The AET Challenge for Large Volume Parenterials (LVPs): Extractables Simulation Studies and How to Design Them

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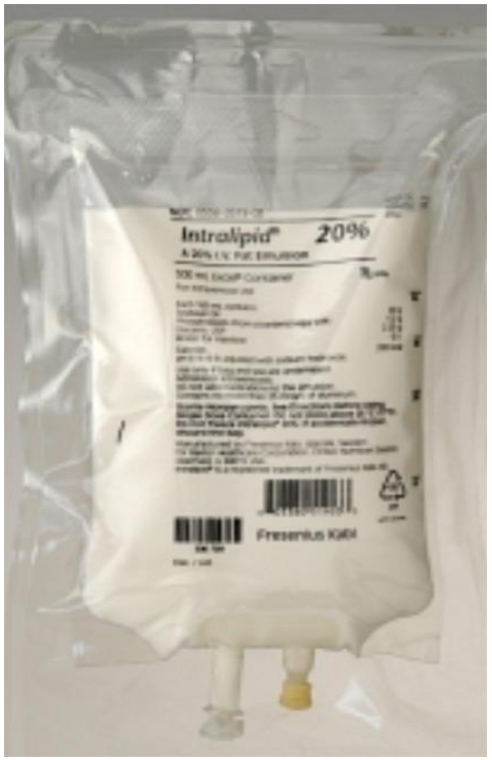
Challenges in Assessing LVPs for Leachables

Among the numerous characteristics that differentiate Large Volume Parenterals (LVPs) from other dosage forms, their composition and large dose volume are particularly noteworthy because of the practical implications of composition and dose volume to the safety assessment of packaging system leachables.

The LVP Challenge; Composition

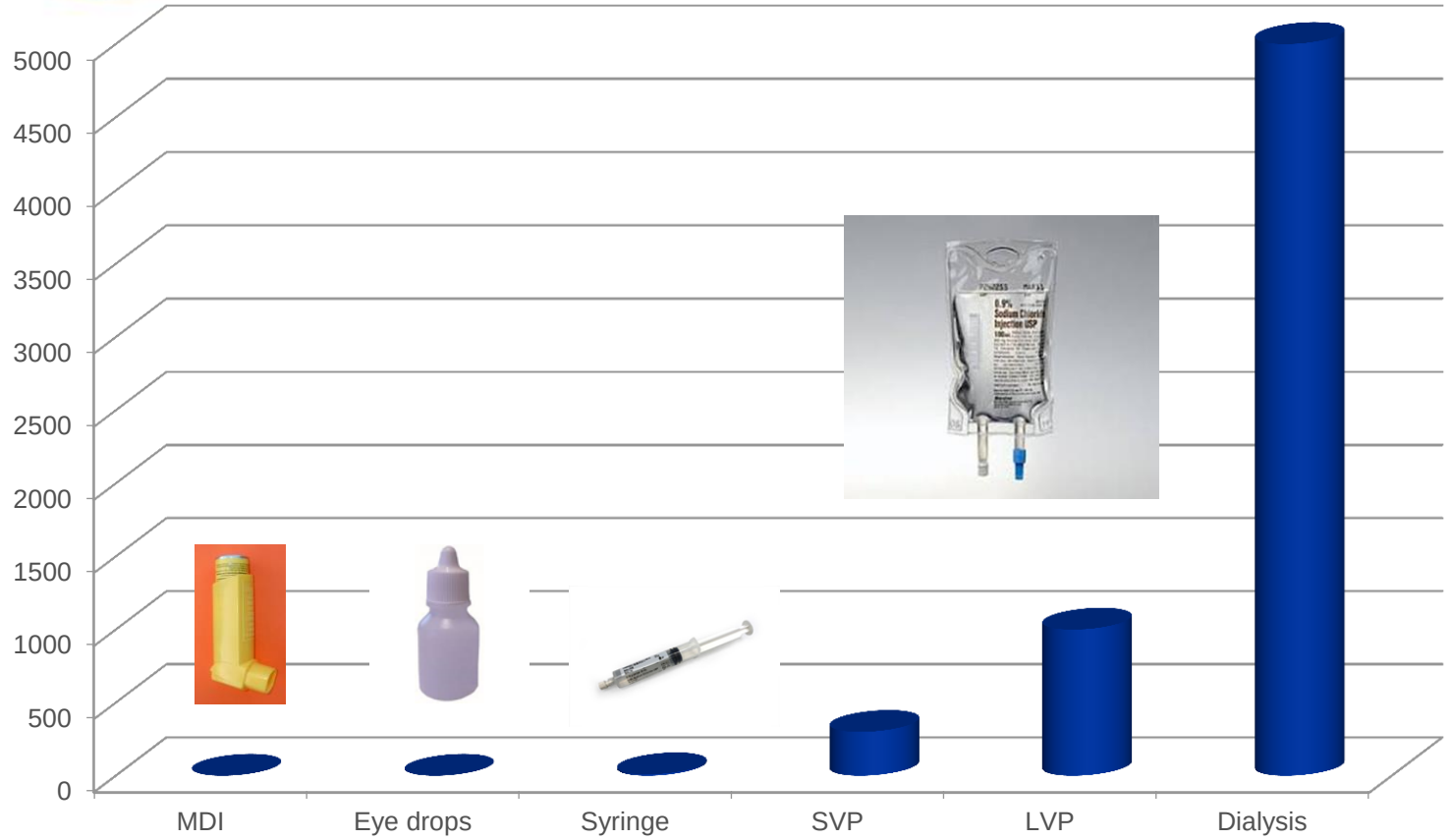


Leachables Profiling Scale:

Easier to do

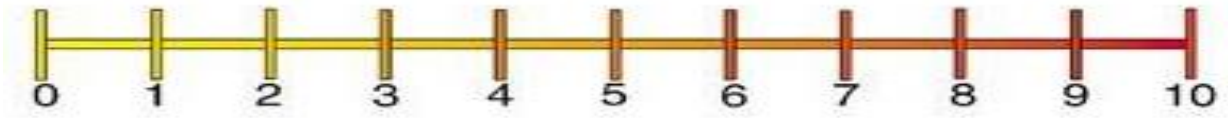
Harder to do

The LVP Challenge – Daily Dose Volume



Easier to do

Leachables Profiling Scale:



Harder to do

What is the Big Deal About Daily Dose Volume?

One of the most basic concepts in toxicological assessment is that:

“The dose makes the poison”

Paracelsus, the “Father” of modern toxicology

A substance can adversely affect health only if the amount of the substance to which an individual is exposed (dose) exceeds a tolerable threshold.

The exposure dose of a substance is the product of the concentration of the substance in the liquid medication and the volume of the liquid medication that is administered:

Dose = concentration in medication x volume of medication used

What is the Big Deal About Daily Dose Volume?

To establish the safety of a medication one must establish that it contains no substances that exceed the permissible daily dose (PDD). PDD is typically expressed in units of amount per day (for example, mg/day).

