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OMICS International is a pioneer and leading science event organizer, which publishes around 700+ open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 1000+ conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Systematic Approach to Development of Aqueous Drug Formulation and Drug-Device Combination Injectable Products & Challenges

Presented By:

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August 19, 2015

OMICS Conference
August 17-19, 2015
Chicago IL, USA

Parenterals & Injectables

LECTURE OUTLINE

- *Introduction*
  - *Injectable products, Drug-Device Combination products*
- *Physico-Chemical Aspects of Drug molecules*
  - *Solubility profile in aqueous and mixed solvent systems*
  - *pH vs solubility profile in aqueous formulations (buffer, tonicity-adjusting agents, antioxidants, solubilizing agent, preservatives)*
  - *pH rate profile of drug and chromatographic profile, potential for particulate matter*

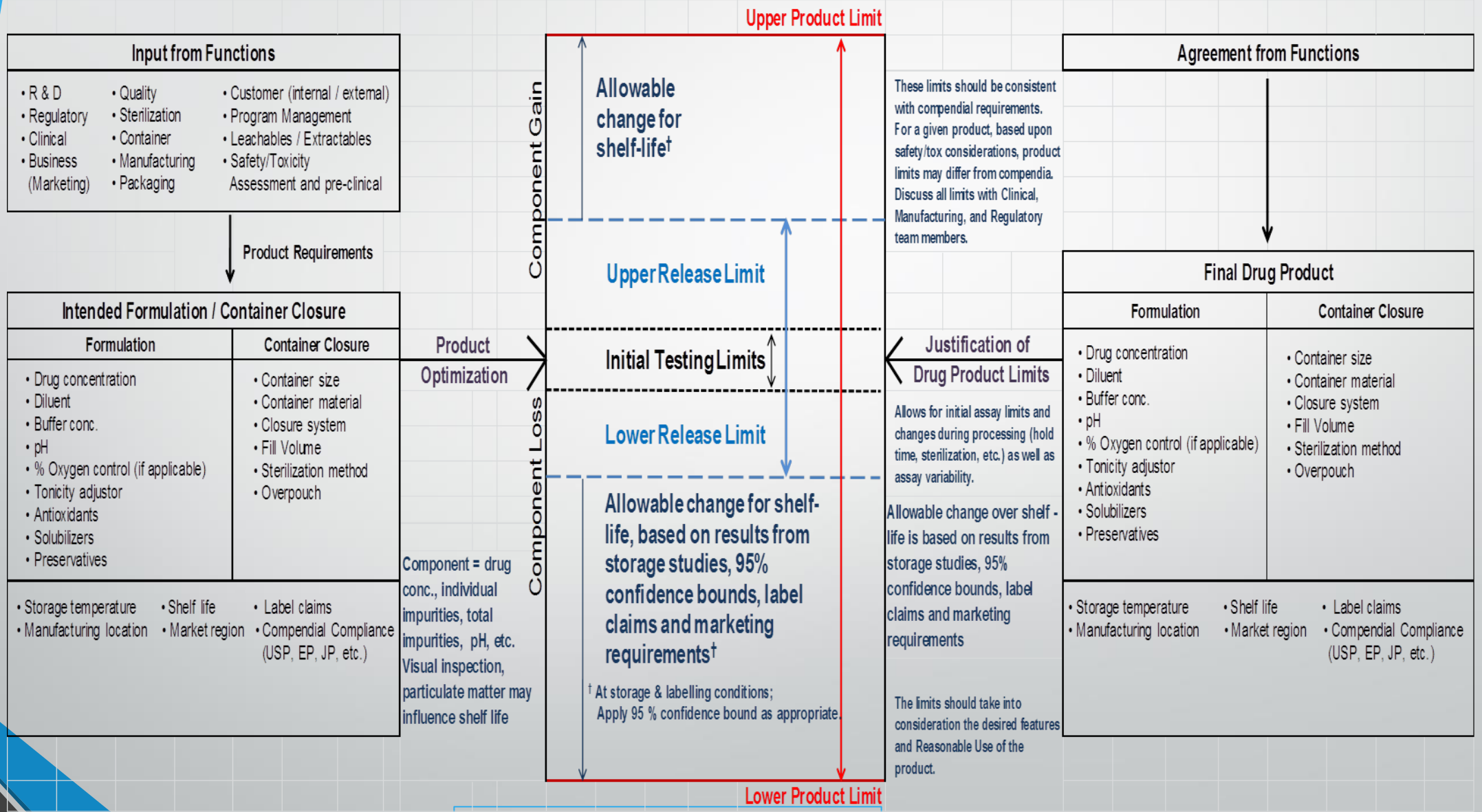
LECTURE OUTLINE

- *Selection of Parenteral Dosage Forms*
  - *Parenteral product categories –*
  - *Decision Tree for selection of a dosage form for a parenteral drug*
  - *Scientific considerations in selection of a parenteral dosage form*
- *Preformulation*
  - *Drug Solubility*
  - *Drug Stability*

LECTURE OUTLINE

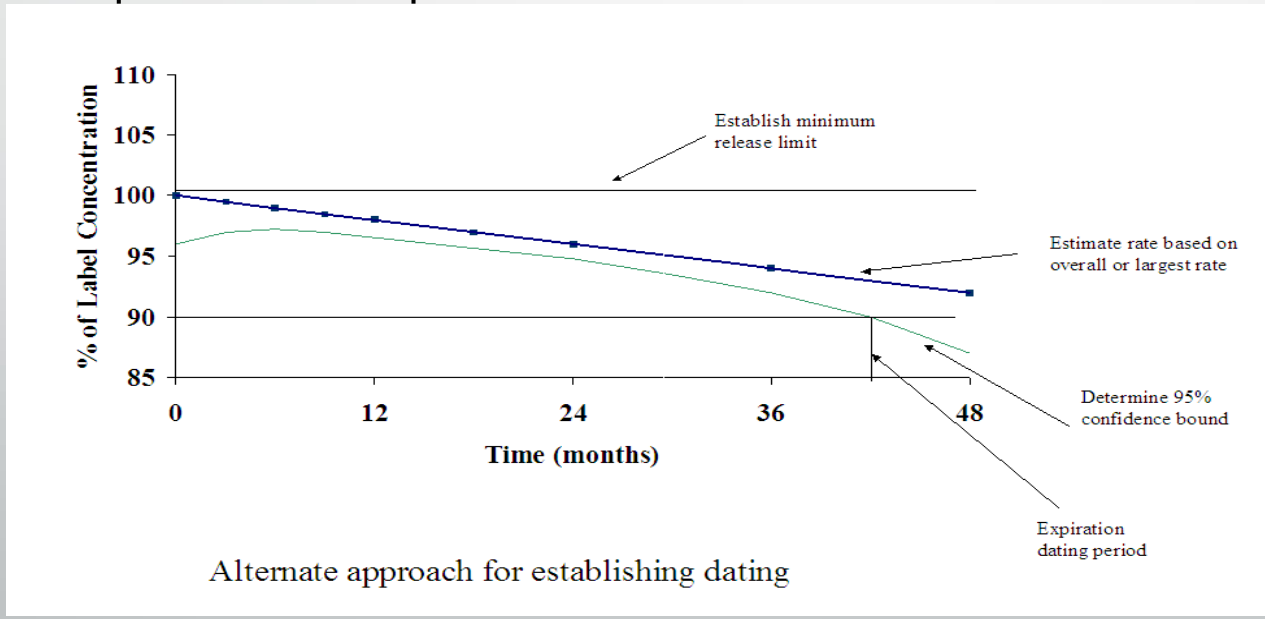
- *Formulation Optimization*
  - *Approaches to minimize drug degradation*
  - *Formulation considerations in frozen drug development*
  - *Influence of container compatibility and enhanced packaging*
- *Manufacturing Process Development*
  - *Overview of manufacturing process – process flow diagrams*
  - *Mixing process optimization*
  - *Mixing process scale up*
  - *Considerations in solution filtration*
  - *Sterilization*
  - *Process validation*

