An Introduction to Large Volume Parenterals (LVPs) as a Pharmaceutical Dosage Form and an E&L Challenge

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Presenter

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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.

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Presentation Outline

- The LVP Parenteral Dosage Form
- Practical issues that make E&L testing for large volume parenteral (LVP) drug products challenging

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Pharmaceutical Dosage Forms

Different Dosage Forms

Types of Dosage Forms

Classifications Based on Route/ Method of Administration

- Oral Dosage Forms
- Topical Dosage Forms
- Rectal Dosage Forms
- Parenteral Dosage Forms
- Respiratory/Inhaled Dosage Forms
- Vaginal Dosage Forms
- Ophthalmic Dosage Forms
- Nasal Dosage Forms
- Otic Dosage Forms

Classifications Based On the Physical Form of the Dosage Form

- Solid Dosage Forms
- Semi-solid Dosage Forms
- Liquid Dosage Forms
- Gaseous Dosage Forms

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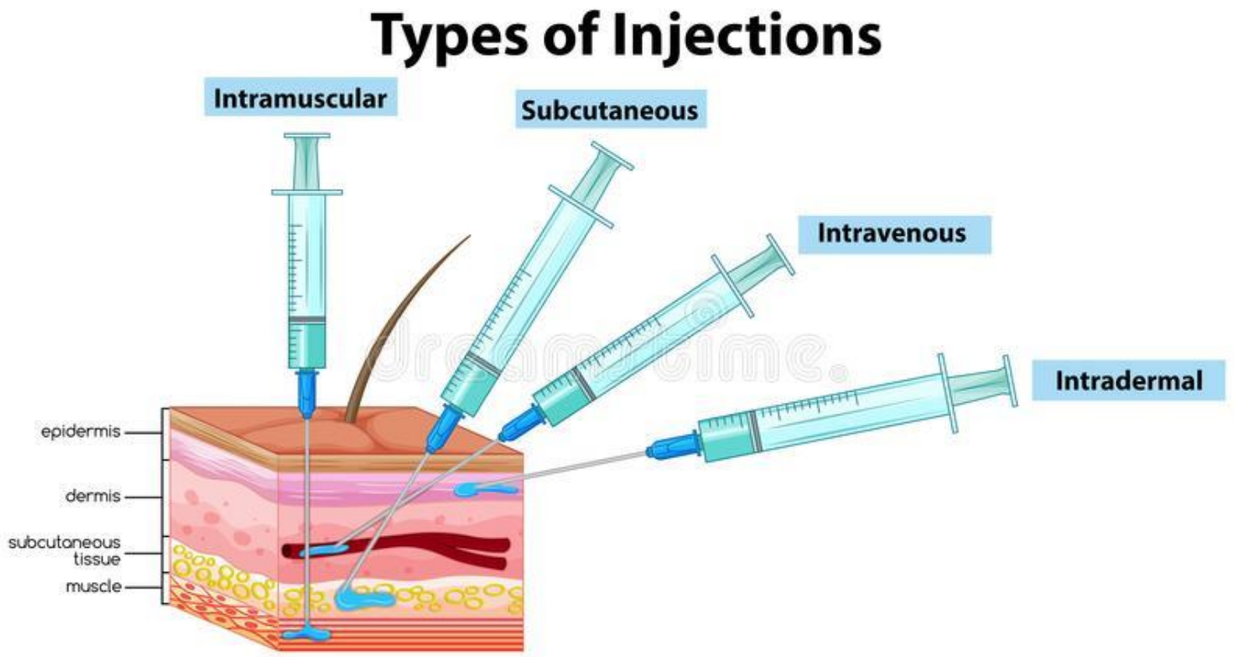
Parenteral Dosage Forms

Parenteral drug products are injected through the skin or other external boundary tissue, or implanted within the body, **to allow the direct administration of the active drug substance**(s) into blood vessels, organs, tissues, or lesions. Parenteral dosage forms include solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), implants (including microparticles), and products that consist of both a drug and a device such as drug-eluting stents.

