The AET Challenge for Large Volume Parenterials (LVPs): Extractables Simulation Studies and How to Design Them
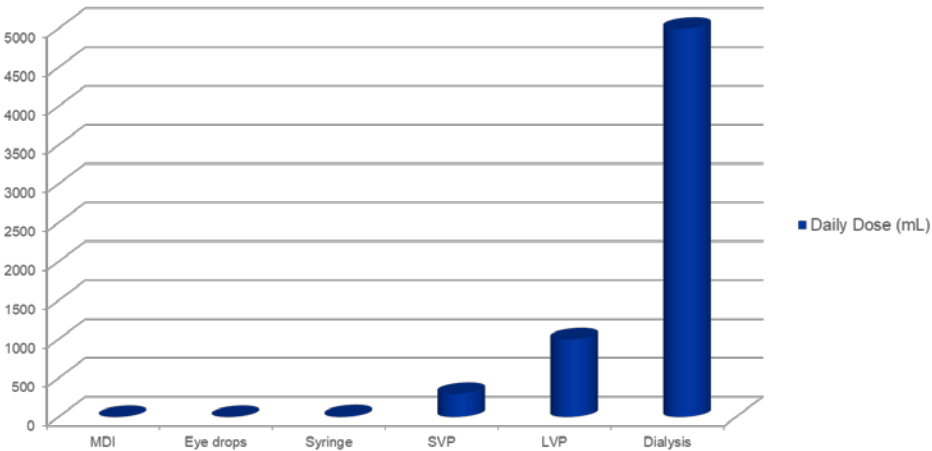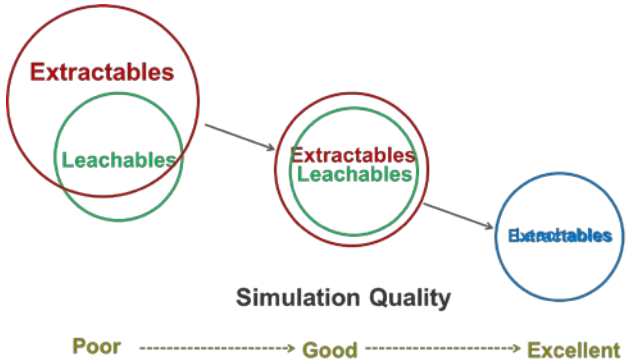
The AET: How Low Can You Go?

Trainer

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- 30 + years of experience in chemical characterization (E&L) of pharmaceutical packaging, manufacturing systems and medical devices, largely spent at Baxter Healthcare.
- Nearly 170 journal articles, numerous book chapters and one book on the topics of analytical chemistry, ion chromatography, theory and practice of chemical characterization.
- If there is something that you do not like about an E&L Standard, Monograph or Recommendation, then chances I am probably to blame.

1. Name

2. Company

3. Department

4. Learning Expectations

Training Course Outline

- The LVP Challenge – How Low Can You Go?

- The Simulation Study as a Means of Addressing the LVP Challenge

- Design Parameters for Effective Simulation Studies

  - Extraction Solvent Composition
  - Temperature and Duration
  - Stoichiometry

Learning Objectives

- Establish the practical issues that drive the AET unmanageably low for large volume parenteral (LVP) drug products

- Clarify the analytical and toxicological implications of unmanageable AETs

- Introduce the concept of a Simulation Study, matching its design to its purpose

- Use good science, practically applied, to design robust and complaint Simulation Studies

    - How to select the proper simulating extraction solvent
    - How to appropriately accelerate an extraction
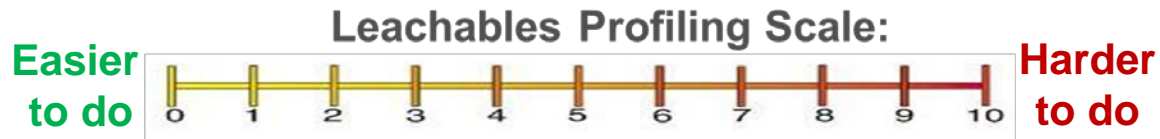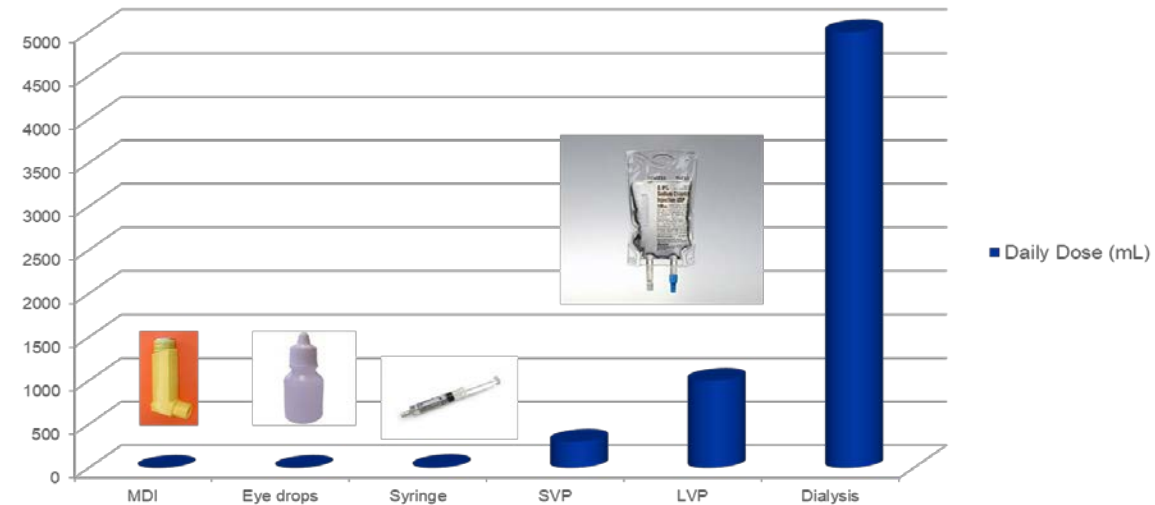   - How to account for surface area to solution volume effects

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.

