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USE OF EXAGGERATED SURFACE AREA TO SOLUTION VOLUME RATIOS IN EXTRACTABLES STUDIES; EQUILIBRIUM CASE

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Purpose

The purpose of this Technical Communication is to establish and justify appropriate practices related to the exaggeration of extracted surface area to extraction solution volume ratios used in extractables studies. This Technical Communication specifically addresses those circumstances where equilibrium is achieved between the extracted test article and the extracting medium.

Situation

The surface area of a test article extracted or leached per unit volume of extracting solution is frequently used in extractables studies as a means to exaggerate the contact that occurs between the test article and a contacting solution under the test article's typical conditions of use. In some situations, the exaggeration is used to produce a worst-case extraction. For example, when a drug product is packaged in containers that can vary in size, it is the smallest available sized container that is typically tested, as the container surface area to fill solution volume ratio is largest for the smallest available size. In other situations, exaggeration factors are used to forecast what extractables levels would be when the conditions of the extraction differ from the conditions of use. For example, a 50-mL I.V bag may include an injection septum. In an extractables study one might extract five septa per 50 mL of extraction solvent in the belief that so doing will produce a more concentrated extract, thus facilitating the identification of extractables. To establish the amount of the extractable one might anticipate to be present in the bag's fill solution as a leachable, one might divide the concentration of an extractable in the extract by the five-fold exaggeration factor. In both situations, the underlying assumption is that the level of extractables in an extracting solution will proportionally increase with increasing surface area to solution volume ratio.

Discussion

Considering Kinetics and Thermodynamics

The ratio of the test article's extracted surface area to the extraction solution's volume ratio can affect both the thermodynamics and kinetics involved with extraction or leaching. Thermodynamically, the greater the surface area to solution volume ratio, the greater the total pool of an extractable or leachable (at constant test article thickness). Kinetically, the increased surface area to solution volume ratio will increase the speed of extraction or leaching.

If the extraction or leaching conditions (e.g., duration and temperature) are such that equilibrium is attained between the test article and the extracting solution, then the kinetics effect is irrelevant and only the thermodynamic aspects are important to consider. For example, terminally sterilized, aqueous packaged drug products may have fairly long ambient temperature shelf lives (multiple years). As a result of the high heat stress of terminal sterilization and the long post-autoclave contact duration, the packaged drug product and the packaging system reach an equilibrium with respect to leachables.

This is the circumstance that is addressed by this Technical Communication.

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The Relationship between the Surface Area/Solution Volume Ratio and the Concentration

The equilibrium partitioning of a substance between a plastic phase (the test article; for example, container or material) and a liquid solution phase (the fill solution or extracting solution) is described by a plastic/liquid partition coefficient, $k_{p/l}$, as follows:

$$k_{p/l} = (m_{p,e}/V_p)/(m_{l,e}/V_l) \quad \text{Equation 1}$$

where m = the mass of a substance in a particular phase, V is the volume of either phase and the subscripts p, l and e refer to the plastic phase, the liquid phase and equilibrium respectively.

Equation 1 can be re-written to express the relationship between the concentration of a substance in the liquid phase at equilibrium ($C_{l,e}$) and the various other relevant parameters as shown in Equation 2 (obtained from reference 1):

$$C_{l,e} = m_{l,e}/V_l = m_{p,o}/[V_l + (k_{p/l} \times V_p)] \quad \text{Equation 2}$$

where the subscript o refers to the initial condition prior to contact. As the volume of a test article shaped as a sheet is the product of the sheet's surface area (SA_p) and its thickness (t_p), equation 2 can be adjusted to produce a relationship that expresses the substance's solution level at equilibrium in terms of the material's surface area and the solution's volume:

$$C_{l,e} = m_{l,e}/V_l = m_{p,o}/[V_l + (k_{p/l} \times SA_p \times t_p)] \quad \text{Equation 3}$$

As noted from equation 3, a substance's plastic/solution partition coefficient ($k_{p/l}$) will significantly impact the effect that changing the extracted surface area to extraction solution volume ratio has on the substance's equilibrium concentration in solution ($C_{l,e}$). When $K_{p/l}$ is large (substance partitions favorably into the plastic phase), the $K_{p/l}$ term is dominant and the effect of surface area is minimized. When $K_{p/l}$ is small (substance partitions favorably into the solution phase), the $K_{p/l}$ term is small and the effect of surface area is maximized.