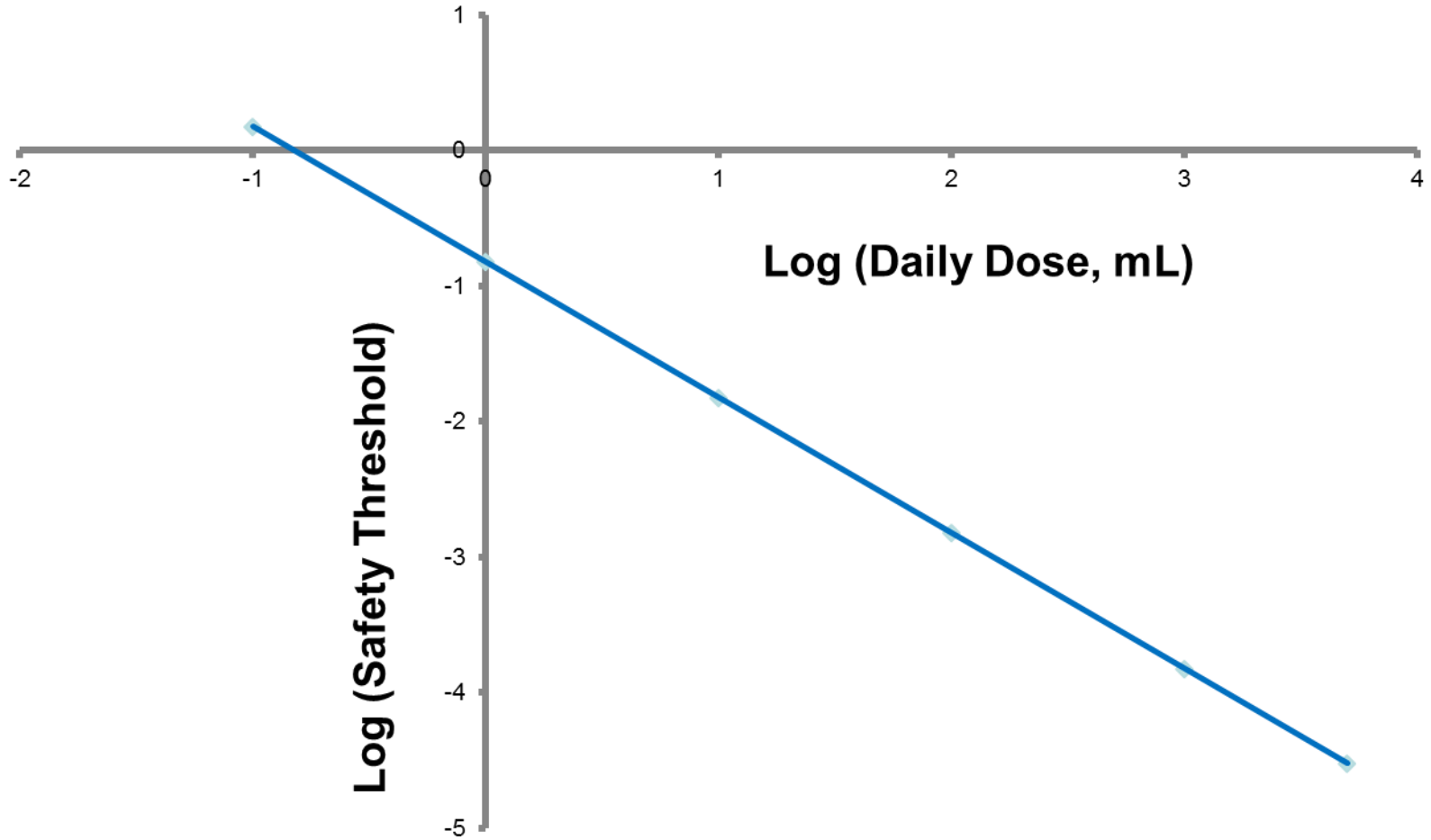
For this reason, medications are tested for their levels of substances that could be potentially unsafe. These test results are expressed as a concentration of the substance in the medication in units of amount per volume (for example, mg/L).

To establish whether the level of the substances exceeds the PDD, the PDD is "converted" to concentration units by dividing the PDD by the daily dose volume V:

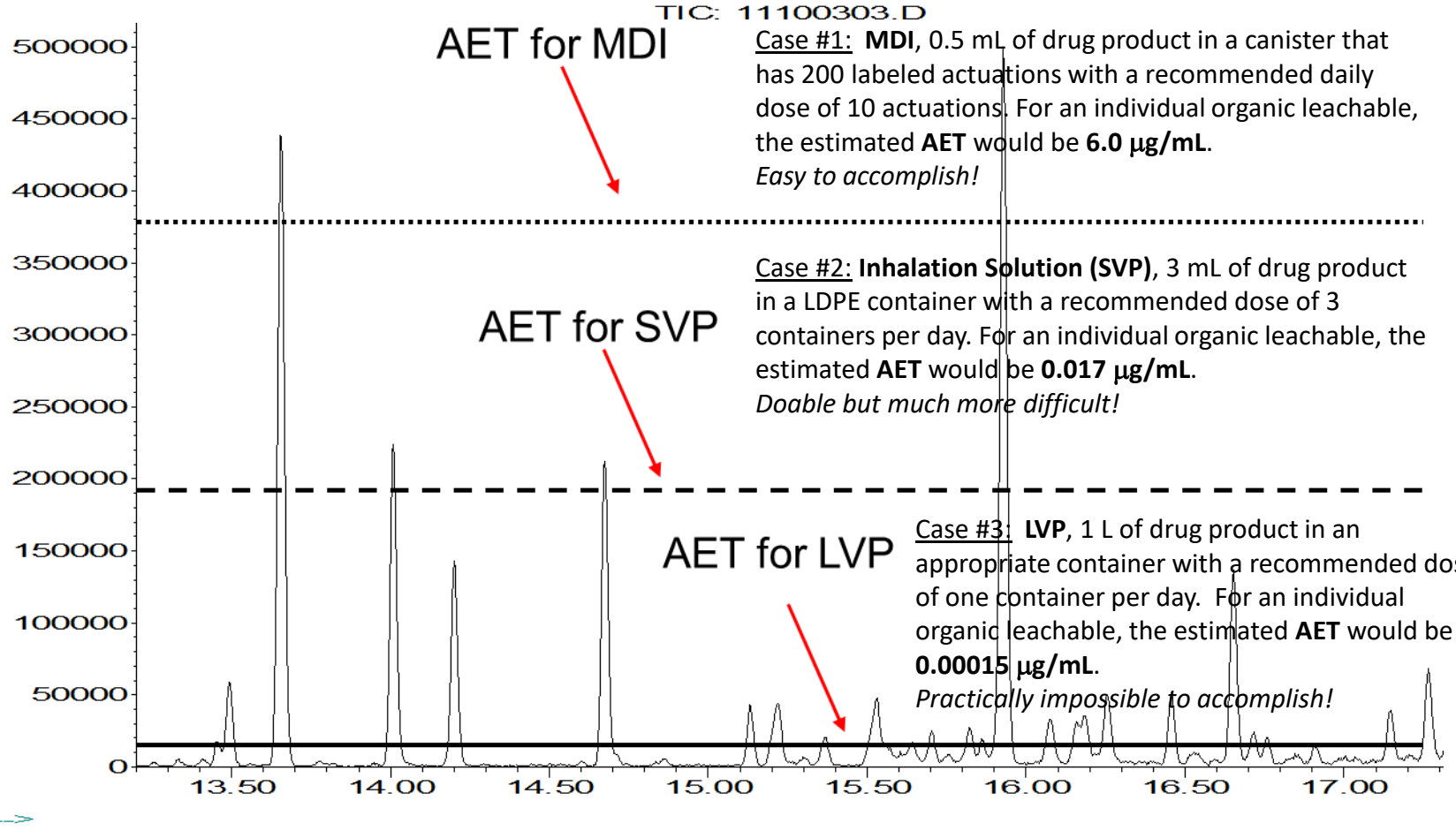
$$\text{Safety Threshold}_{\text{concentration}} = \text{PDD}_{\text{amount}}/V$$

What is the Big Deal About Daily Dose Volume?

The value of the Safety Threshold decreases in direct proportion to the increase in Daily Dose Volume.



What is the Big Deal About Daily Dose Volume?



Case #1: **MDI**, 0.5 mL of drug product in a canister that has 200 labeled actuations with a recommended daily dose of 10 actuations. For an individual organic leachable, the estimated **AET** would be **6.0 µg/mL**.
Easy to accomplish!

Case #2: **Inhalation Solution (SVP)**, 3 mL of drug product in a LDPE container with a recommended dose of 3 containers per day. For an individual organic leachable, the estimated **AET** would be **0.017 µg/mL**.
Doable but much more difficult!

Case #3: **LVP**, 1 L of drug product in an appropriate container with a recommended dose of one container per day. For an individual organic leachable, the estimated **AET** would be **0.00015 µg/mL**.
Practically impossible to accomplish!