Composition

Daily Dose Volume

Leachables Profiling Scale:

Easier to do — 0 1 2 3 4 5 6 7 8 9 10 — Harder to do

Leachables Profiling Scale:

Easier to do — 0 1 2 3 4 5 6 7 8 9 10 — Harder to do

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

"The dose makes the poison."

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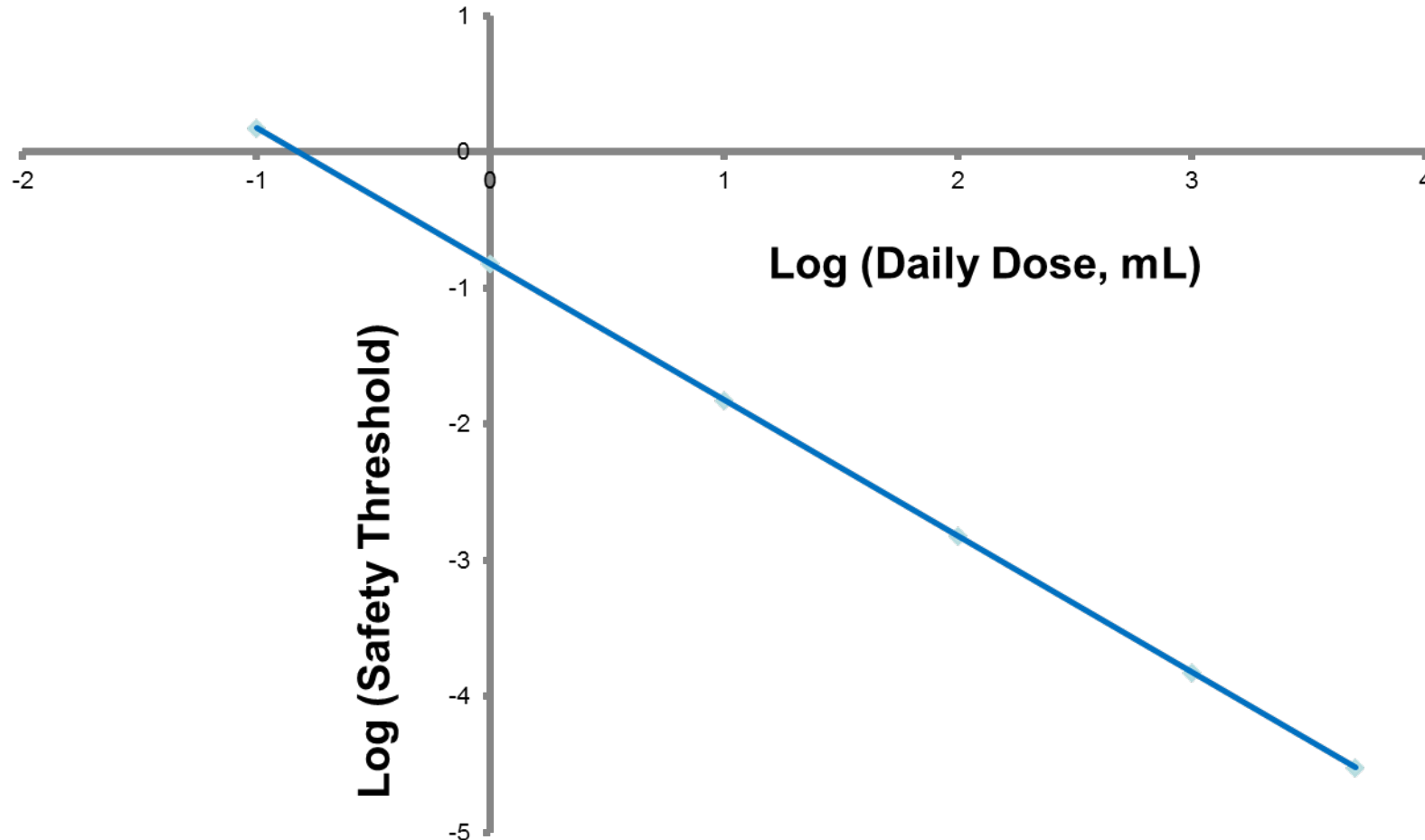
Paracelsus, the "Father" of modern toxicology