PRODUCT DEVELOPMENT OVERVIEW



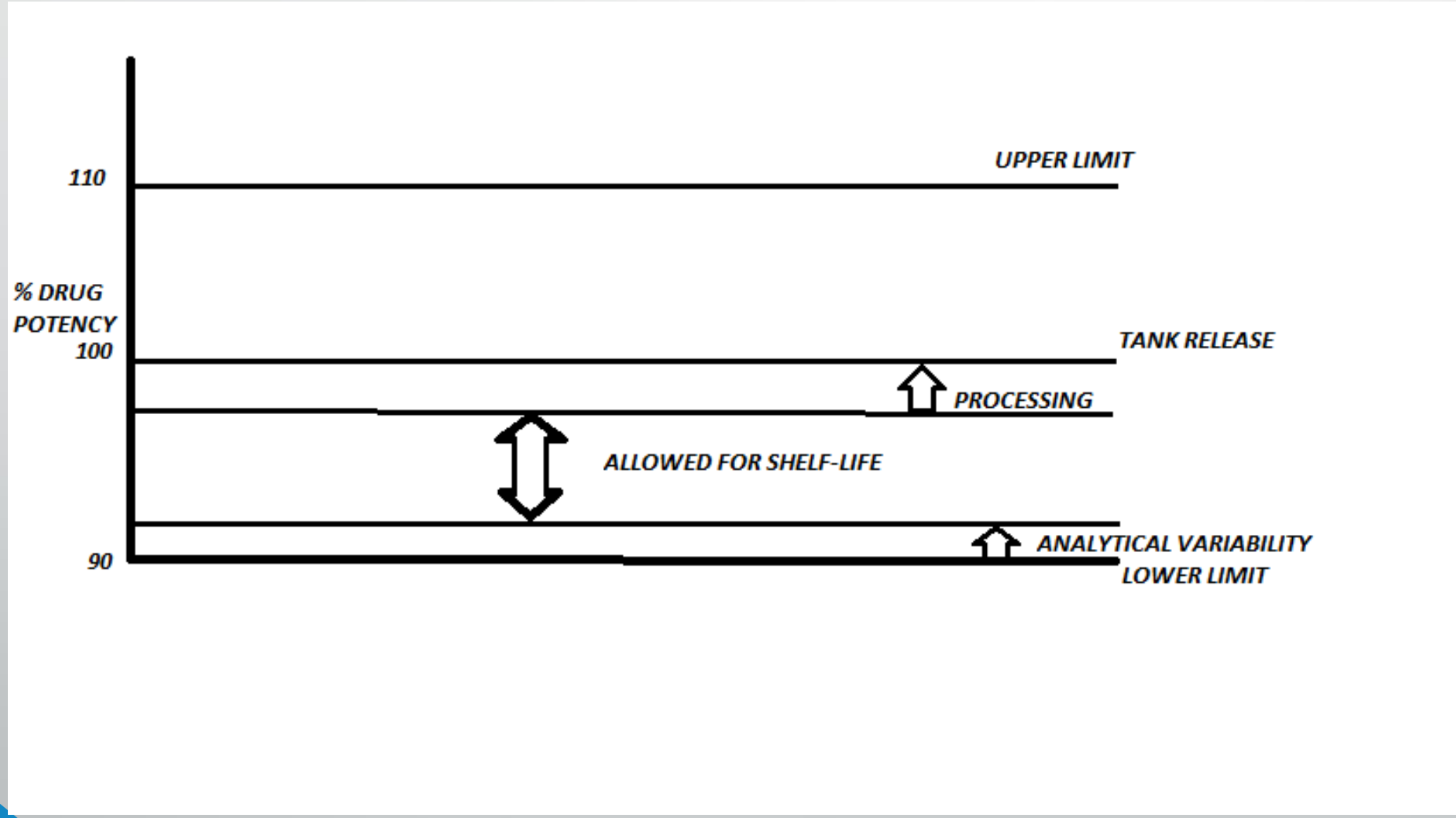
RELEASE & PRODUCT LIMITS

- For attributes known to decrease over time, the lower one-sided 95% confidence bound is compared to acceptance criterion.
- For attributes known to increase over time, the upper one-sided 95% confidence bound is compared to acceptance criterion.
- For attributes that can either increase or decrease over time, two-sided 95% confidence bounds are compared to acceptance criterion.