To examine this effect more closely, the following situation is considered:

$m_{p,o}$ = 10 mg/cm2,
V_l = 100 mL = 100 cm3,
t_p = 1 cm, and
$k_{p/l}$ takes values ranging from 0.1 (substance highly soluble in the solution) to 1000 (substance poorly soluble in the solution)

Under these conditions, the effect of increasing the extracted surface area of the test article (SA_p) on the equilibrium concentration of the substance in the solution ($C_{l,e}$) is shown in Figures 1 and 2. As anticipated, the effect of surface area is greatly reduced as the substance's $k_{p/l}$ increases. For a substance that is highly soluble in the solution, an increase in material surface area produces nearly a proportional increase in the concentration of the substance in the solution. For example, when the surface area is increased by a factor of 100 for a substance with a $k_{p/l}$ of 0.1, the increase in the substance's concentration in solution is also nearly a factor of 100. For a substance that is poorly soluble in the solution ($k_{p/l}$ = 100) a 100-fold increase in surface area produces barely a doubling of the substance's concentration in solution.

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Figure 1. Relationship between the Test Article's Surface Area and the Concentration of an Extractable in an Extracting Solution at a Constant Extracting Solution Volume. The relationship is shown for extractables with polymer/liquid partition coefficients ($k_{p/l}$) ranging from 0.1 (extractable is highly soluble in the solution) to 1000 (extractable is poorly soluble in the solution).

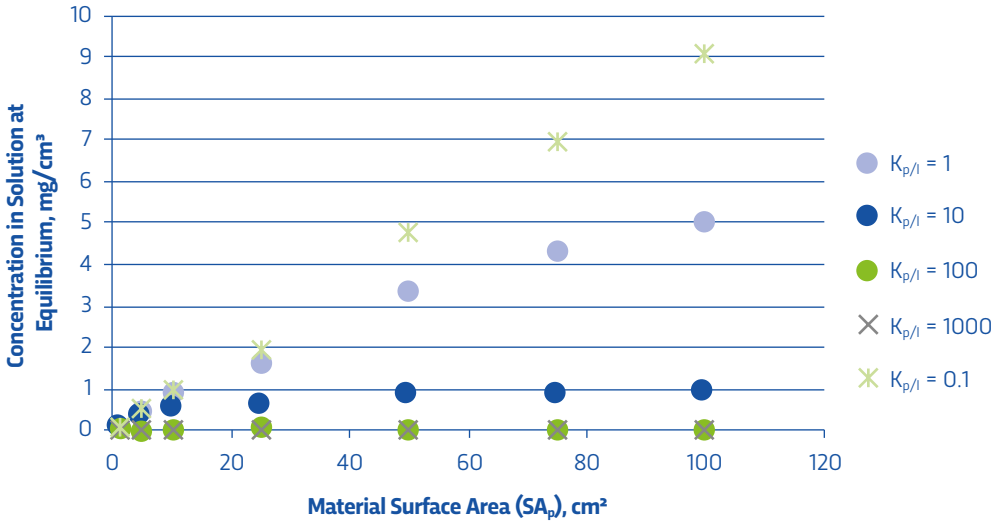
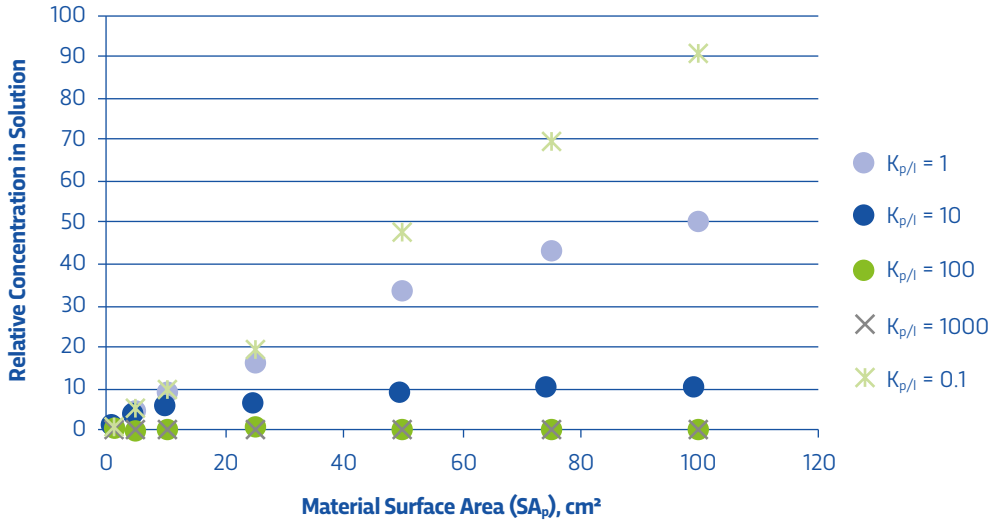