Dose = concentration in medication x <u>volume</u> of medication used
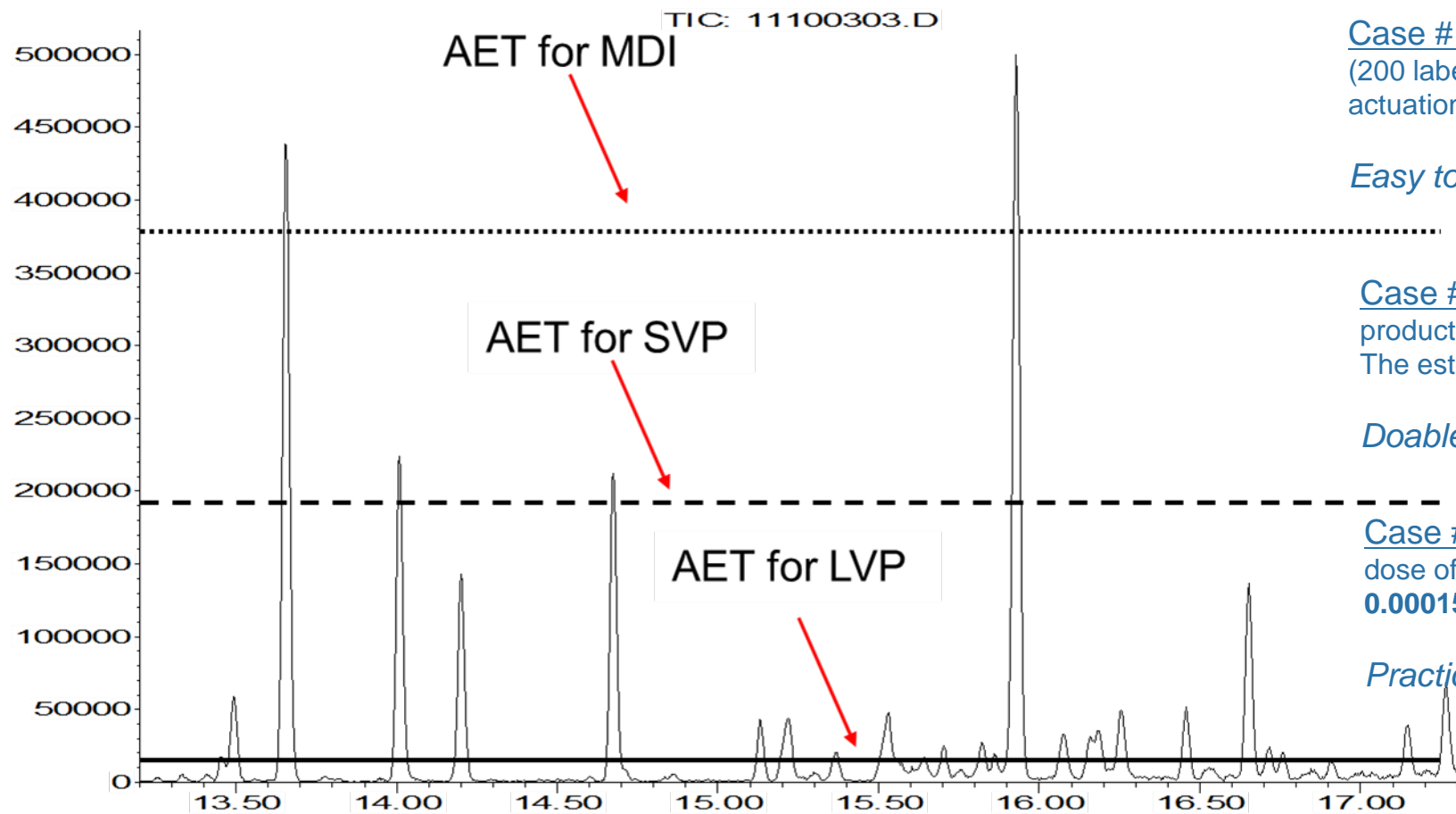
The Daily Dose Volume Affects the Safe Dose Level

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

Case #1: **MDI**, 0.5 mL of drug product in a canister (200 labeled actuations) with a daily dose of 10 actuations. 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 bottle with a dose of 3 bottles per day. The estimated **AET** would be **0.017 µg/mL**.

Doable but much more difficult!

Case #3: **LVP:** 1 L of drug product in an bag with a dose of one bag per day. The estimated **AET** would be **0.00015 µg/mL**.

Practically impossible to accomplish!

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.
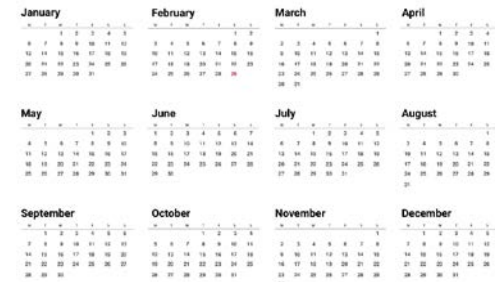
1. The drug product formulation has been replaced with one or more simulating solvents that are easier to test.

