a coherent study strategy that is accepted by the authorities						
Count	9	7	6	0	1	23
Row %	39.1%	30.4%	26.1%	0.0%	4.3%	
Evaluation of chromatograms with many overlapping and co-eluting peaks						
Count	1	6	6	5	5	23
Row %	4.3%	26.1%	26.1%	21.7%	21.7%	
Totals						
Total Responses						23

5. Different challenges may appear when an AET is set for leachable screening and interpretation of the data from the detection system. For example, due to the matrix many peaks appear in the chromatogram which can overlap/co-elute and make it challenging to distinguish between matrix/drug product related peaks and leachables. In addition, when screening at trace levels, contaminations from, e.g., solvents used in sample preparation or consumables could be detected and interfere with leachables or result in false positives.What is the greatest difficulty in leachable studies for screening that have low AETs? Please rank each with 1 being least difficult and 5 being most difficult (rank each option individually) - comments

ResponseID	Response
	Ability to develop analytical methods
	Currently no experience with FDA
	High resolution equipment and software is used to minimise problems with overlapping and co-eluting peaks
	Whats a high number of leachable compounds >10.
	High number of compounds that come from extraction studies, specially with harsher solvents
	Things like polysorbate in the sample formulation can present a challenge with respect to interpretation, in some cases
	Regarding "Defining a coherent study strategy that is accepted by the authorities": guidance is ambiguous and open to interpretation; reviews are inconsistent and rigid. Aspects the reviewers are rigid about are also inconsistent.

6. The ability to reach the AET is influenced by the sensitivity of the detection system deployed. The detection system used for leachable screening is assumed to reach a certain sensitivity. The sensitivity can be influenced by the complexity of the sample resulting in drug product or formulation specific sensitivity for leachable screening.For each of the matrices that you work with, what is the lowest range concentration (LOQ) in ppb (nanogram/gram) for the drug product that you have achieved for each method when screening for leachables (e.g., volatiles, semi-volatiles, or non-volatiles)?

Selected from: The matrix of a drug product can interfere when screening for leachables. The matrix can be very complex and is typically difficult to remove during s

	< 1 ppb (nanogram/gram)	1 - 10 ppb (nanogram/gram)	10 – 100 ppb (nanogram/gram)	100 - 1000 ppb (nanogram/gram)	> 1000 ppb (nanogram/gram)	Responses
API in Simple Aqueous (e.g., saline/dextrose/buffer vehicle) Count Row %	2 12.5%	9 56.3%	3 18.8%	1 6.3%	1 6.3%	16
Formulation with (co)solvents (e.g., PEG, PG, Glycerol, Benzyl alcohol, etc.) Count Row %	0 0.0%	4 40.0%	4 40.0%	1 10.0%	1 10.0%	10
Lipid-based formulations with or without emulsifiers (e.g., Lecithin, fatty acid esters, polysorbates, etc.) Count Row %	0 0.0%	4 36.4%	5 45.5%	2 18.2%	0 0.0%	11

	< 1 ppb (nanogram/gram)	1 - 10 ppb (nanogram/gram)	10 – 100 ppb (nanogram/gram)	100 - 1000 ppb (nanogram/gram)	> 1000 ppb (nanogram/gram)	Responses
Pressurized liquids (e.g., from MDIs) Count Row %	0 0.0%	0 0.0%	0 0.0%	1 100.0%	0 0.0%	1
Gels Count Row %	0 0.0%	0 0.0%	3 100.0%	0 0.0%	0 0.0%	3
Creams Count Row %	0 0.0%	0 0.0%	2 50.0%	1 25.0%	1 25.0%	4
Other (Please specify):: Count Row %	0 0.0%	1 25.0%	0 0.0%	2 50.0%	1 25.0%	4

Referring to: oil in water emulsion; high alcohol content

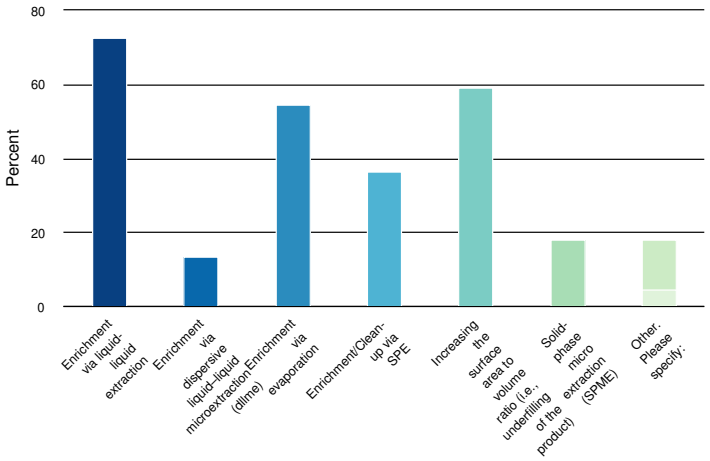
Referring to: proteins in aqueous solutions, with amino acids, salts, sugars, surfactants