Figure 2. Relationship between the Test Article Surface Area and the Relative Concentration of an Extractable in an Extracting Solution at a Constant Extracting Solution Volume. The relationship is shown for extractables with $k_{p/l}$ ranging from 0.1 (extractable is highly soluble in the solution) to 1000 (extractable is poorly soluble in the solution).



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Applying the Equation Relating the Extracted Surface Area to the Extraction Solution's Volume

Earlier in this Technical Communication (specifically in the Situation section), two scenarios were considered in terms of the use of exaggerated surface area to solution volume ratios. The first scenario addressed the situation where a family of packaged products, differing in size, where deemed to be represented by the one product which had the highest packaging surface area to solution volume ratio. For a package, the highest surface area to solution volume ratio is attained by the smallest sized package in the family as it is usually the case that the size of the package does not increase in direct proportion to its fill volume. The rationale for choosing the size with the largest surface area to solution volume ratio was that this would be the product size that had the highest concentration of substances in solution and thus which was worst case in terms of substance concentration. The analysis shown in Figures 1 and 2 confirms this rationale, as it always the case that the substance's concentration in solution is highest at the highest surface area to solution volume ratio.

The second scenario addressed the situation where one would use an exaggeration factor to extrapolate an extractable's concentration in solution obtained at one surface area to volume ratio to the extractable's concentration in solution at another surface area to solution volume ratio. In this situation, it was supposed that the exaggeration factor would be equal to the ratio of surface area to solution volume ratios. More specifically, if the surface area to solution volume ratio in case 2 was twice the surface area to solution volume ratio in case 1, then the solution concentration of a substance in case 2 would be twice the solution concentration in case 1.

Figures 1 and 2 clearly show that this practice is not always proper and correct. While a hundred-fold increase in surface area to solution volume ratio produces nearly a hundred-fold increase in the solution concentration for a substance that is highly soluble in the solution ($k_{p/l}$ = 0.1), the increase becomes much less as the substance's solution solubility decreases. For example, the increase in the substance's concentration in solution is roughly 50-fold when the $k_{p/l}$ is 1. For poorly soluble substances ($k_{p/l}$l = 1000), a 100-fold increase in surface area to solution volume ratio produces less than a 10% increase in the substance's solution concentration.

Thus while it is clear that 100-fold extrapolations of surface area to volume ratios are not proper or viable in many cases, it may be the case that smaller extrapolations would be acceptable. Table 1 addresses this possibility by collating the concentration exaggeration factors when surface area to solution ratio is changed by a factor of 5 or less.

Table 1. Relative Substance Concentrations in Solution at Various Surface Area to Volume Ratios.

Surface Area	Relative Concentration in Solution, $C_{e,l}$				
(SA_p, cm2)	$K_{p/l}$ = 0.1	$K_{p/l}$ = 1	Kp/l = 10	$K_{p/l}$ = 100	$K_{p/l}$ = 1000
1	1	1	1	1	1
2	2.00	1.98	1.83	1.33	1.05
3	2.99	2.94	2.54	1.50	1.07
5	4.98	4.81	3.67	1.67	1.08

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One notes from this Table that when the surface area is increased from 1 to 3 (a potential exaggeration factor of 3), even in the case of a poorly soluble compound ($k_{p/l}$ = 100), the actual exaggeration factor is close to the potential factor (1.5 versus 3, or approximately 50%). However, at a surface area exaggeration factor of 5, the actual exaggeration factor for a substance with kp/l = 100 is only 33% of its potential value.

Case Study

This case study is obtained from the Primary Reference.