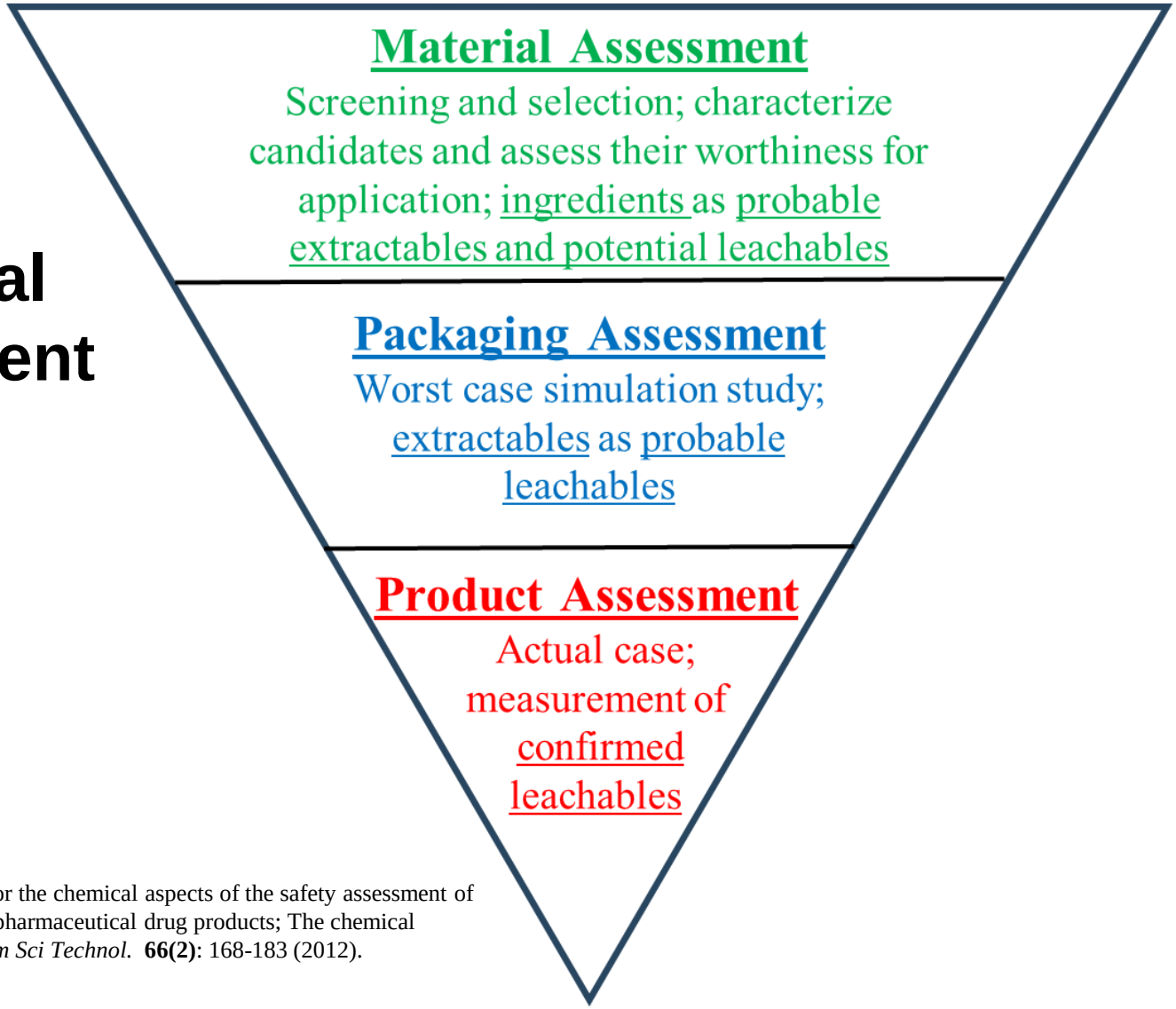
The “LVP Challenge”

AETs for LVPs may be so low that even state of the art, best demonstrated practice analytical methods may not be able to accomplish the functions of discovery and identification for all necessary leachables.

If leachables cannot be detected and identified then obviously they cannot be toxicologically assessed by numerical means and thus their potential safety impact cannot be established by such numerical means.

The Solution to the "LVP Challenge"

The Chemical Assessment Triad



D. Jenke. A general strategy for the chemical aspects of the safety assessment of extractables and leachables in pharmaceutical drug products; The chemical assessment triad. *PDA J Pharm Sci Technol.* **66(2)**: 168-183 (2012).

The Simulation Study – Value Proposition

Problem:

Occasions may arise in which it is not analytically feasible (due to challenging thresholds, for example) to successfully discover and identify all actual leachables in a drug product leachables study.

Solution:

This circumstance can be managed if the activities of discovery and identification of probable leachables can be accomplished in an extraction study, where samples and analyte concentrations are more easily manipulated to achieve the necessary analytical performance.

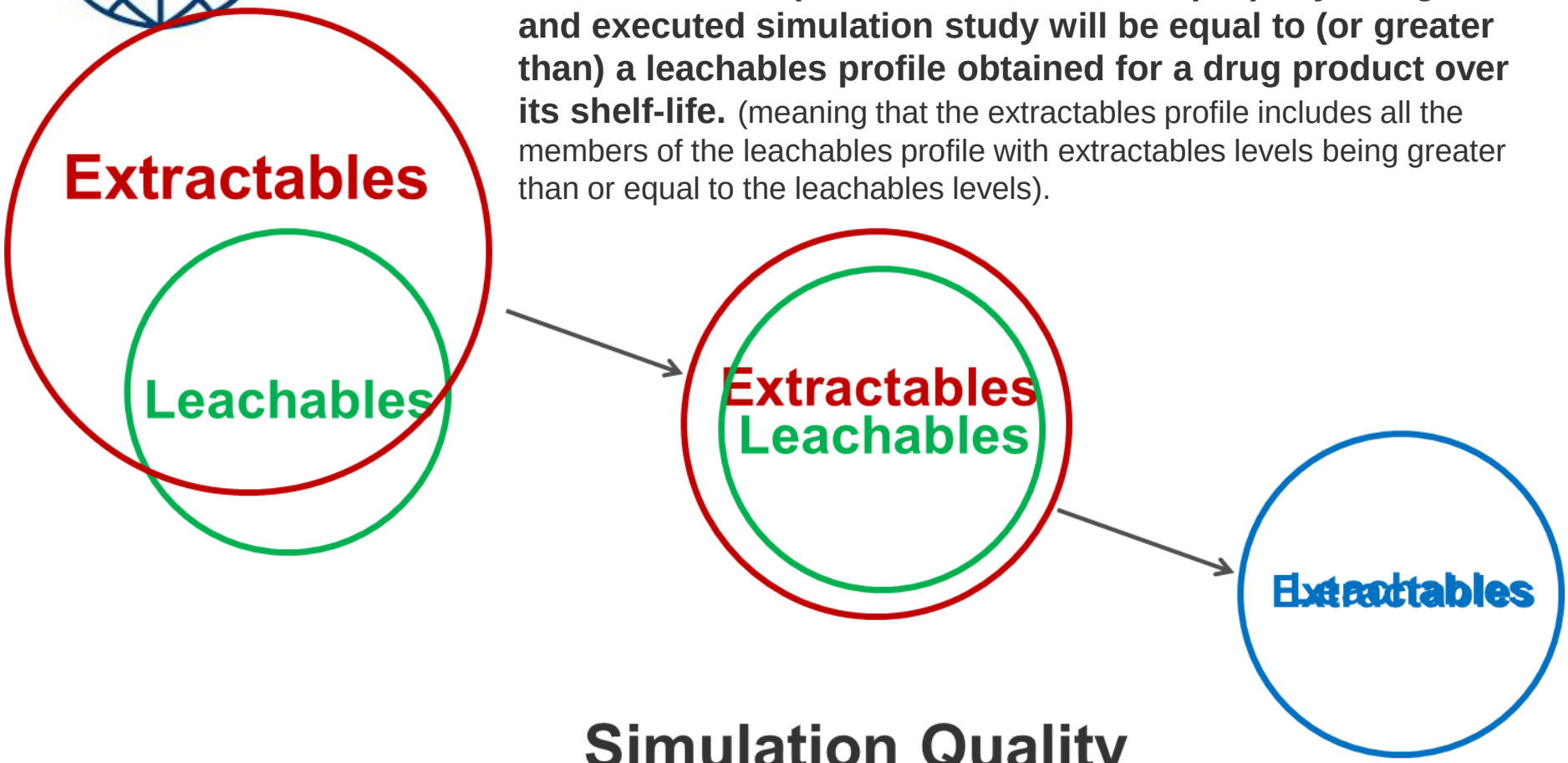
Source: *<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.* USP 38 – NF 33 (First Supplement), pp. 7181 – 7193. August 1, 2015.