Becomes

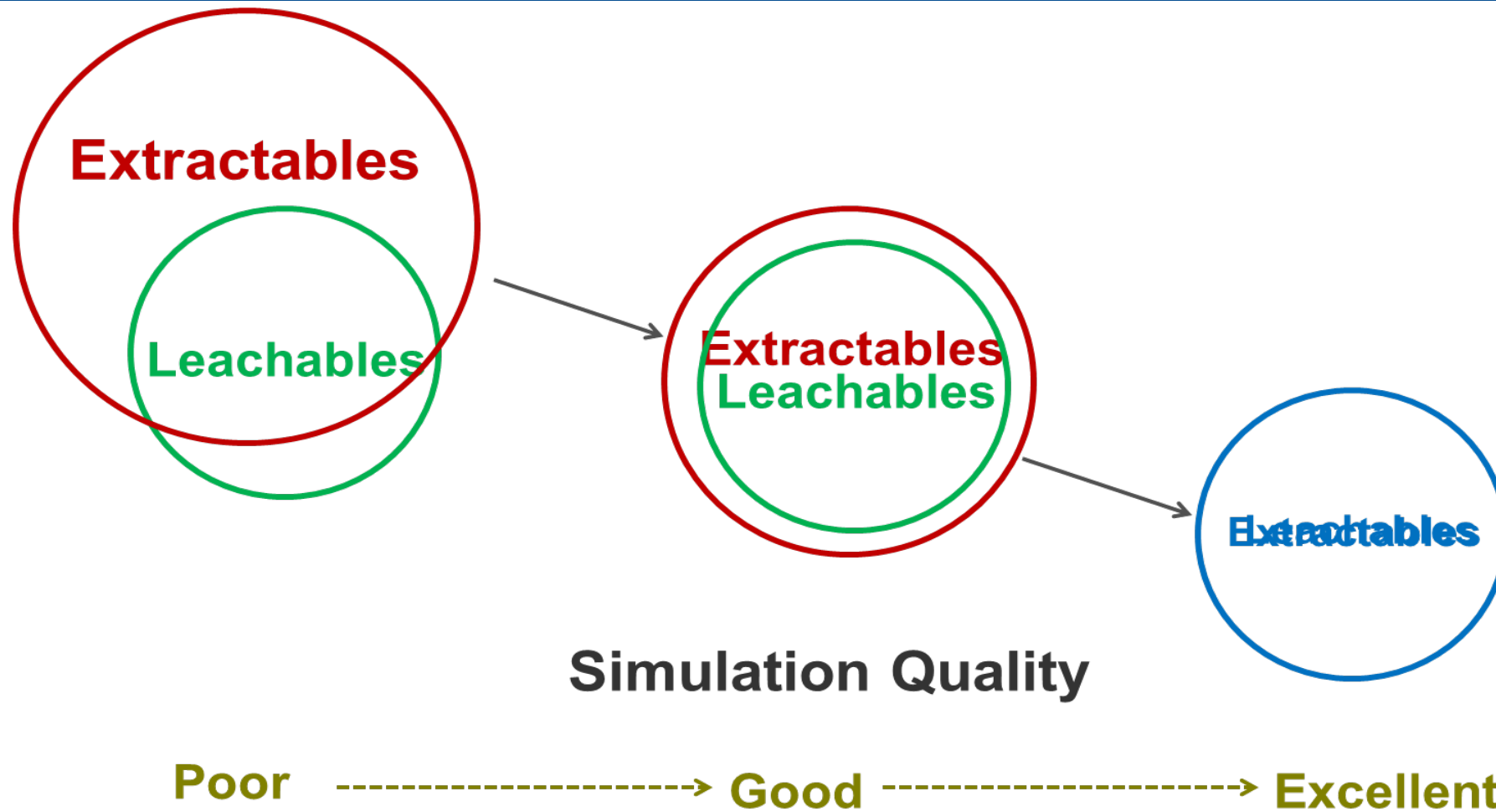2. The actual use conditions of contact have been accelerated.