One of the examples previously considered was the case of a drug product that is commercially available in multiple package sizes (e.g. multiple fill volumes), as can be the case for certain drug products used as parenteral injections. The measurement of targeted leachables over storage time across multiple package sizes for one or more parenteral solutions of similar composition produces a set of data relevant to a consideration of the effect of the ratio of surface area to solution volume (SA/V) on the leachable's concentration in the drug product.

The test articles for this case study were three different packaging systems that are used to package aqueous parenteral injections such as Sterile Water, Normal Saline and Dextrose injections. Filled packages of multiple sizes (25-mL – 3000-mL) were treated in a manner appropriate for such products, which means that the filled units were terminally sterilized (autoclaved) and then stored for a period of time reflecting multiple year, ambient temperature shelf-lives. Over the course of such storage, the fill solutions were sampled and the samples tested for their levels of targeted leachables. Leachables were targeted based on their known association with the three container systems studied and included Di-(2-ethylhexyl) phthalate (DEHP) and Zn from a plasticized poly(vinyl chloride) packaging, caprolactam from a plastic package whose materials of construction included Nylon 6 and a class of compounds termed cyclic esters from a laminated plastic structure that included polyurethane-based tie layers. Validated analytical methods for quantifying the targeted leachables included inductively coupled plasma atomic emission spectroscopy (ICP-AES) for Zn, liquid chromatography with UV detection (LC/UV) for DEHP, liquid chromatography with mass spectrometric detection (LC/MS) for caprolactam and gas chromatography with flame ionization detection (GC/FID) for the cyclic esters.

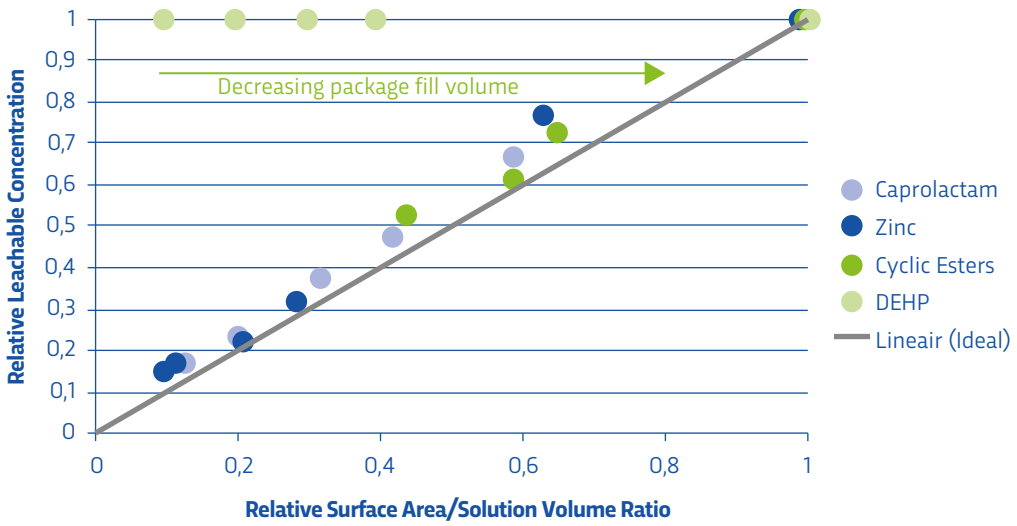
Polymer/solution partition coefficients ($k_{p/l}$) for these targeted leachables are contained in Table A.1.

A typical use of exaggeration factors is extrapolating the higher concentrations measured in the smallest package to lower concentrations relevant to larger packages. To illustrate this situation, Figure 3 is constructed from the experimental data, normalizing is the data by using the smallest package as the point of reference.

Figure 3 shows a divergence between the experimental behavior and the ideal outcome. The significance of the divergence is illustrated in the following situation. The equilibrium concentration of a targeted leachable has been measured in the smallest sized package and the investigator seeks to extrapolate that outcome to a larger package that has a 5 times smaller SA/V ratio. Were the "ideal" situation to be encountered, the investigator would project the leachable's concentration in the larger package to be one-fifth its level in the smaller package. As shown in Figure 3, however, the actual "extrapolation factor" for the leachables with low partition coefficients would be closer to a factor of one-fourth, yielding a higher concentration estimate.