Routes of Parenteral Administration

- Intravenous injections and infusions
- Subcutaneous injections
- Intramuscular injections
- Intradermal injections
- Intra-arterial injections
- Intra-cardic injections
- Intraspinal injections
- Intra-articular injections



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Classification of Parenteral Preparations

Based on Type of Packaging:

- Single dose units: ampoules, infusions, pre-filled disposable syringes
- Multiple dose units: multiple dose vials

Based on Fill Volume:

- Small volume parenteral (SVP): volume < 100 mL
- Large-volume parenteral (LVP): volume ≥ 100 mL

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What is an LVP?

A single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing more than 100 mL.

Characteristics of LVPs

- Packaged in glass bottles or in large volume flexible containers.
- May contain greater than 100 mL to greater than 1 or 2 L
- Sterile (e.g., many LVP are **sterilized in their container via heat**, although some are sterile-filled)
- Pyrogen-Free
- Essentially free of particulate matter
- No anti-microbial agents
- Isotonicity
- Longer term use

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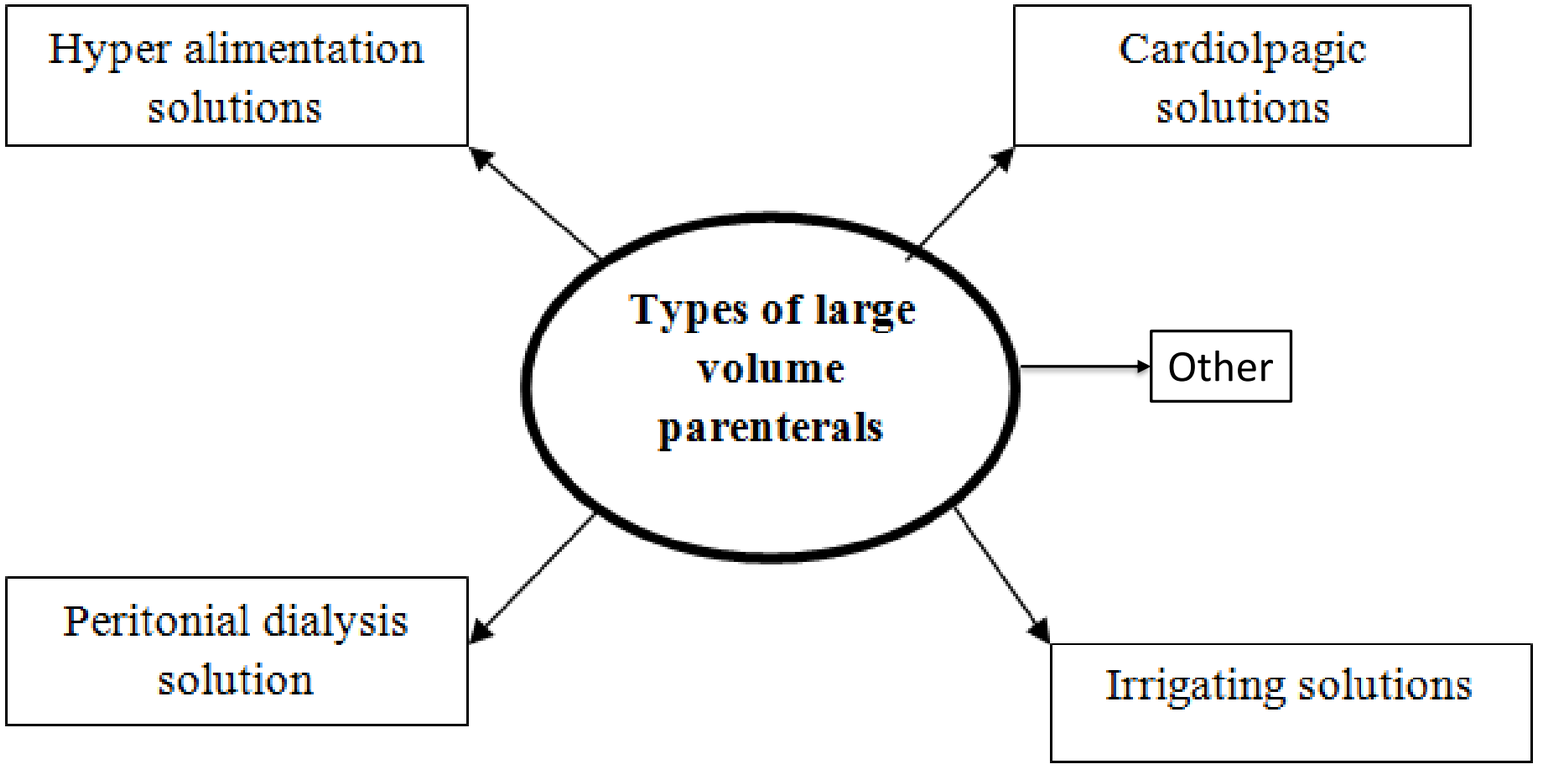
Types of LVPs