Becomes

3. The test article may have been altered (somewhat) to provide an exaggerated and presumably worst case.

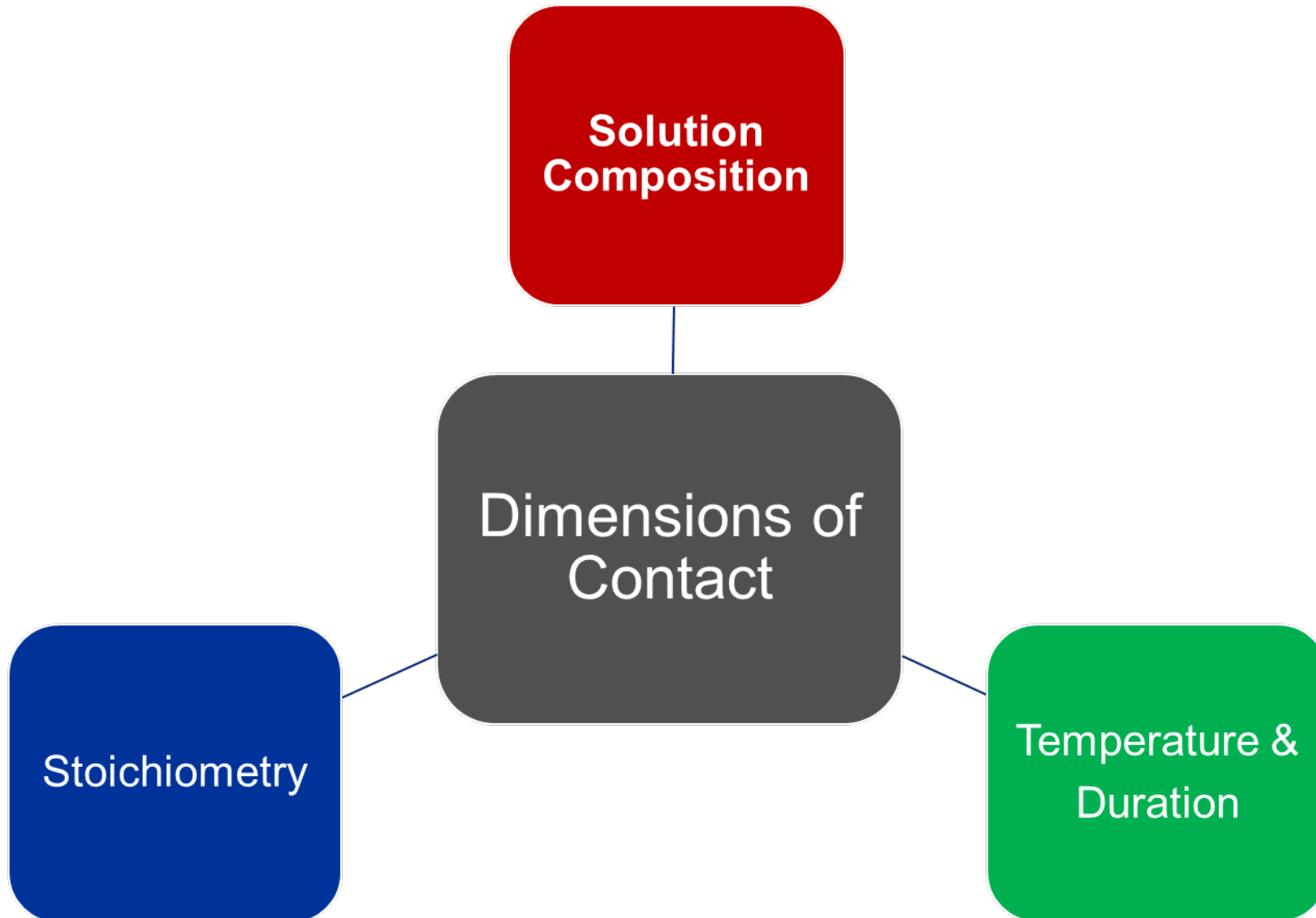**Becomes**

An extractables profile obtained from a properly designed and executed simulation study will the same as a drug product's leachables profile (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).

Solution Composition

1. Polarity

2. pH

3. "Reactivity"

Simulating Polarity

- 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").

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

$y = 28.841x$
$R^2 = 0.9986$

Chart labels: 20% Lipid Emulsion, 1% Polysorbate 80, 25% Albumin, Water for Injection

Y-axis: % Ethanol (0 to 90)
X-axis: (DEHP Conc, mg/L)^0.1 (0 to 3)