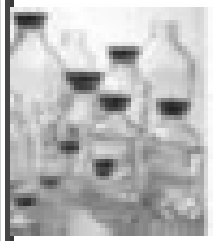
Alternate approach for establishing dating

SHELF-LIFE CONSIDERATIONS

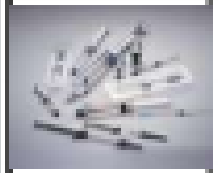


Selection of Parenteral Dosage Forms

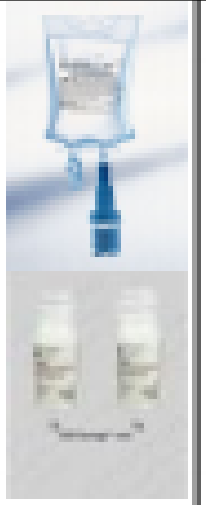
PARENTAL DOSAGE FORMS

	Dosage Form	Fill Volume	Application
	Ampoules	1 to 25 mL	•Intramuscular •Intravenous – Bolus •Intravenous – Infusion after dilution
	Vials - Liquid	1 to 100 mL	•Intramuscular •Intravenous – Bolus •Intravenous – Infusion after dilution
	Vials – Solid (Vials, infusion pack, pharmacy bulk package)	50 mg to 10 g	•Intramuscular after reconstitution •Intravenous – Bolus after reconstitution •Intravenous – Infusion after reconstitution and dilution

PARENTAL DOSAGE FORMS CONT'D

	Dosage Form	Fill Volume	Application
	Glass Bottles	100 to 1500 mL	•Intravenous Infusion
	Syringes, Glass & Plastic	1 to 50 mL	•Intramuscular •Intravenous – Bolus •Intravenous – Infusion after dilution or with syringe pump
	Plastic Bags	25 mL to 5 L	•Intravenous •Dialysis (1 to 5 L) – PD – CRRT – Hemodialysis •Irrigation

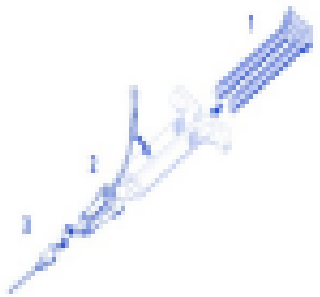
PARENTAL DOSAGE FORMS- ENHANCED PACKAGING

	Dosage Form	Fill Volume	Application
	Plastic Bag with Vial Adaptor •MINI-BAG™ Plus (Baxter) •ADD-Vantage® (Hospira)	50, 100 & 250 mL	Intravenous, after connecting vial and bag, and reconstituting
	Premixed Frozen MINI-BAGS •Galaxy® Bags (Baxter)	50, 100 & 200 mL	Intravenous, after thawing