- Electrolytes (Cardioplegia)
- Carbohydrates
- Nutritional (Hyper-alimentation)Solutions–Proteins–Lipid Emulsions
- Peritoneal Dialysis
- Irrigating Solutions
- Blood derivatives (e.g. albumin)
- Drug Premixes
- Contrast agents

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Composition of an LVP

- Vehicle
  - Water
  - Water miscible vehicle
  - Non-aqueous vehicle
  - Solid Vehicle
- Active ingredient
- Added substances
  - Tonicity Adjusters
    - Electrolyte, NaCl, 0.5 – 0.9%
    - Non-electrolyte, Dextrose, 4 – 5%
  - Buffers
    - Acetate/Citrate, pH 3 - 6
    - Phosphate, pH 6 - 8
    - Glutamate, pH 8 - 10
  - Antioxidant, 0.1 – 0.5 %
  - Preservatives, 1 – 2%
  - Complexing agents, 0.01 – 0.05%
  - Surfactants, 0.05 – 0.5%
  - Competitive Binders, variable
  - Antimicrobial agents, 0.01%
  - Cryoprotectors/Lyoprotectors (Bulking agents), e.g., 1 – 10%
  - Etc.

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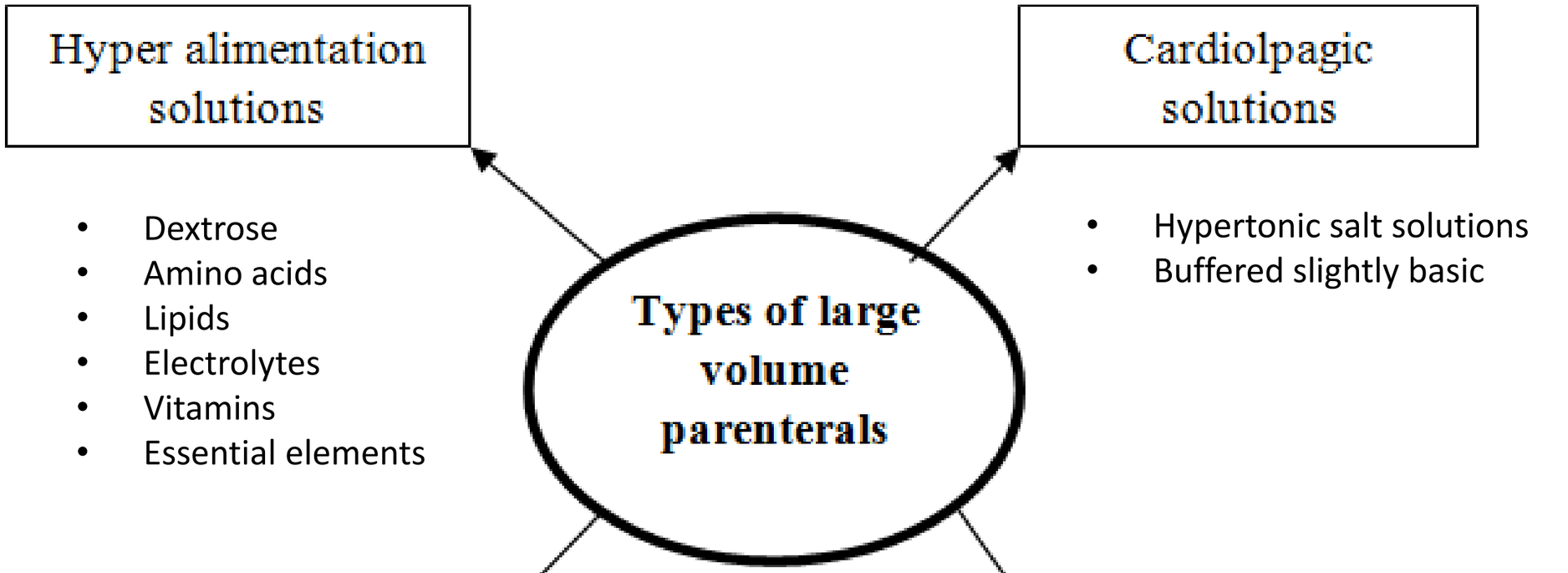
Composition of LVPs