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).
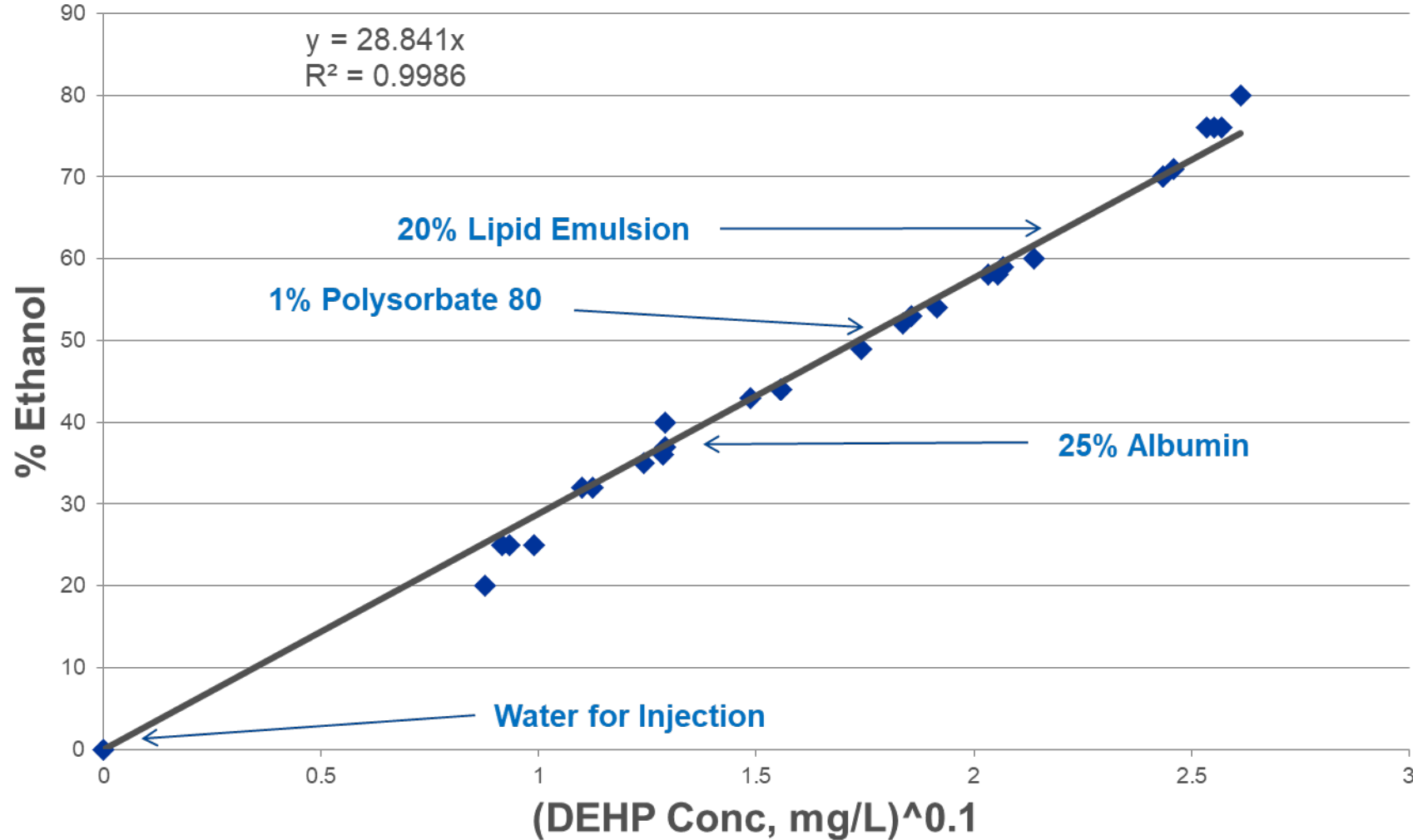
- A leachable will accumulate in a drug product to a level dictated by its solubility in the drug product.
- The solubility of an acidic or basic leachable will depend on the acid/base dissociation constant (pK_a) of the leachable and the pH of the drug product.
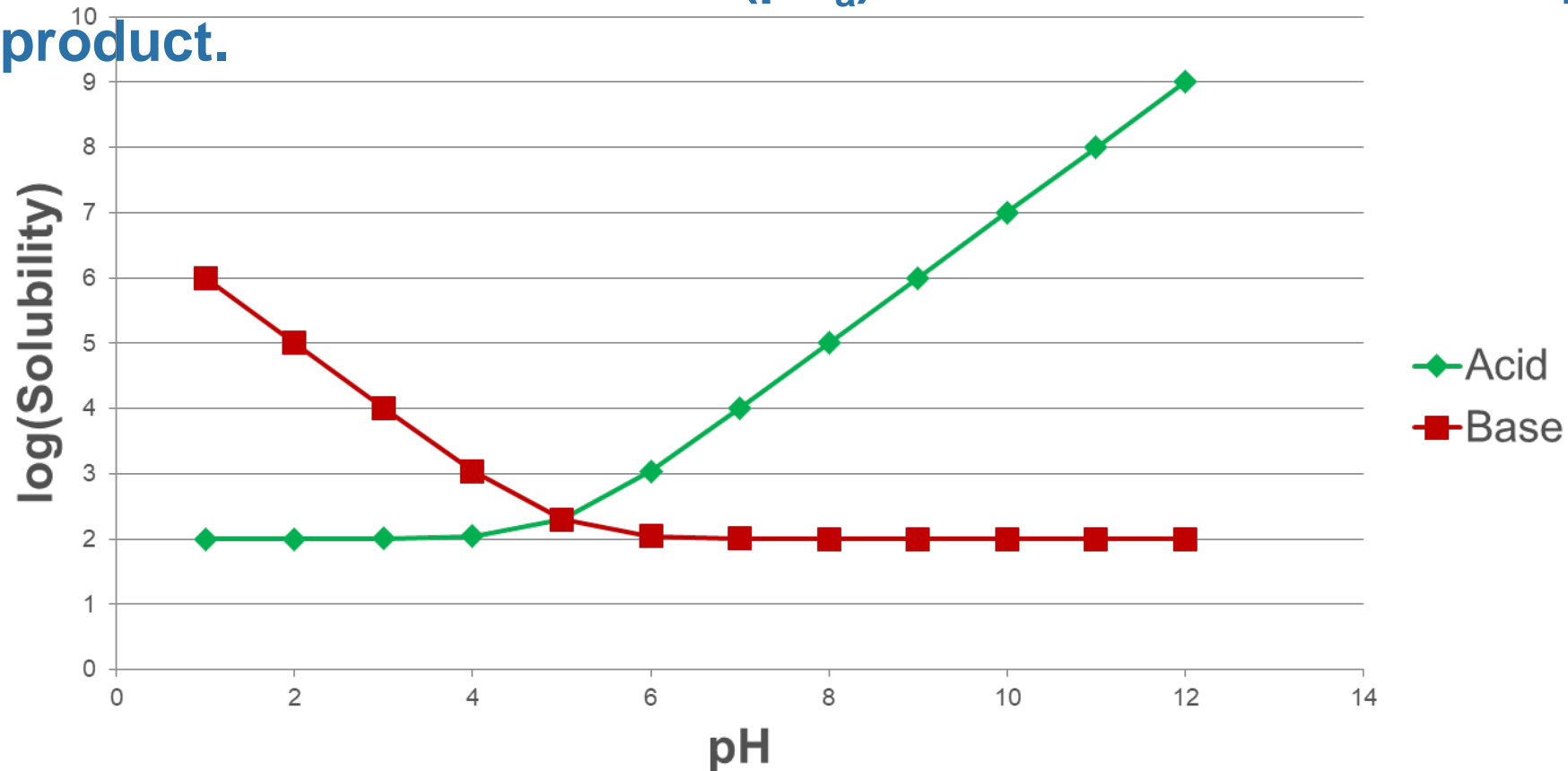
- Most commonly encountered acidic leachables have a pK_a of 7 or less.

- Most commonly encountered basic leachables have a pK_a of 3 or more.

- Most aqueous drug products have a pH between 3 and 9.

Therefore:

Two simulating solvents, one prepared at pH 3 and one prepared at pH 10, reasonably bracket the universe of leachables and drug products, although acceptations may require more extreme pH values