Differences between Simulation and Actual Use

1. The drug product formulation has been replaced with one or more simulating solvents.
2. The actual use conditions of contact have been accelerated.
3. The test article may have been altered (somewhat) to provide an exaggerated and presumably worst case.

The Simulation Study Concept

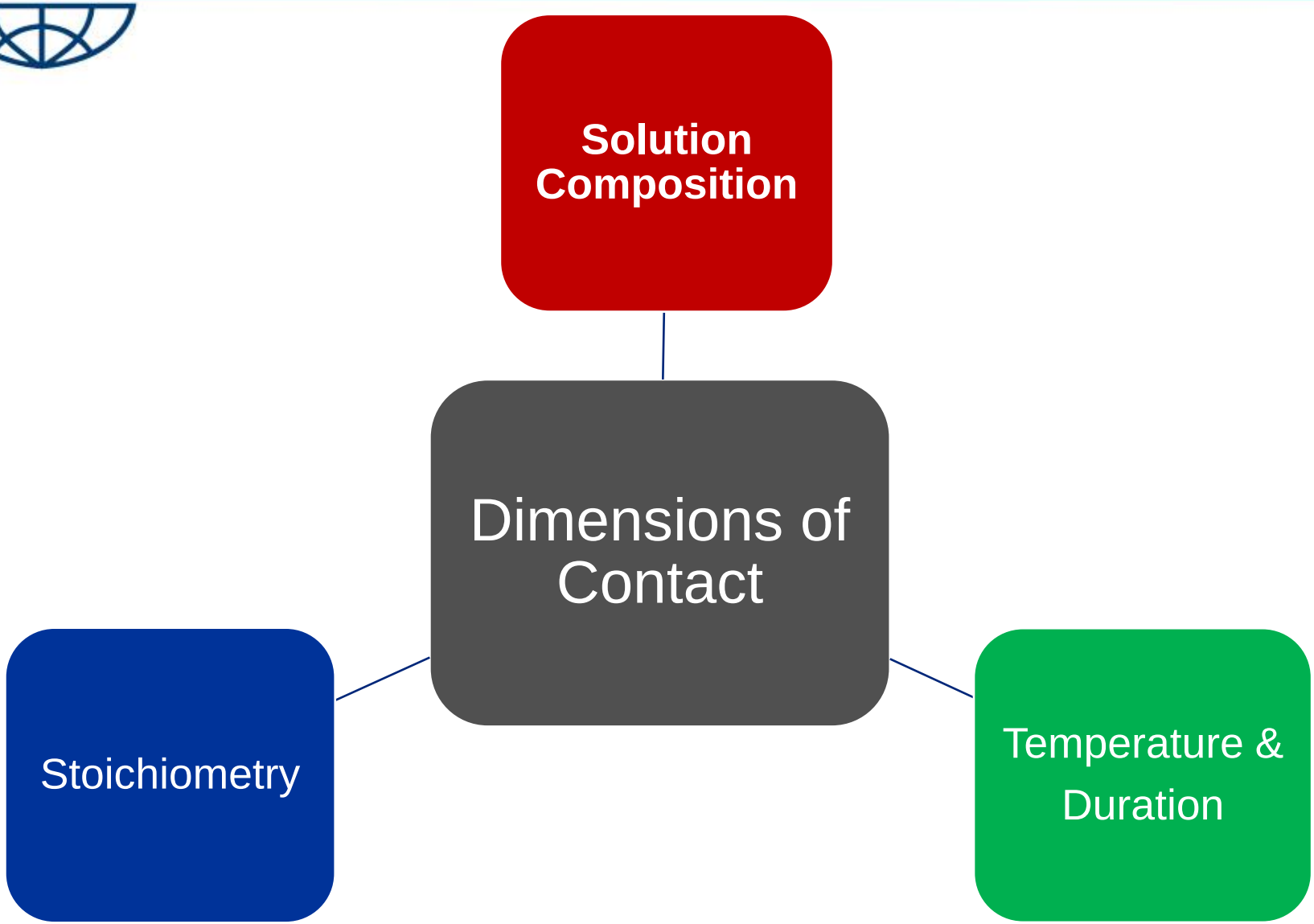
An extractables profile obtained from a properly designed and executed simulation study will be equal to (or greater than) a leachables profile obtained for a drug product over its shelf-life. (meaning that the extractables profile includes all the members of the leachables profile with extractables levels being greater than or equal to the leachables levels).



Simulation Quality

Poor ----------> **Good** ----------> **Excellent**

Dimensions of Contact to be Simulated



Simulating Solution Composition

Solution Composition

1. Polarity
2. pH
3. "Reactivity"

Simulating Solution Composition - Polarity

Thermodynamically:

A leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.

A leachable's solubility in a drug product will depend on the "polarity" of the leachable and the drug product.

"Like dissolves like"

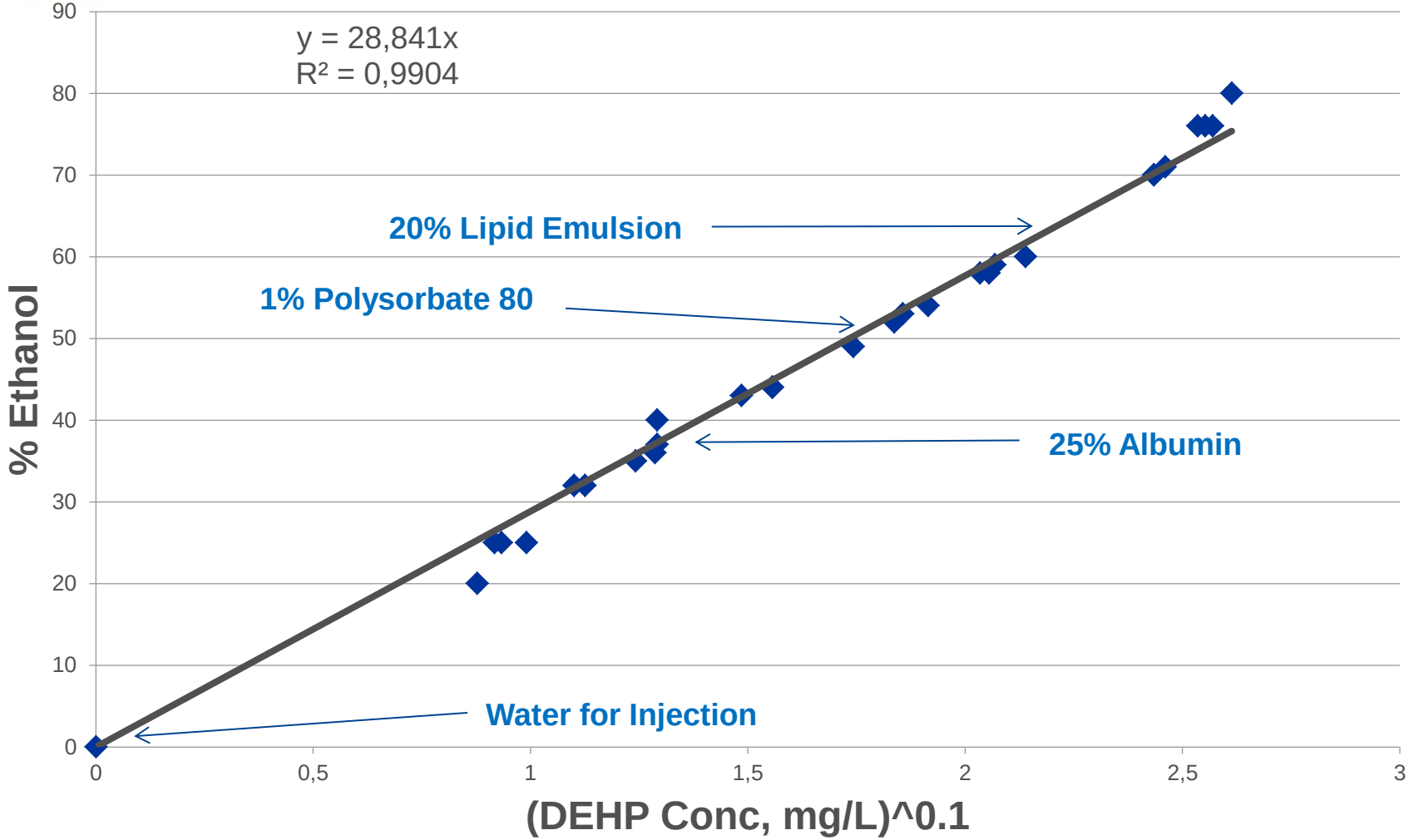
Simulating Solution Composition - Polarity

Means of Establishing a Solution's Polarity:

1. Polarity Tables for Solvents
2. Correlation with Measurable Fundamental Properties – Dielectric Constant
3. Use of Polarity Markers (e.g., solvatochromic Reichardt's dye)
4. Experimental Determination via "Extraction Power" Scales

The Relative "Leaching Power" of Drug Products; Polarity Effects

Source: Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* **69(3):** 366-38 2(2015).