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Containers for LVPs

Rigid Containers for LVPs

A. Glass
B. “Glass-like” Plastics (e.g., Cyclic Olefin Polymer, CoC)

Flexible Containers for LVPs

A. PVC – polyvinylchloride - first polymer used for collapsible containers

- Performs best with respect to collapsibility and transparency
- May leach DEHP (di (2-ethyl hexyl) phthalate; Banned by countries such as Germany, Sweden, France, and Canada
- Produces dioxin when incinerated

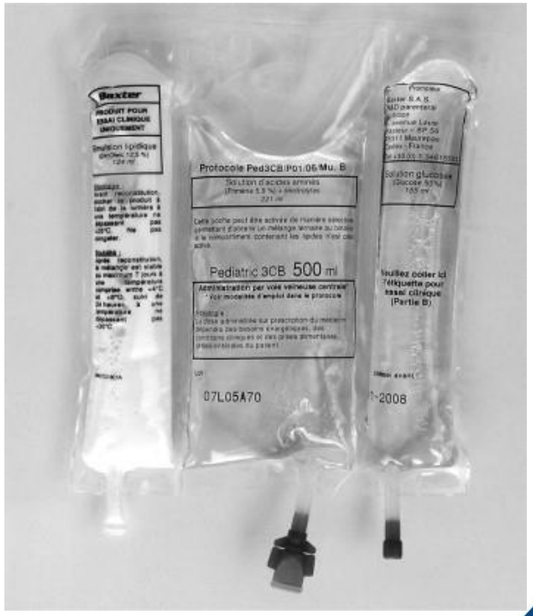
B. Ethylene vinyl acetate films (EVA)

- Developed to improve compatibility and moisture permeation characteristics
- However, moisture permeation is poor and film requires overwrap

C. Combinations

- Multilayer films developed to reduce moisture permeation
- Ethylene vinyl alcohol can be used as core film for its high gas barrier properties.
- Physically bonded between two layers of EVA

D. Blow-Fill-Seal Technology



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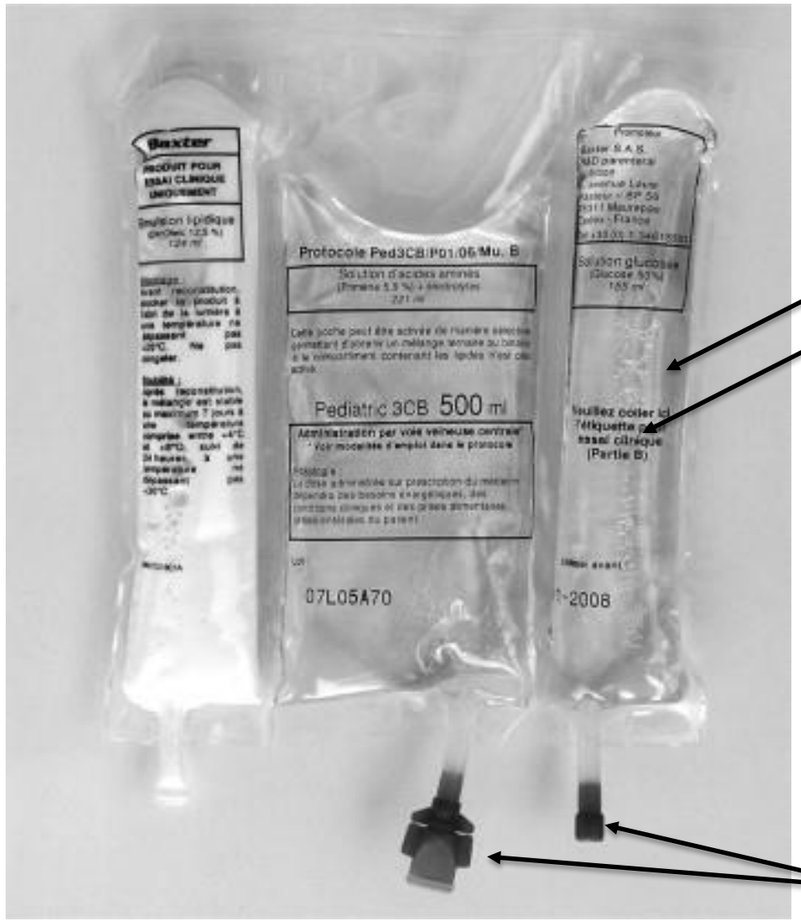
Packaging for LVPs