Temperature
and
Duration

Accelerating an Extraction

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.
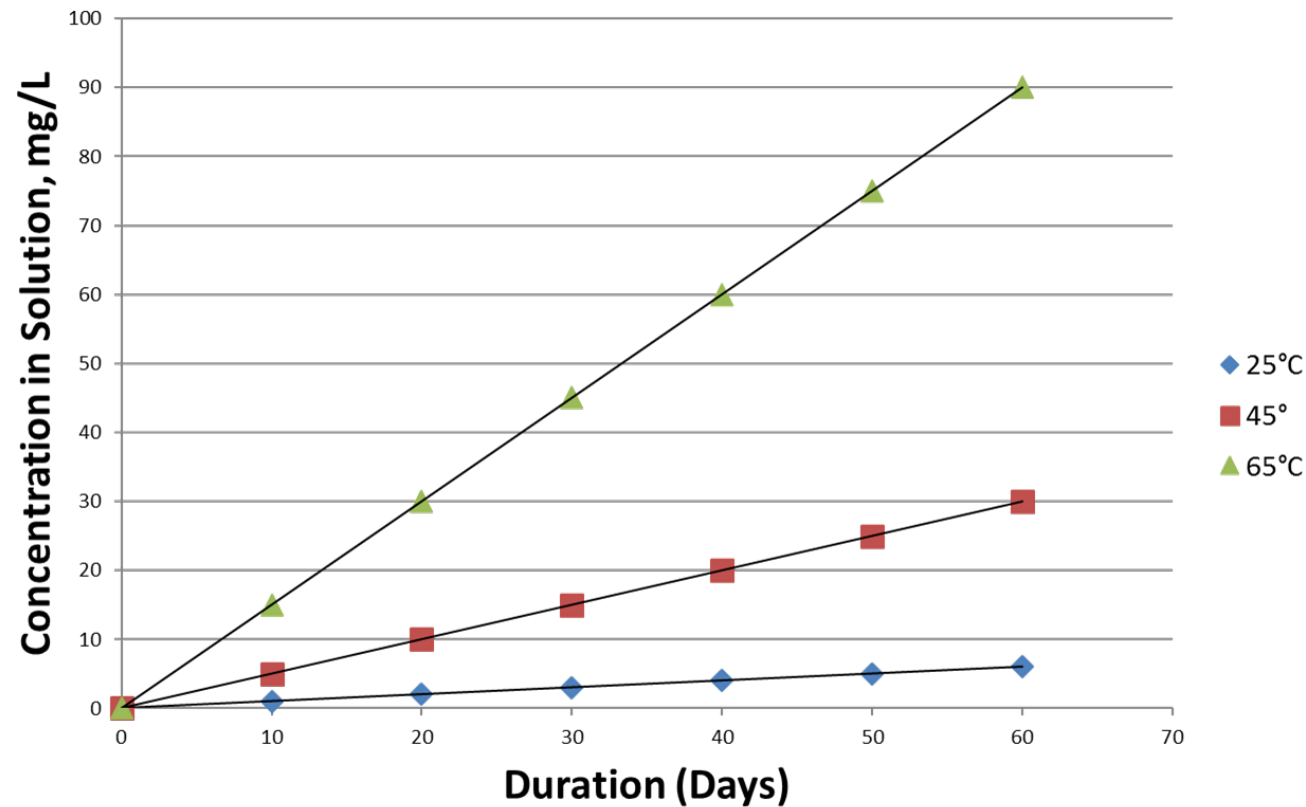
1. **ASTM F1980-16**: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

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)

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

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

Comparison of the Two Approaches:

Acceleration of a Two-Year (730 days) Ambient Temperature Shelf-life
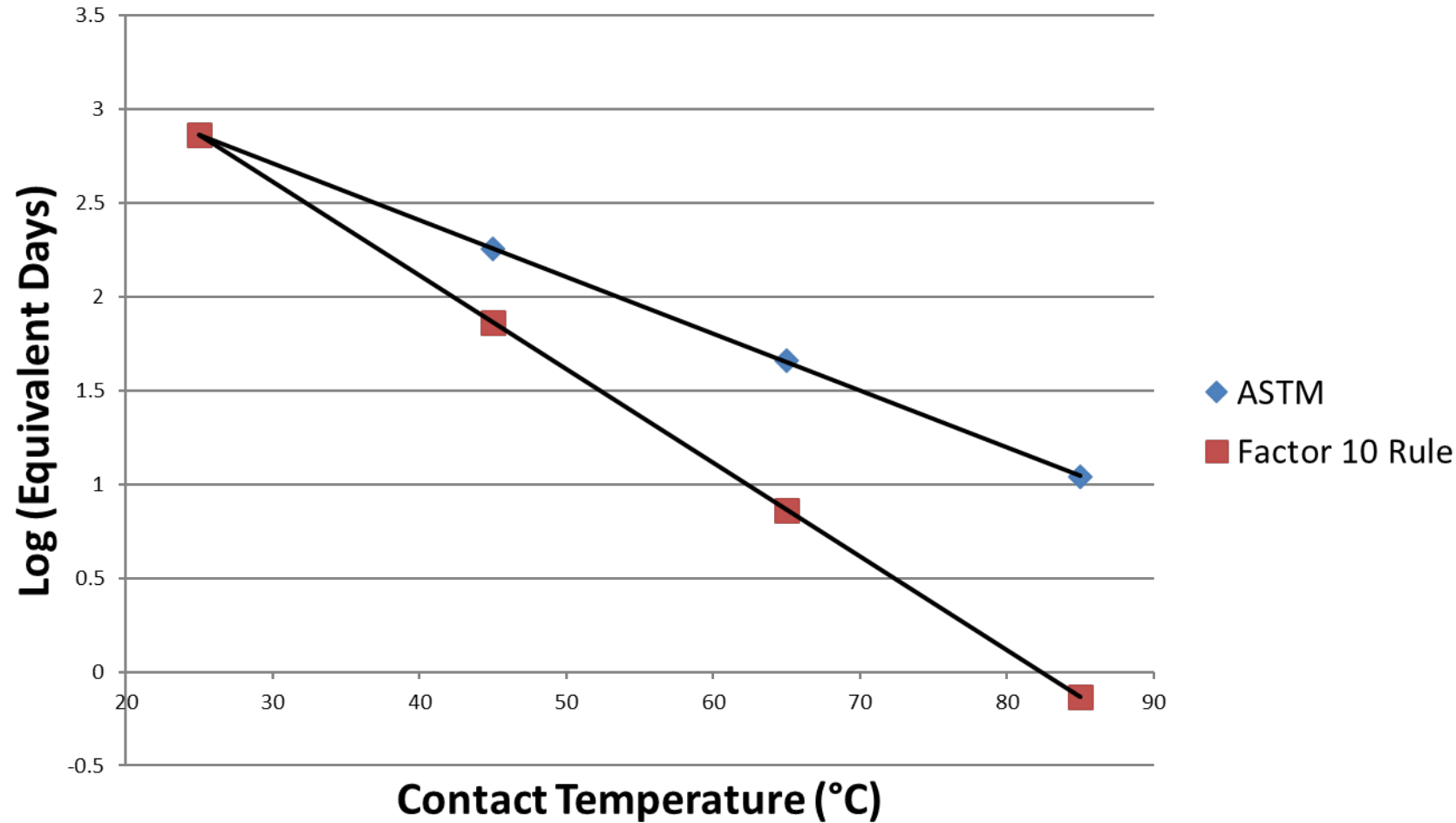
The ASTM approach produces the longest duration is thus is the most conservative approach.