Simulating Solution Composition - pH

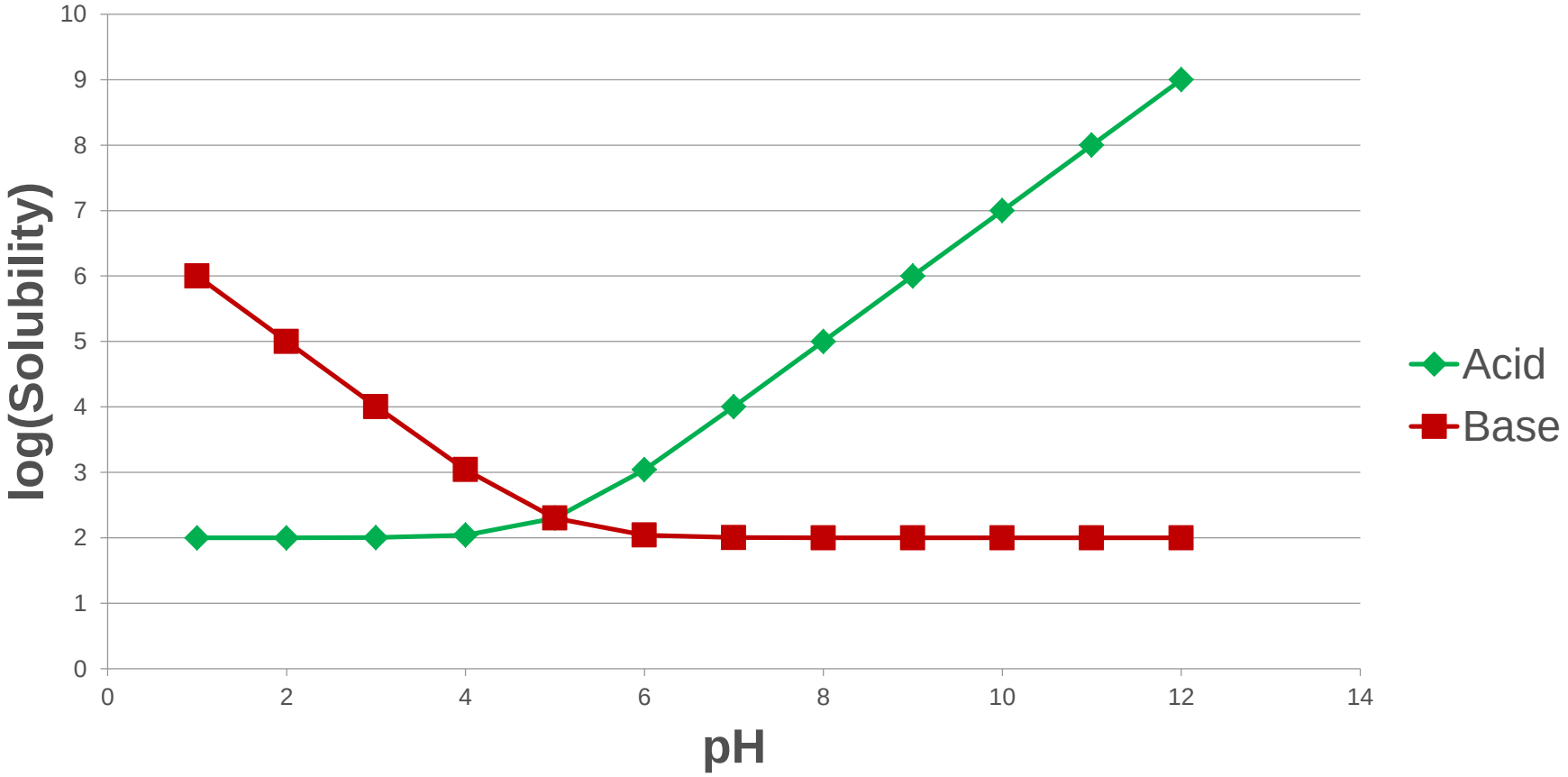
Thermodynamically:

A leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.

The solubility of an acidic or basic leachable in a drug product will depend on the acid/base dissociation constant (pK_a) of the leachable and the pH of the drug product.

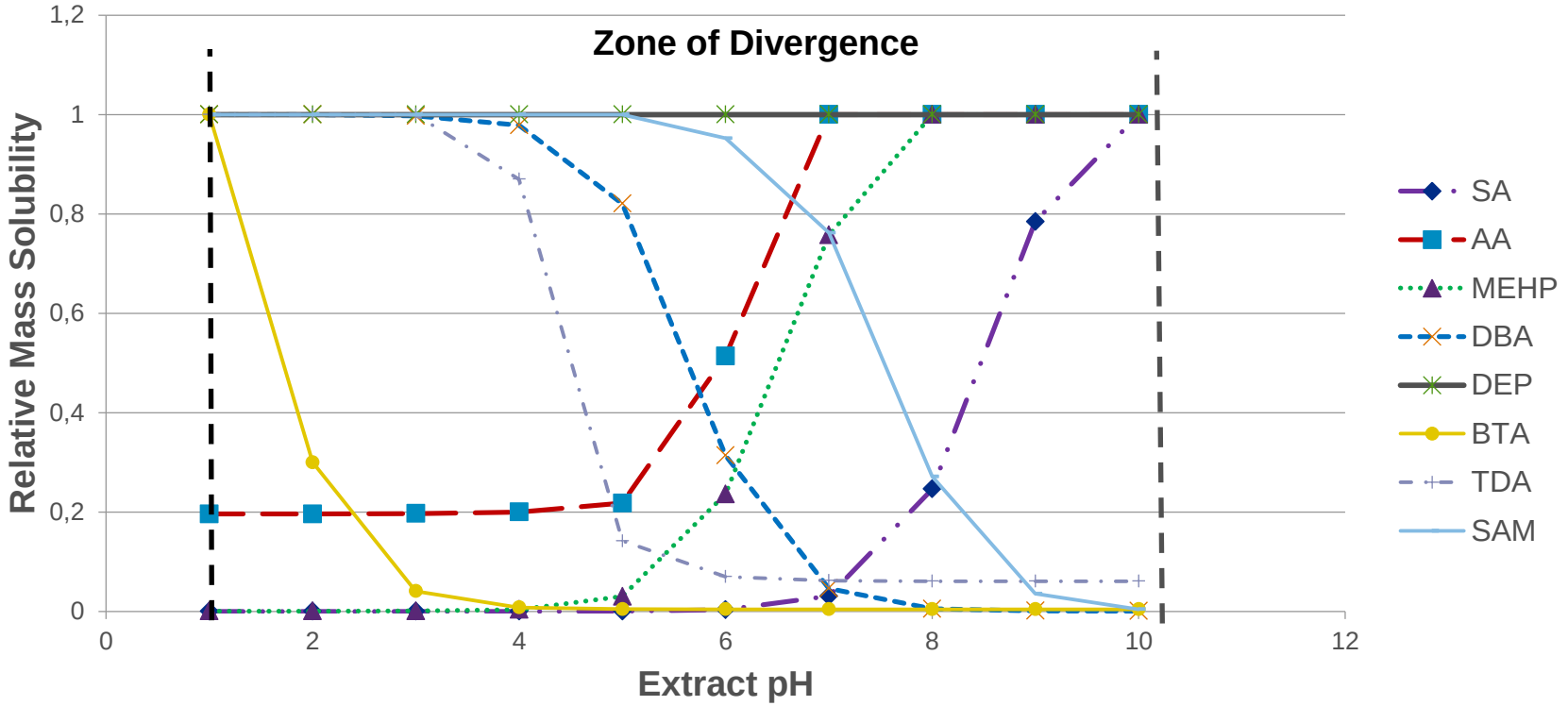
The Relative "Leaching Power" of Drug Products - pH

The Effect of pH on the Solubility of an Acidic or Basic Extractable. The Figure considers an acidic or basic extractable with a pK_a of 5.0 and a solubility of 100 (arbitrary units). As the pH of the extracting medium increases, the solubility of the acidic extractable increases. Similarly, as the pH of the extracting medium decreases, the solubility of a basic extractable increases.