Container

Printing (label)

Access Port
(elastomeric septum not shown)

Printing (label) on overwrap

Overwrap

Auxiliary Items
(e.g. oxygen absorber)

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Materials of Construction for Flexible LVP Packaging

- Polyethylene (PE)
- Polypropylene (PP)
- Poly vinyl chloride, plasticized (PVC)
- Polyamide (Nylon)
- Polycarbonate (PC)
- Ethylene vinyl acetate (EVA)
- Polyolefin (layered structures of PE, PP, EVA and Nylon)
- Elastomers

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Advantages and Disadvantages of Flexible Containers for LVPs

Advantages

- Durable.
- Light weight.
- No air interchange. The bag collapses as it empties.

Disadvantages

- Permeation of vapors and other molecules in either direction through the walls.
  - Resolved by overwrapping the containers
- **Leaching of constituents from the plastic into the product**.
  - Plasticizers, anti-oxidants, other additives
- Sorption of drug molecules or ions on the plastic material.
  - Proteins, warfarin sodium, diazepam

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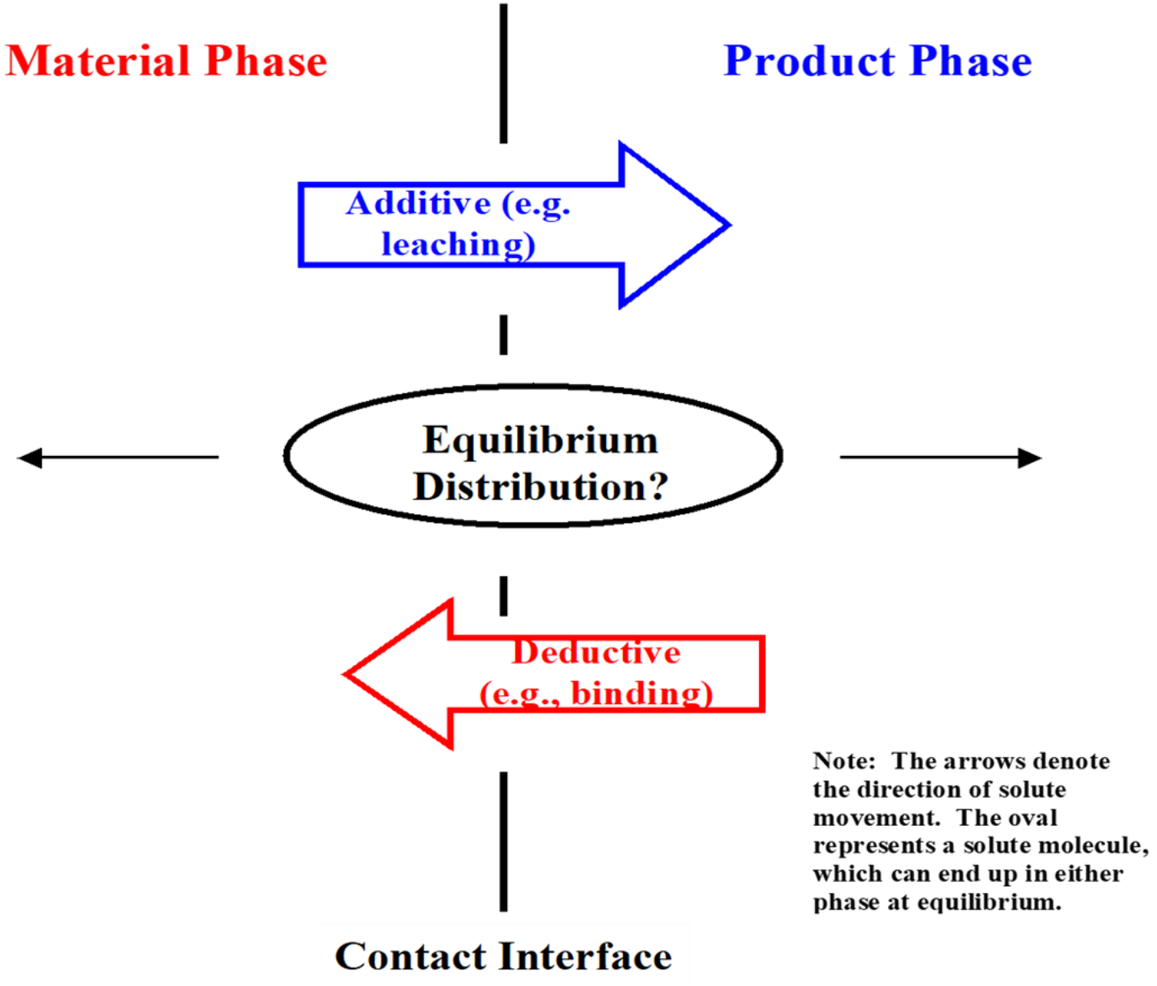
Leachables