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Figure 3. Normalized Plot Showing the Experimental Effect of a Package's Surface Area to Solution Volume Ratio (SV/A) on the Equilibrium Concentration of Leachables in the Contained Solution. As the package's size (fill volume) decreases, its surface area to solution volume increases, resulting in an increased extractable concentration in the contained solution. Concentrations and SA/V ratios have been normalized to the corresponding values for the smallest package.



The under-exaggeration is far worse for a higher partition coefficient extractable such as DEHP. As was the case for the other leachables, the ideal extrapolation would indicate that the DEHP level in the smaller package should be one-fifth that measured in the larger package. In fact, the experimental data shows that the concentrations of DEHP in the two packages are essentially equal.

Thus, extrapolating small package data to larger packages based on the "ideal" circumstance under-estimates the leachable's concentration and under-estimates its safety risk. The higher the leachable's polymer/solution partition coefficient $k_{p/l}$, the larger the under-estimation.

Cause or Effect?

To this point, the phenomenon that is being investigated has been expressed in terms of a test article's surface area to solution volume ratio. So doing implies a cause and effect relationship; that is, that it is the changed SA/V that causes the change in the extractable's concentration in the extract. However, in most situations, the increase in SA/V is reflected in an increase in the mass of material extracted per volume of extracting solution and it may be the case that it is the change in extracted mass, and not the change in surface area, which drives the change in the extractable's concentration. For example, the surface area and the material mass are proportionally related for a container of whose composition and thickness is constant over the range of sizes.

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Conclusions and Recommendations

The following conclusions and recommendations can be drawn about the proper use of exaggerated test article surface area to extraction solution volume ratios in exaggerated extractables studies:

1. Extractables concentrations can be extrapolated as a function of surface area to solution volume ratios so long as the exaggeration factor is no more than three.

2. Exaggeration factors larger than three can be justified on a case by case basis if the nature of the extractables can be established (specifically their $k_{p/l}$ values).

3. Exaggeration factors larger than 10 should rarely be used and only in those circumstances were the $k_{p/l}$ values for all extractables are less than 10. Use of exaggeration factors greater than 10 would require justification on a case by case basis.

4. If one proportionally extrapolates concentrations from a lower surface area to solution volume ratio to a higher surface area to solution volume ratio, the extrapolated concentration will always be greater than or equal to the actual concentration (making the extrapolated concentration a worst case). The larger a substance's $k_{p/l}$, the greater the relative difference between the extrapolated and actual concentrations.

5. If one proportionally extrapolates concentrations from a higher surface area to solution volume ratio to a lower surface area to solution volume ratio, the extrapolated concentration will not be greater than the actual concentration (and thus the extrapolated concentration will not be a worst case). The larger a substance's $k_{p/l}$, the greater the relative difference between the extrapolated and actual concentrations.

Since knowing $k_{p/l}$ values for extractables is essential in the application of the above conclusions, Appendix A provides a means of calculating $k_{p/l}$ values from the more commonly available octanol-water partition coefficient, $P_{o/w}$.

References

Primary Resource

D.R. Jenke and B.E. Rabinow. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol.* **71(3)**: 225-233 (2017). Doi:10.5731/pdajpst.2016.007195.

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2. D.S. Hayward, D.R. Jenke. Interactions between polymer containers and parenteral solutions: Correlating equilibrium polymer-water interaction constants with solute partition coefficients. *Int. J. Pharm.* **66**: 87-96 (1990).

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3. D. Jenke, T. Couch, A. Gillum. Comparison of solute-binding properties of plastic materials used as pharmaceutical product containers. *PDA J. Pharm. Sci. Technol.* **64(1)**: 37-43 (2010).

Appendix A: Polymer/solution Partition Coefficients, $k_{p/l}$, for Extractables

A polymer/solution partition coefficient ($k_{p/l}$) is equivalent to a solvent/water partition coefficient ($k_{s/w}$) in terms of tis mathematical derivation and its application. If one could identify an organic solvent which behaved in the same manner as a particular polymer, then a substance's polymer/solution and solvent/water partition coefficients would be equivalent.