The Effect of Solution pH on the Reported Solubility of Selected Extractables

As DEP is non-ionic, its solubility is unaffected by pH. The solubility of the acidic extractables (AA, SA and MEHP) increases with increasing pH, depending on their pK_a. The solubility of the basic extractables (SAM, DBA, TDA, BTA) increases with decreasing pH, consistent with their pK_a. The Zone of Divergence spans those pH values where the weakest acid (SA) and the weakest base (BTA) achieve their maximum solubilities. A set of extraction solvents that captures essentially all possible acidic or basic extractables at their likely highest concentration must have a pH values that span the Zone of Divergence.



Source: Jenke, D. Establishing the proper pH of simulating solvents used in organic extractables assessments for packaging systems and their materials of construction used with aqueous parenteral drug products. *Pharm Outsourcing.* **15(4)**:20, 22, 24-27 (2014)

Simulating Solution Composition - Reactivity

Issue: An extractable from the container reacts with some chemical component of the drug product, altering the chemical structure of the extractable and resulting in a disconnect between the extractables and leachables profile.

- Simulation Study reveals the extractable
- Leachables Study reveals the degradation products(s)
- It is the leachable that potentially impacts a product's quality attribute.

Accelerating Clinical Contact: Temperature and Duration

Temperature

and

Duration

Accelerating Clinical Contact: Temperature and Duration

Kinetically:

A leachable will accumulate in a drug product at a rate dictated by the speed with which the leachable diffuses through the packaging.

The diffusion rate will depend on the diffusion coefficient for the leachable in the packaging material and the contact temperature.

The amount of a leachable that accumulates in a drug product will depend on the diffusion coefficient, the diffusion distance and the duration of contact.

Accelerating Clinical Contact: Temperature and Duration

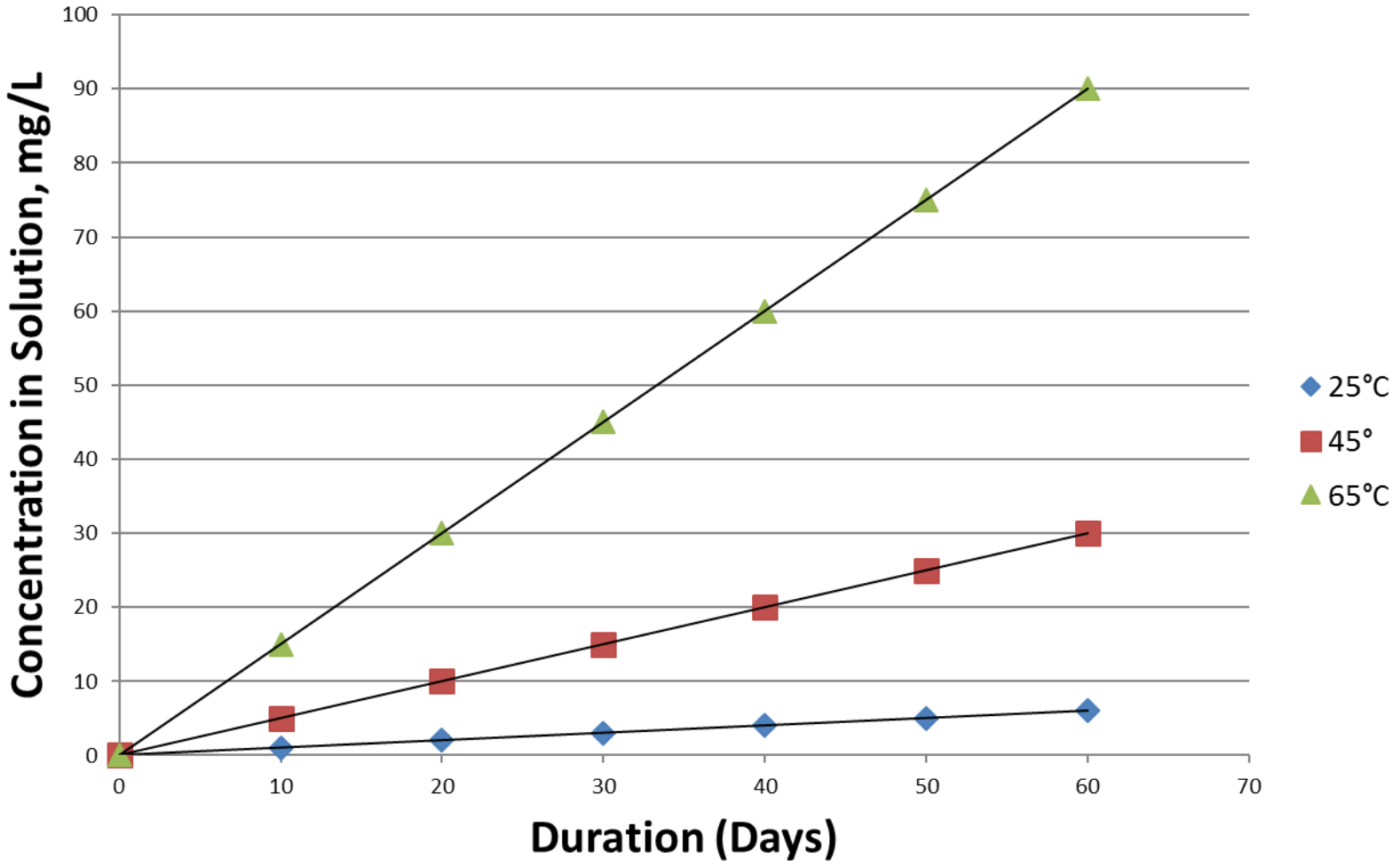
Kinetically:

The higher the temperature, the longer the contact time and the larger the diffusion coefficient …

1. The larger will be the leachable's concentration in the drug product.

2. The more likely an equilibrium leachable concentration will be achieved.

Accelerating Clinical Contact: Temperature and Duration



Accelerating Clinical Contact: Temperature and Duration

Two Approaches for Calculating and Justifying Accelerating Conditions

1. **ASTM F1980-07 (Reapproved 2016)**: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

Accelerated Aging Time at T2 = Actual Aging Time at T1 ÷ C

$$C = Q_{10}^{[(T2 - T1)/10]}$$

where Q_{10} = 10°C Reaction Rate Constant
T2 = accelerating temperature (°C)
T1 = actual temperature of contact (°C)

Note: This standard does not purport to address all of the safety concerns, if any, associated with its use.

