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

Dennis Jenke, Ph.D.
Principal Consultant, Nelson Labs
Presenter

Dennis Jenke, Ph.D.
Chief Executive Scientist
Triad Scientific Solutions, LLC
Principal Consultant, Nelson Labs - Europe

• 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.
Presentation Outline

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

Types of Dosage Forms

Classifications Based on
Route/Method of Administration

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

Types of Injections
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
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
Types of LVPs

- Electrolytes (Cardioplegia)
- Carbohydrates
- Nutritional (Hyper-alimentation) Solutions – Proteins – Lipid Emulsions
- Peritoneal Dialysis Solution
- Drug Premixes
- Contrast agents
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.
Composition of LVPs

- **Hyper alimentation solutions**
  - Dextrose
  - Amino acids
  - Lipids
  - Electrolytes
  - Vitamins
  - Essential elements

- **Cardiopagic solutions**
  - Hypertonic salt solutions
  - Buffered slightly basic

- **Types of large volume parenterals**

- **Peritoneal dialysis solution**
  - Glucose
  - Electrolytes
  - Buffer
  - Antibiotics

- **Irrigating solutions**
  - 0.9% Saline
  - Sterile Water for Irrigation
  - Lactated Ringer’s
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
Packaging for LVPs

Container

Printing (label)

Access Port (elastomeric septum not shown)

Overwrap

Printing (label) on overwrap

Auxiliary Items (e.g. oxygen absorber)
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
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
Leachables

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.

Note: The arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.
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.
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: 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
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.
Contact the presenter at:
dennisjenke@triadscientificsolutions.com
www.triadscientificsolutions.com