Note: The arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.

Leachable:

A foreign impurity that is present in a finished drug product as a result of its contact with a packaging system under the actual product conditions of distribution, storage and use.

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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 daily dose volume** are particularly noteworthy because of the practical implications of composition and dose volume to the safety assessment of packaging system leachables.

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Challenges in Assessing LVPs for Leachables

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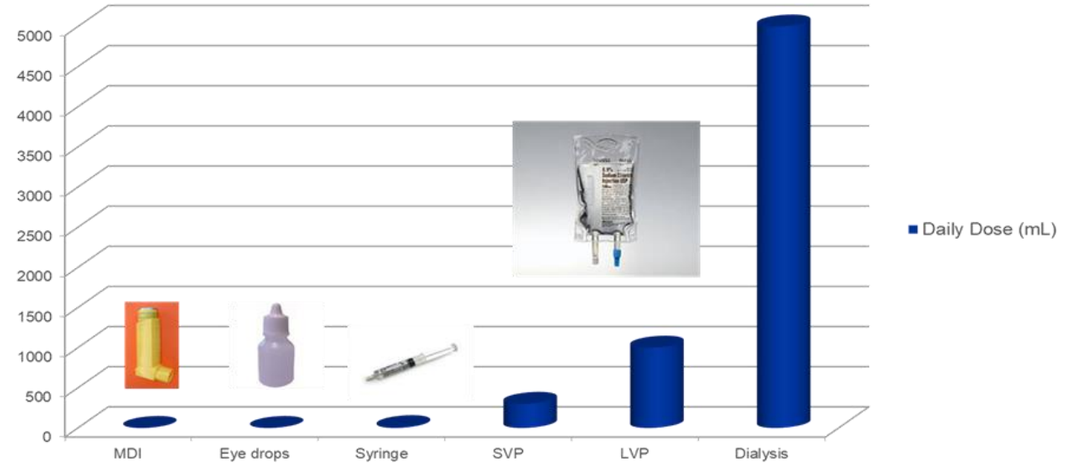
Composition

Leachables Profiling Scale:

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

Daily Dose Volume



Leachables Profiling Scale:

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

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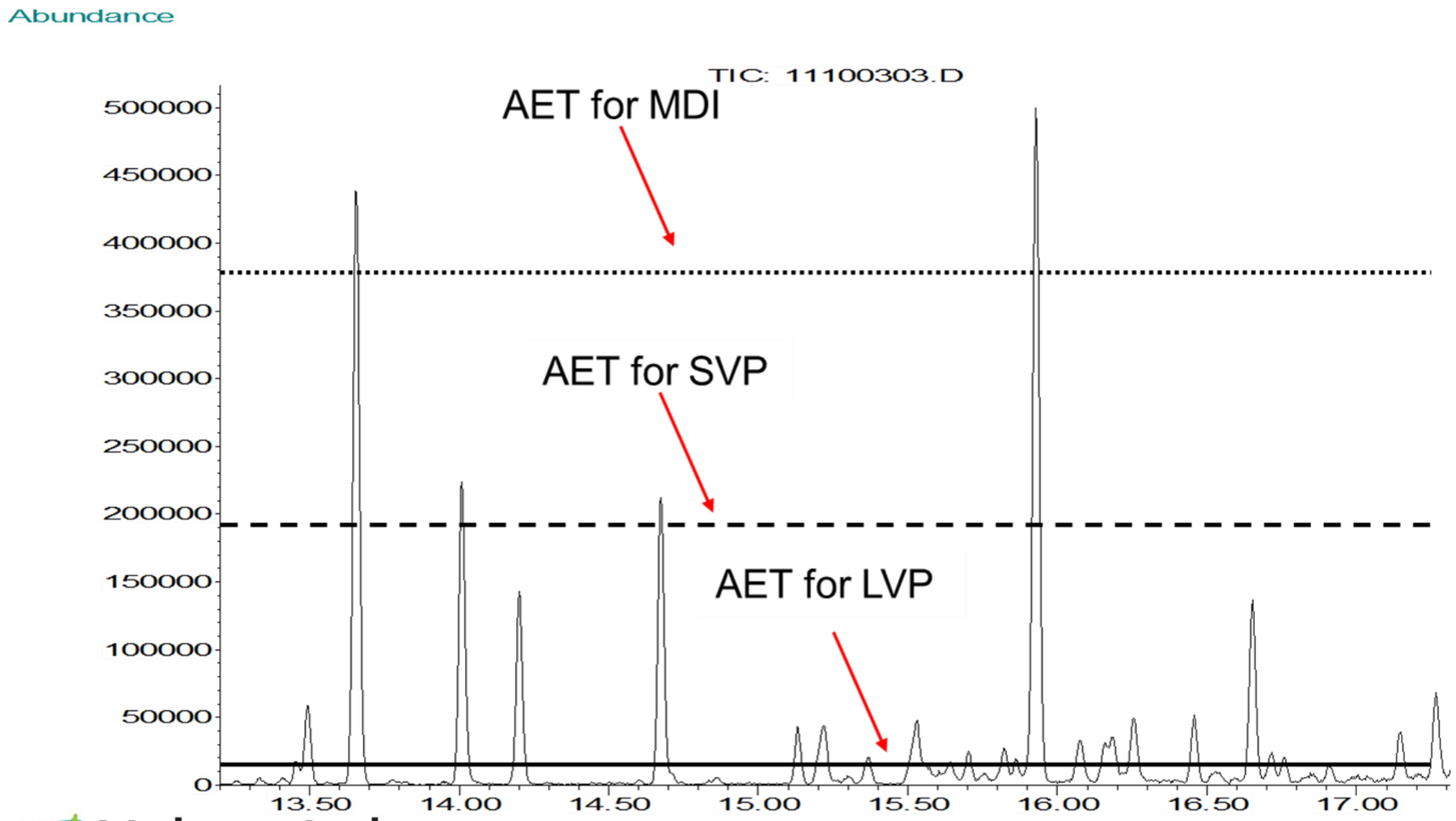
The LVP Challenge: The Analytical Evaluation Threshold, AET

AET = Concentration at or above which a leachables must be reported for toxicological safety risk assessment (identification & quantitation).



- Greater numbers of peaks to assess
- Greater difficulty in assessing the peaks

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The LVP Challenge: How Low Can You Go?

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.

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Thank you!

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