Example of an Accelerated Extraction Calculation

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:

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

Stoichiometry

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

1. **Its all about surface area**.

   In fact, what is generally attributed to surface area effects is actually due to changes in the amount (mass) of the extracted item.

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

   In fact, the relationship between the ratio and the concentration depends on the plastic/solution partition coefficient of the extractables in question.

   - **"Solution-loving" extractables' concentrations will increase in proportion to increased ratio (but not 1 to 1)**
   - **"Plastic-loving" extractables' concentration will change very little as the ratio increases.**

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

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.

Theoretical Relationship between the Material Surface Area and the Concentration of an Extractable in an Extracting Solution at a Constant Extracting Solution Volume.

In Review
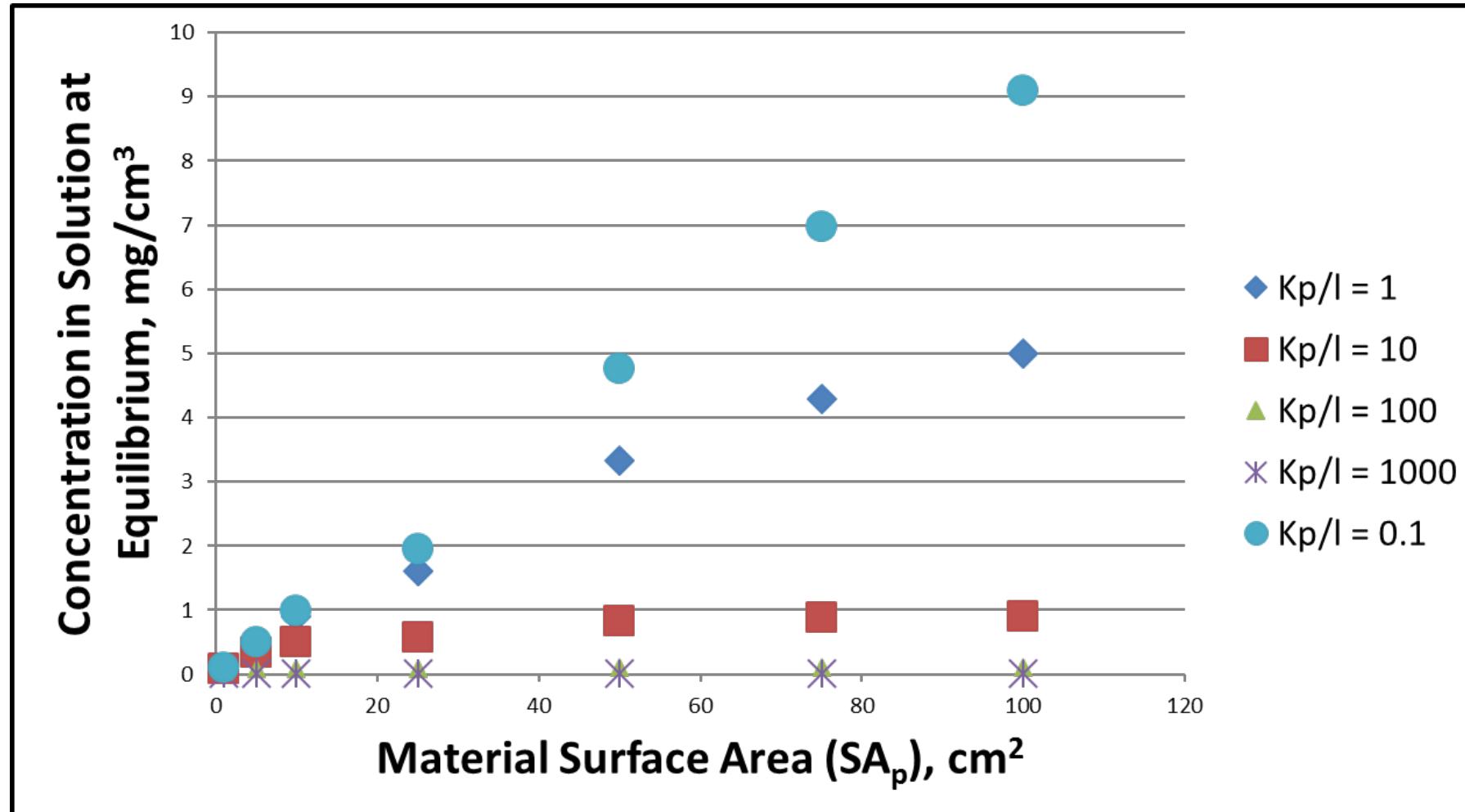
- A properly designed and implemented extractables simulation study produces an extractables profile that is equal to or slightly exaggerated than the leachables profile for a packaged drug product.

- 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.

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.* 73(2): 135-168 (2019).

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Thank you!