Accelerating Clinical Contact: Temperature and Duration

Two Approaches for Calculating and Justifying Accelerating Conditions

2. "Factor 10 Rule" [1] This factor 10 rule is based on the observation that activation energies for migrating substances in polymers relevant to packaging are typically in the range of 80 to 100 kJ/mole. In such a circumstance, the diffusion coefficient increases by roughly an order of magnitude for every 20°C increase in contact temperature. Thus for example, the migration rate at 40°C is ten times faster than the migration rate at 20°C

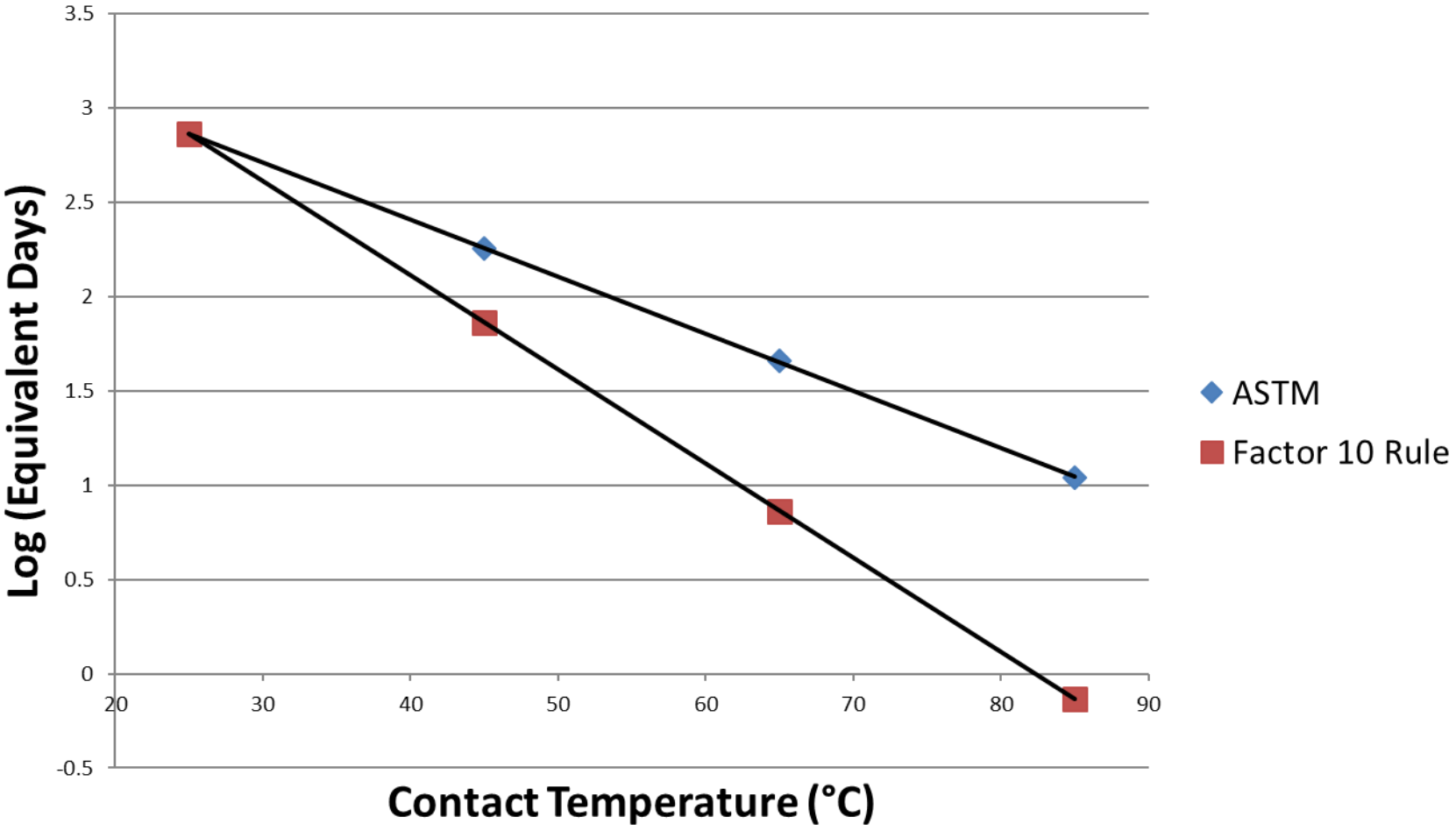
$$\text{Accelerated Aging Time at T2} = \text{Actual Aging Time at T1} \div C$$

$$C = 10^{[(T2 - T1)/20]}$$

[1]R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.

Accelerating Clinical Contact: Temperature and Duration

Acceleration of a Two-Year (730 days) Ambient Temperature Shelf-life



Accelerating Clinical Contact: Temperature and Duration Recommendations

1. In general, the concentration (C_2) of an extractable at a certain duration of contact at temperature T2 can be estimated from the concentration of the same extractable (C_1) at the same duration of contact at a reference temperature T1 using the following equation, although exceptions will occur:

$$C_2 = C_1 \times 1.5^{[(T2-T1)/10]}$$

For example, if the concentration achieved by an extractable after 20 hours of storage at 25°C is 2.0 mg/L, the concentration achieved by the extractable after 20 hours of storage at 45°C will be:

$$C_{45} = C_{25} \times 1.5^{[(45-25)/10]}$$

$$C_{45} = 2.0\ mg/L \times 1.5^2$$

$$C_{45} = 4.5\ mg/L$$

Accelerating Clinical Contact: Temperature and Duration Recommendations

2. In general, the time (t_2) required for an extractable to reach a certain concentration at a temperature T2 can be estimated from the time (t_1) required for the same extractable to reach the same concentration at a reference temperature T1 using the following equation, although exceptions will occur:

$$t_2 = t_1 \div 10^{[(T2-T1)/20]}$$

For example, if the time it takes for an extractable to achieve a concentration of 2.0 mg/L at 25°C is 10 hours, the time it takes for the same extractable to achieved the same concentration of 2.0 mg/L at 45°C will be:

$$t_{45} = t_{25} \div 10^{[(45-25)/20]}$$
$$t_{45} = 10 \text{ hours} \div 10^{1}$$
$$t_{45} = 1 \text{ hour}$$

The Effect of Stoiciometry

Stoichiometry

1. Surface area/Solution volume
2. Material weight/Solution volume

Stoiciometry Fallicies

1. Its all about surface area.
2. As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear and 1 to 1 manner for all leachables.

Stoiciometry Fallicies Debunked!

1. **Its all about surface area**. In fact, the way most experiments are designed, when one increases the surface area/solution volume ratio they are also increasing the material weight to solution volume ratio. More likely, then **it is all about material weight**.

Stoiciometry Fallicies Debunked!

2. As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear way for all leachables.

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

Where C is the extractable's concentration,

- m is the mass of the extractable in either phase,
- SA is the surface area of the sample being extracted,
- t is the thickness of the sample being extracted,
- $K_{p/l}$ is the extractable's plastic/solution partition coefficient,
- V is the volume of either phase, and
- the subscripts p, l, e and o refer to the plastic phase, the liquid phase, equilibrium and original respectively

R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.

Stoiciometry Fallicies Debunked!

2. As the surface area to solution volume ratio increases, the concentration of leachables will increase in the same linear way for all leachables.