Referring to: monoclonal antibody aqueous solution with 0.4% polysorbates

Referring to: implants

	< 1 ppb (nanogram/gram)	1 - 10 ppb (nanogram/gram)	10 – 100 ppb (nanogram/gram)	100 - 1000 ppb (nanogram/gram)	> 1000 ppb (nanogram/gram)	Responses
Other (Please specify):: Count Row %	0 0.0%	0 0.0%	0 0.0%	1 100.0%	0 0.0%	1
Totals				Referring to: human derived blood plasma		50 100.0%

7. Different sample preparation techniques can be used to increase concentration levels of leachables in the sample solution. What sample preparation techniques have you used for achieving a higher concentration of leachables to meet the requirement of a low AET in screening leachables studies? (Check all that apply)



Value	Percent	Responses
Enrichment via liquid-liquid extraction	72.7%	16
Enrichment via dispersive liquid–liquid microextraction (dllme)	13.6%	3
Enrichment via evaporation	54.5%	12
Enrichment/Clean-up via SPE	36.4%	8
Increasing the surface area to volume ratio (i.e., underfilling of the product)	59.1%	13
Solid-phase micro extraction (SPME)	18.2%	4
Other. Please specify:	18.2%	4
Other. Please specify:	4.5%	1

Other. Please specify:	Count
High injection volumes of samples vs. standards	1
a variety of analytical tools/strategies required to address diverse product portfolios.	1
none	1
using butylethylether as solvent	1
Totals	4

Other. Please specify:	Count
Several of the above mention also has the potential to introduce contaminations which can be challenging	1
Totals	1

8. If the calculated AET cannot be achieved for leachable screening, alternative approaches can be used. Examples of alternative approaches are: Simulation leachable study to mimic the manufacturing process and/or storage conditions of a DP by using an extraction solvent instead of DP formulation. Use of a placebo by omitting the API Targeted leachable study; Developing a targeted leachable method to determine levels of compounds which were detected or reported as extractables. Paper based risk assessment, based on available information about e.g., material, potential leachables, interaction of the DP with the material. Have you tried submitting alternative approaches to leachables screening to the FDA and EMA, and have they been accepted?

	FDA	EMA	Responses
Simulation leachable studies **Note**: No company indicated that they had submitted simulation leachable studies that were "Not Accepted"			
Accepted	9 50.0%	9 50.0%	18 39.1%
Unsure (still under review)	1 50.0%	1 50.0%	2 4.3%
Not Applicable (did not try this approach)	13 50.0%	13 50.0%	26 56.5%
Total			46 100.0%
Use of placebo (without API)			
Accepted	9 47.4%	10 52.6%	19 41.3%
Not accepted	1 100.0%	0 0.0%	1 2.2%
Unsure (still under review)	1 100.0%	0 0.0%	1 2.2%
Not Applicable (did not try this approach)	12 48.0%	13 52.0%	25 54.3%
Total			46 100.0%
Targeted leachable studies			
Accepted	14 48.3%	15 51.7%	29 64.4%
Unsure (still under review)	1 50.0%	1 50.0%	2 4.4%
Not Applicable (did not try this approach)	7 50.0%	7 50.0%	14 31.1%
Total			45 100.0%
Risk assessment (e.g., good understanding of material, potential leachable, interaction with DP)			
Accepted	4 36.4%	7 63.6%	11 23.9%
Not accepted	2 50.0%	2 50.0%	4 8.7%
Unsure (still under review)	1 100.0%	0 0.0%	1 2.2%

	FDA	EMA	Responses
Not Applicable (did not try this approach)	16 53.3%	14 46.7%	30 65.2%
Total			46 100.0%

Alternative detection method (LC/UV instead of LC/MS) for lipid matrix + higher AET based on ICH M7:

Accepted	0 0.0%	1 100.0%	1 50.0%
Not Applicable (did not try this approach)	1 100.0%	0 0.0%	1 50.0%
Total			2 100.0%

Combination of targeted leachable and leachable screening studies:

Accepted	1 50.0%	1 50.0%	2 100.0%
Total			2 100.0%

NA:

Not Applicable (did not try this approach)	1 50.0%	1 50.0%	2 100.0%
Total			2 100.0%

non targeted approach for leachables:

Accepted	1 50.0%	1 50.0%	2 100.0%
Total			2 100.0%

9. If you have submitted a simulation leachable study, please describe how you designed the simulation study, and what parameters were considered important. In particular how did you justify your solvent choice? If you have not submitted a simulation leachable study, please respond "N/A"

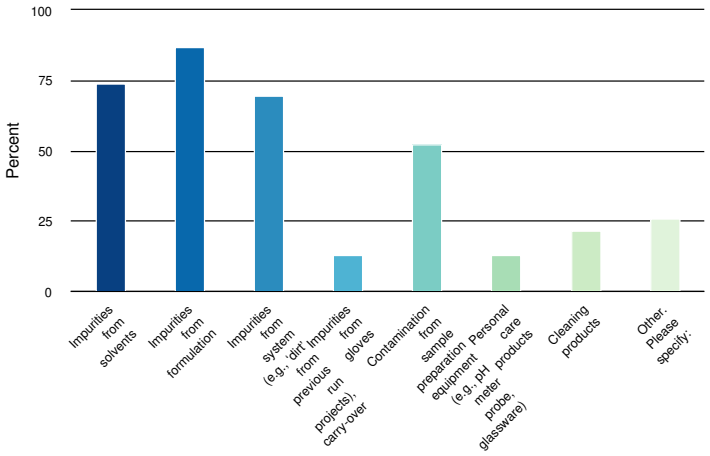
ResponseID	Response
	N/A
	Solvent choice based on scientific literature Considered contact time, contact area, and temperature Otherwise study just like an extractable study
	Simulation done based upon past extractables studies and summarized by vendor. Results analyzed by toxicology to determine risk.
	N/A
	Higher surface area to volume simulation studies has been done as a risk mitigation study before going to long term leachables documentation. Both the simulated and the long term studies were described in regulatory submission.
	NA
	N/A
	N/A
	formulation buffer matrix (model solvent), temp, volume, ccs, dose, concentration
	Exaggerate the temperature within the limits formulation can be used. Simulation solution without API otherwise corresponding to formulation. Simulation solution with higher or lower polarity, pH and solvent strength.
	N/A
	Submission of study with solution of same extracting power,mainly based on the pH and bracketing approach analyses in a smaller bag 100ml instead of 250 or500ml. Or container with custom made labels having a higher contact ratio than normal and using accelerated ageing
	N/A
	Used placebo formulation without the components that might interfere with the analysis. A justification was added to the report.
	N/A
	A model solvent closest to the parameters of the drug product was selected. The simulation study was performed on each contact part.
	Strategy used for biologics Solvent choice was justified based on solvent polarity comparison Other approach was the use of placebo (without API)
	N/A
	N/A
	Simulation study was submitted for Cell Therapy product – Rationale for simulation study was the interferences with the matrix (cells, HAS etc) – Solvent was chosen as worst-case solvent with a slightly increased concentration of cryopreservant.
	N/Ap. In the cases we did not include the API, we have opted to use a placebo. Simulation studies of final drug product are always paired with a real-time study with product.
	N/A Should we submit this type of study we would use a solvent that would be as close as possible to the drug product.
	For medical devices this is a common approach, according to ISO10993-18. For drugs (EMA), a simulation study was performed where bracketing extraction solvents were used (low and high pH bracketing the different DPs). This was combined with a screening leachables study on only 2 of a large range of DPs and a targeted leachables study as well. Hence, we did not submit the simulation study on its own.

CLARIFICATION (POST-SURVEY):

- I wanted to highlight that for medical devices in direct (e.g. blood contact) or indirect (e.g. through contact with a fluid) patient contact, a simulation study is very common. However, I realize that the scope of the survey is drug containers, so this might not be relevant.
- For drug product containers, we conducted a study with low AET, and encountered significant challenges. To simplify the analysis, we selected only two of the many drug products for leachables studies, and the results were deemed representative of the others. This can be considered a simulation study for the remaining drugs, as the chosen products had didn't have exactly the same formulation as the others.

However, I supplemented this data with worst-case extractables studies, as well as targeted leachables studies (monitoring of relevant targets over shelf-life), materials composition data, etc. I wanted to highlight this as I think it's important to understand that regulators might accept simulated leachables, but only as part of a larger evaluation/dataset.