Octanol/water partition coefficients ($k_{o/w}$) are commonly available for a large number of organic substances (including extractables), thus making $k_{o/w}$ an excellent starting point for determining $k_{p/l}$ values. While octanol is not an exact model solvent for polymers used in pharmaceutical applications, relationships between $k_{p/l}$ and $k_{o/w}$ have been documented in the literature, for example, reference 2,3. Such relationships for three types of polymers, plasticized PVC, polyolefin and rubber, are as follows:

For plasticized PVC: $\log k_{p/l} = (0.892 \times \log k_{o/w}) - 0.494(*)$

For polyolefin: $\log k_{p/l} = (0.908 \times \log k_{o/w}) - 1.48(*)$

For rubber: $\log k_{p/l} = (0.546 \times \log k_{o/w}) - 0.15(\#)$

(*) = obtained from data in reference 3.

(#) = adjusted from data in reference 2.

Although these correlations are neither particularly strong for a given polymer and certainly not applicable to all polymer of a given class, they are sufficiently applicable in a general sense that they can be used to estimate $k_{p/l}$ values for the purpose of designing extractables or leachables studies in terms of surface area to solution volume ratio.

The following Table A1 lists $k_{o/w}$ values for a number of more commonly encountered extractables and provides $k_{p/l}$ values derived from the equations provided above.

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Table A1. Frequently Encountered Extractables and Their ko/w and kp/l Values.

Extractable	CAS RN	Log $k_{o/w}$	Approximate $k_{p/l}$		
			PVC	Polyolefin	Rubber
Stearic acid, pH 3	57-11-4	7.82	>1000000	419000	13200
Stearic acid, pH 9	57-11-4	4.21	1830	221	141
2-Ethylhexanoic acid, pH 3	149-57-5	2.57	62.9	7.17	17.9
2-Ethylhexanoic acid, pH 9	149-57-5	-1.03	0.039	0.0039	0.194
Caprolactam	105-60-2	-0.04	0.295	0.031	0.673
Bisphenol A	80-05-7	3.64	566	67.2	68.8
Cyclic ester CE 228 (I)	5578-82-5	1.19	3.69	0.400	3.16
Cyclic ester CE270	94113-50-5	2.49	53.3	6.07	16.2
Butylated hydroxytoluene (BHT)	128-37-0	5.17	13100	1650	471
Irganox degradate, pH 3	20170-32-5	3.54	461	54.5	60.7
Irganox degradate, pH 9	20170-32-5	-0.12	0.251	0.026	0.609
Irganox degradate	82304-66-3	2.47	51.2	5.82	15.8
Mono-(2-ethylhexyl) phthalate, pH 3	4376-20-9	4.39	2640	322	177
Mono-(2-ethylhexyl) phthalate, pH 9	4376-20-9	1.39	5.57	0.608	4.06
Di-(2-ethylhexyl) phthalate (DEHP)	117-81-7	8.52	>1000000	> 1000000	31763
Irganox 1010	6683-19-8	18.8	>1000000	>1000000	>1000000
Irgafos 168	31570-04-4	13.7	>1000000	>1000000	>1000000

Bolded substances are illustrated in the Case Study.

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About the Author



In March 2017, Dr. Dennis Jenke has taken the role of Principal Consultant for Nelson Laboratories, Europe. In this role, Dr. Jenke supports the customers of Nelson Labs Europe in the discussion of general principles, concepts, tactics and/or strategy related to chemical characterization and qualification of materials, components and systems used in these industries. Furthermore, as Principal Consultant, Dr. Jenke can provide Nelson Labs Europe clients with science-based expert insights into the design, justification, interpretation and regulatory requirements of the related chemical assessment studies and programs.

Dennis Jenke is also the founder of Triad Scientific Solutions LLC, a consultant-based technical service organization that provides the pharmaceutical, cosmetic, food and related industries with integrated, science-based, and practical solutions to suitability for use challenges for packaging, manufacturing components and systems, and devices.

Dr. Jenke was a Distinguished Scientist at Baxter Healthcare Corporation for more than three decades where his primary responsibility involved the assessment of material/product compatibility, including extractables and leachables testing. He has published extensively in the areas of analytical chemistry, material/solution compatibility and extractables and leachables. Dr. Jenke serves as an expert reviewer for numerous pharmaceutical and analytical journals and is a member of several industry groups such as USP, PQRI, AAMI/ISO and ELSIE.

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