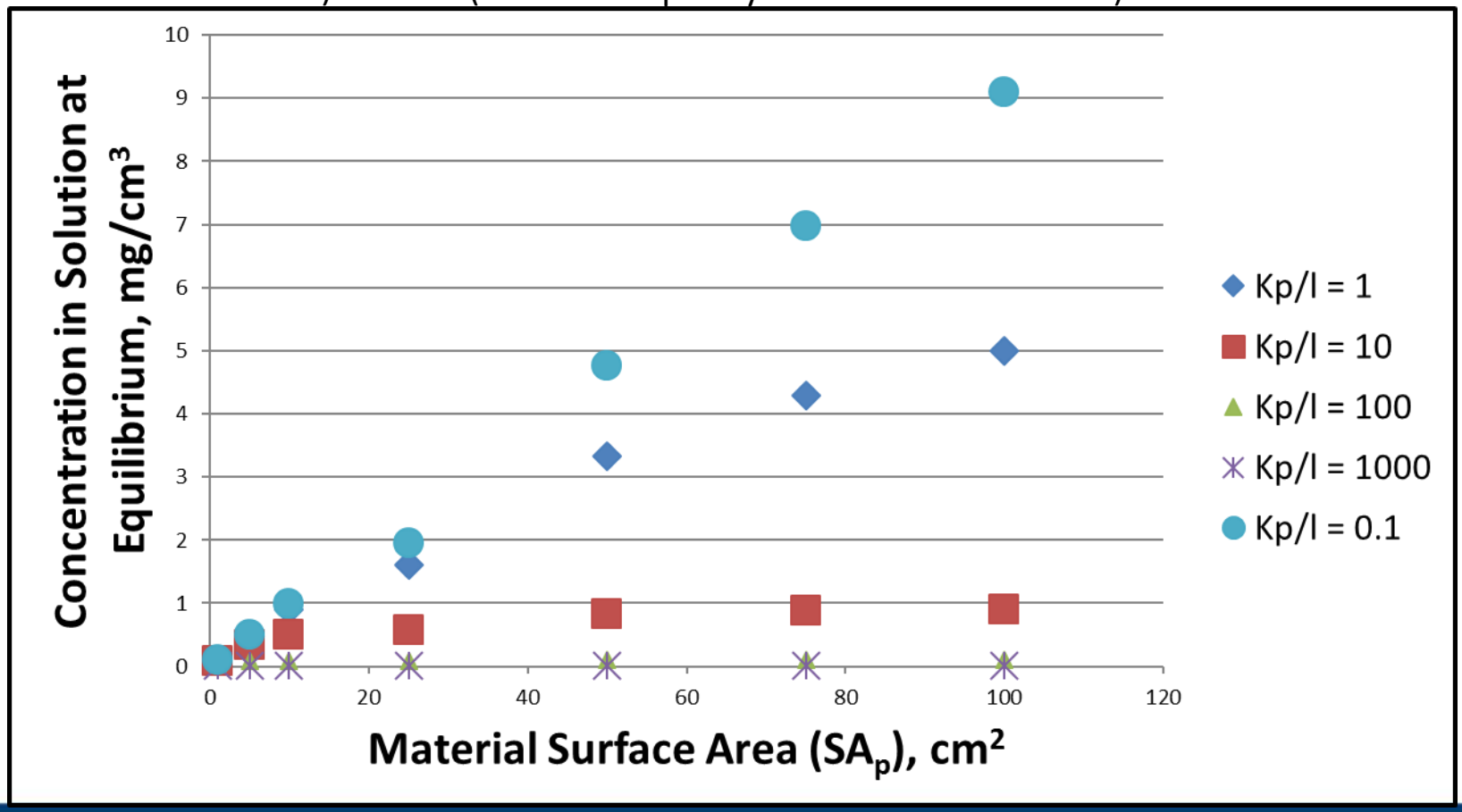
- **For a substance that is highly soluble in the solution, an increase in material surface area produces nearly a proportional increase in the concentration of the substance in the solution.** For example, when the surface area is increased by a factor of 100 for a substance with a $k_{p/l}$ of 0.1, 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.**

To examine the nature of this effect, the following situation is considered:

$m_{p,o}$ = 10 mg/cm^2,
V_l = 100 mL = 100 cm^3,
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).

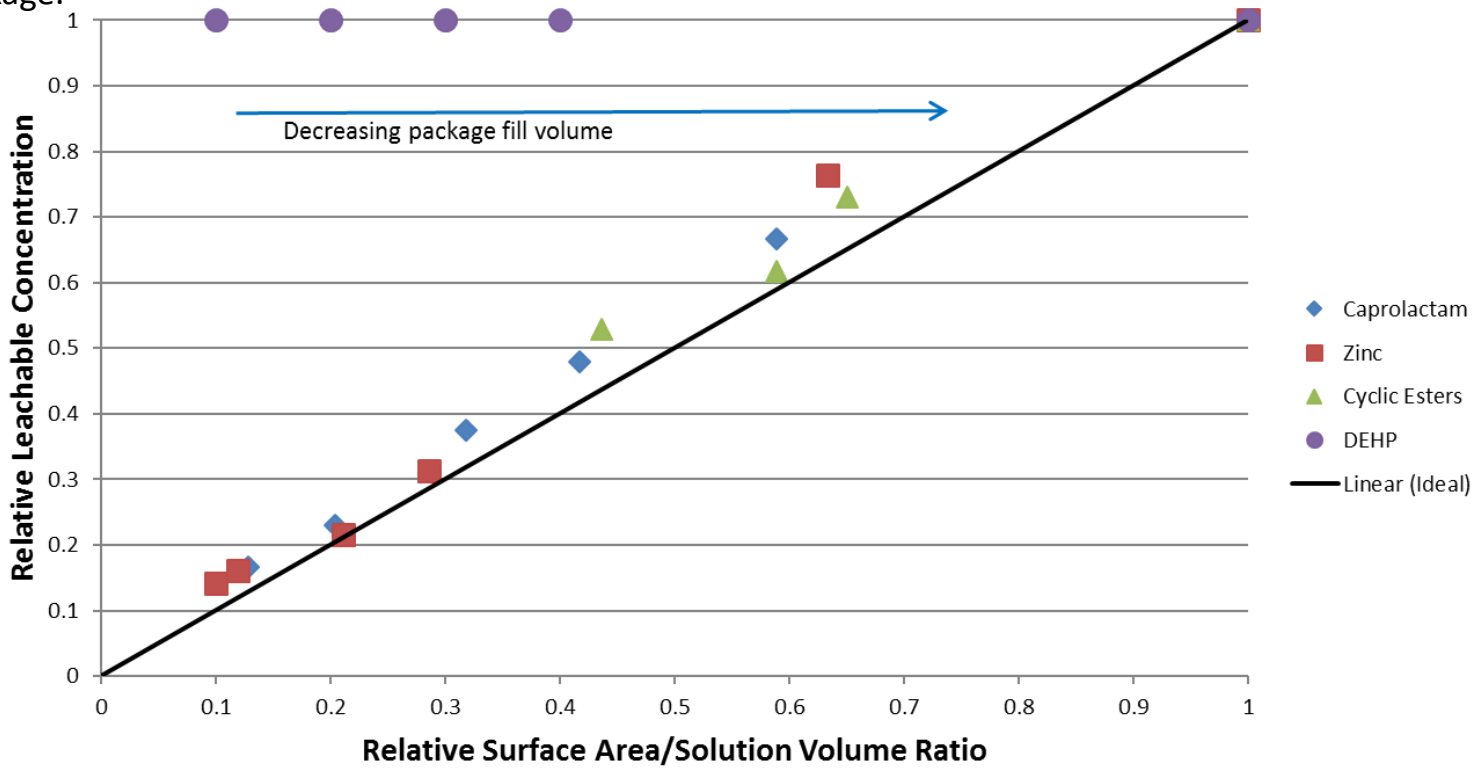
Stoiciometry Fallicies Debunked!

Theoretical Relationship between the Material 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 poorly soluble in the solution).



Stoiciometry Fallicies Debunked!

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.



Source: Jenke, D; Rabinow, B. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol*. **71(3)**: 225-233 (2017)

In Review:

- A properly designed and implemented extractables simulation study produces an extractables profile that is equal to or slightly exaggerated than the leachables profile for a packaged drug product.
- Critical design parameters for a simulation study include:
  - Solution Composition
  - Temperature and Duration
  - Stoichiometry
- In considering Solution Composition, the aspects of “polarity”, pH and “reactivity” should be considered. Of these three, “polarity” and pH are relatively straightforward, while “reactivity” needs further consideration.
- In considering Temperature and Duration, certain mathematical conventions can be quite useful in terms of accelerating leaching.
- In considering Stoichiometry, it is noted that in many cases the surface area to solution volume ratio is just another way of saying material weight to solution volume. More importantly, the assumption of a linear relationship between stoichiometry and leachables accumulation may or may not be true.

References:

1. <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. USP 38 – NF 33 (First Supplement), pp. 7181 – 7193. August 1, 2015.
2. Jenke, D.; Liu, N.; Hua, Y.; Swanson, S.; Bogseth, R. A means of establishing and justifying binary ethanol/water mixtures as simulating solvents in extractables studies. *PDA J Pharm Sci Technol.* 69(3): 366-38 2(2015).
3. Jenke, D. Establishing the proper pH of simulating solvents used in organic extractables assessments for packaging systems and their materials of construction used with aqueous parenteral drug products. *Pharm Outsourcing.* 15(4):20, 22, 24-27 (2014).
4. ASTM F1980-07 (Reapproved 2016): Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.
5. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 368.
6. R. Franz, A. Stormer. Migration of Plastic Constituents. In Plastic Packaging: Interactions with Foods and Pharmaceuticals. Wiley-VCH; Second Edition, 2008, pp. 370.
7. Jenke, D; Rabinow, B. Proper accounting for surface area to solution volume ratios in exaggerated extractions. *PDA J Pharm Sci Technol.* 71(3): 225-233 (2017).
8. Jenke, D. Application of Arrhenius Kinetics to Acceleration of Controlled Extraction Studies. *PDA J Pharm Sci Technol.* (in press).

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Thank you!