10. Background noise in detection system and interferences can cause interfering peaks or “false positives” that impact ability to achieve the AET.What are common sources of background responses that you have encountered? (Check all that apply)

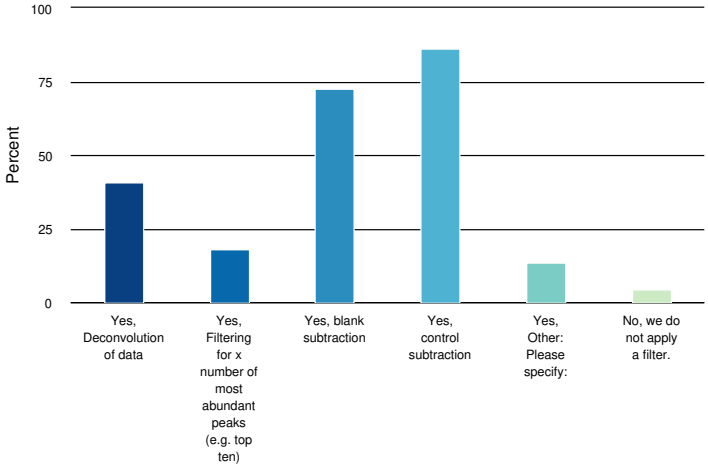


Value	Percent	Responses
Impurities from solvents	73.9%	17
Impurities from formulation	87.0%	20
Impurities from system (e.g., ‘dirt’ from previous run projects), carry-over	69.6%	16
Impurities from gloves	13.0%	3
Contamination from sample preparation equipment (e.g., pH meter probe, glassware)	52.2%	12
Personal care products	13.0%	3
Cleaning products	21.7%	5
Other. Please specify:	26.1%	6

Other. Please specify:	Count
Drug-related impurities	1
Impurities from process commodities	1
NA	1
We specify that polymeric materials should not be used in the sample preparation where possible	1
degradation related to API or formulation components	1
detergents from glassware cleaning procedures, solvent impurities are elevated after concentrating samples	1
Totals	6

Other. Please specify:	Count
Totals	0

11. Data from leachable screening studies can be processed in different ways to filter the data, e.g., using software tools like deconvolution, subtracting peaks detected in blank (solvent) or control (solution that went through the same preparation process as the sample) from the peaks detected in the sample solution.Do you apply a filter for data processing to reduce the number of background (control-related) peaks in the chromatogram? (Check all that apply)



Value	Percent	Responses
Yes, Deconvolution of data	40.9%	9
Yes, Filtering for x number of most abundant peaks (e.g. top ten)	18.2%	4
Yes, blank subtraction	72.7%	16
Yes, control subtraction	86.4%	19
Yes, Other: Please specify:	13.6%	3
No, we do not apply a filter.	4.5%	1

Yes, Other: Please specify:	Count
COMMENT: challenge of identifying compounds at low ppb levels needs to be acknowledged/communicated by the industry as a whole. Lack of transparency/acknowledgment could cause misconception that ID at low concentrations is a relatively easy process, which is not true.	1
Testing of dublicates -> check of reproducibility of sample preparation	1
Visual correction of reference samples from test samples	1
Totals	3

Yes, Other: Please specify:	Count
Totals	0

12. Another contributing factor to a low AET may be the inclusion of an uncertainty factor (which is indeed included in most derivations of an AET). This factor can range from 1 to 10, and may contribute to an unattainable AET.Where it is not been possible to achieve the calculated AET, which of the approaches below would you consider to be the most likely to be accepted as an alternative by a regulatory authority? Please rank with 1 being most likely and 5 being most unlikely (rank each option individually)

	1	2	3	4	5	Responses
Only the highest X number of peaks will be evaluated (e.g. top ten)						
Count	2	2	4	4	8	20
Row %	10.0%	10.0%	20.0%	20.0%	40.0%	
Use the LOD of the method						
Count	3	9	3	2	4	21
Row %	14.3%	42.9%	14.3%	9.5%	19.0%	
Use the LOQ of the method						
Count	6	4	4	3	2	19
Row %	31.6%	21.1%	21.1%	15.8%	10.5%	
If uncertainty factor has been applied initially, use a lower or no Uncertainty Factors (UFs)						
Count	7	6	4	2	2	21
Row %	33.3%	28.6%	19.0%	9.5%	9.5%	
Consider the risk/benefit of the drug product to justify a higher SCT & AET						
Count	9	3	5	4	1	22
Row %	40.9%	13.6%	22.7%	18.2%	4.5%	
Careful examination of MS data to exclude other than formulation related signals						
Count	0	0	1	0	0	1
Row %	0.0%	0.0%	100.0%	0.0%	0.0%	
Simulation or mock up with higher surface to volume ratio						
Row %	1	0	0	0	0	1
	100.0%	0.0%	0.0%	0.0%	0.0%	
Use of Cramer classification to calculate SCT						
Count	0	0	1	0	0	1
Row %	0.0%	0.0%	100.0%	0.0%	0.0%	
Totals						
Total Responses						22