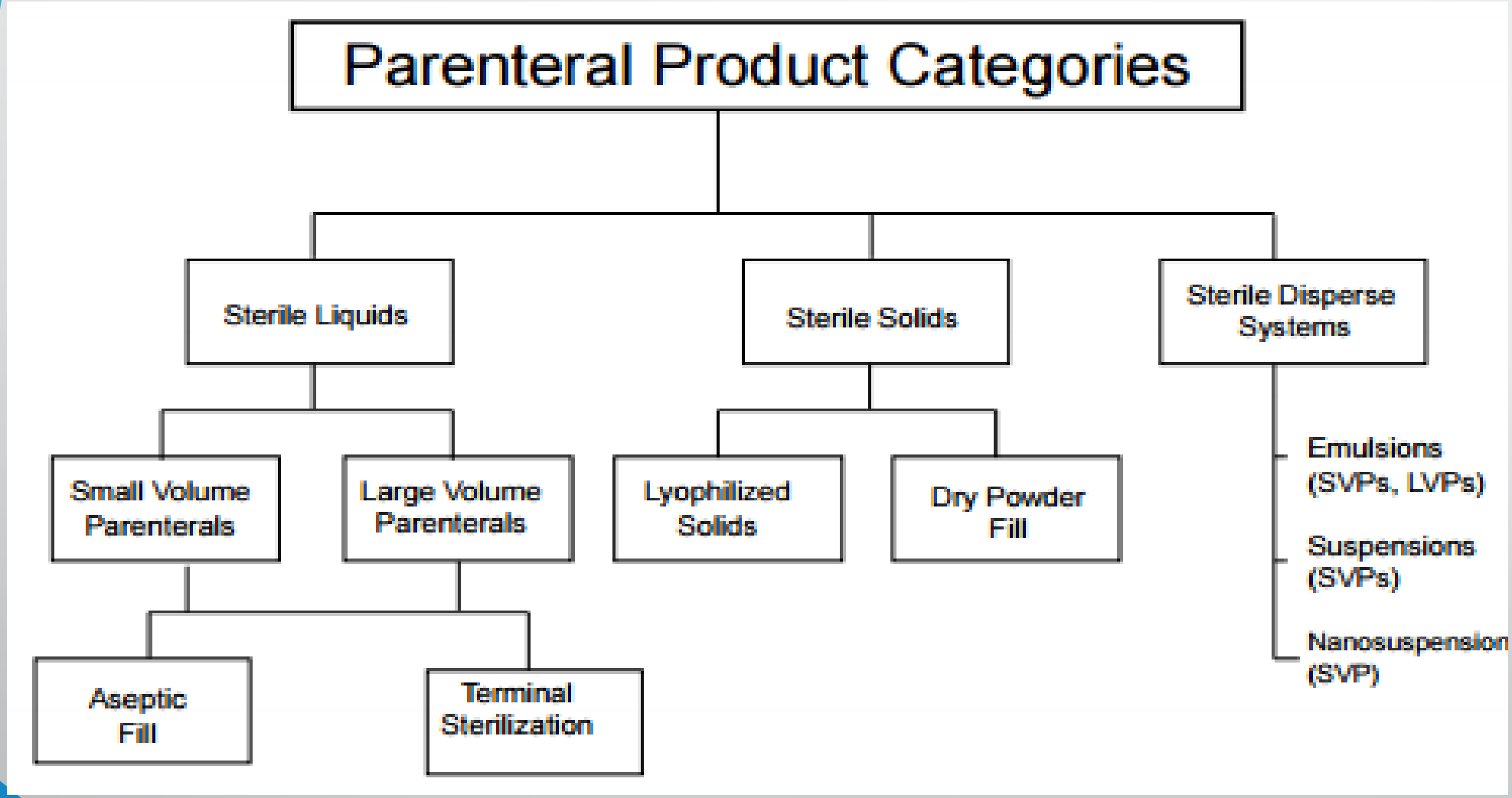
PARENTAL DOSAGE FORMS- ENHANCED PACKAGING CONT'D.

	Dosage Form	Fill Volume	Application
	Double Chambered Bags with liquid drug and liquid diluent •Heparin – Dextrose Bags (Baxter)	250 – 2000 mL	Intravenous, after admixing liquid drug and liquid diluent
	Triple Chambered Bags for Total Parenteral Nutrition •Amino acids – dextrose-fat emulsion (Baxter – Europe)	1.0, 1.5, 2.0, & 2.5 L	Intravenous, after admixing the liquids from the 3 chambers
	Double Chambered Bags with powder drug and liquid diluent •DUPLEX® Bags (B.Braun)	50 mL	Intravenous, after admixing powder drug and liquid diluent

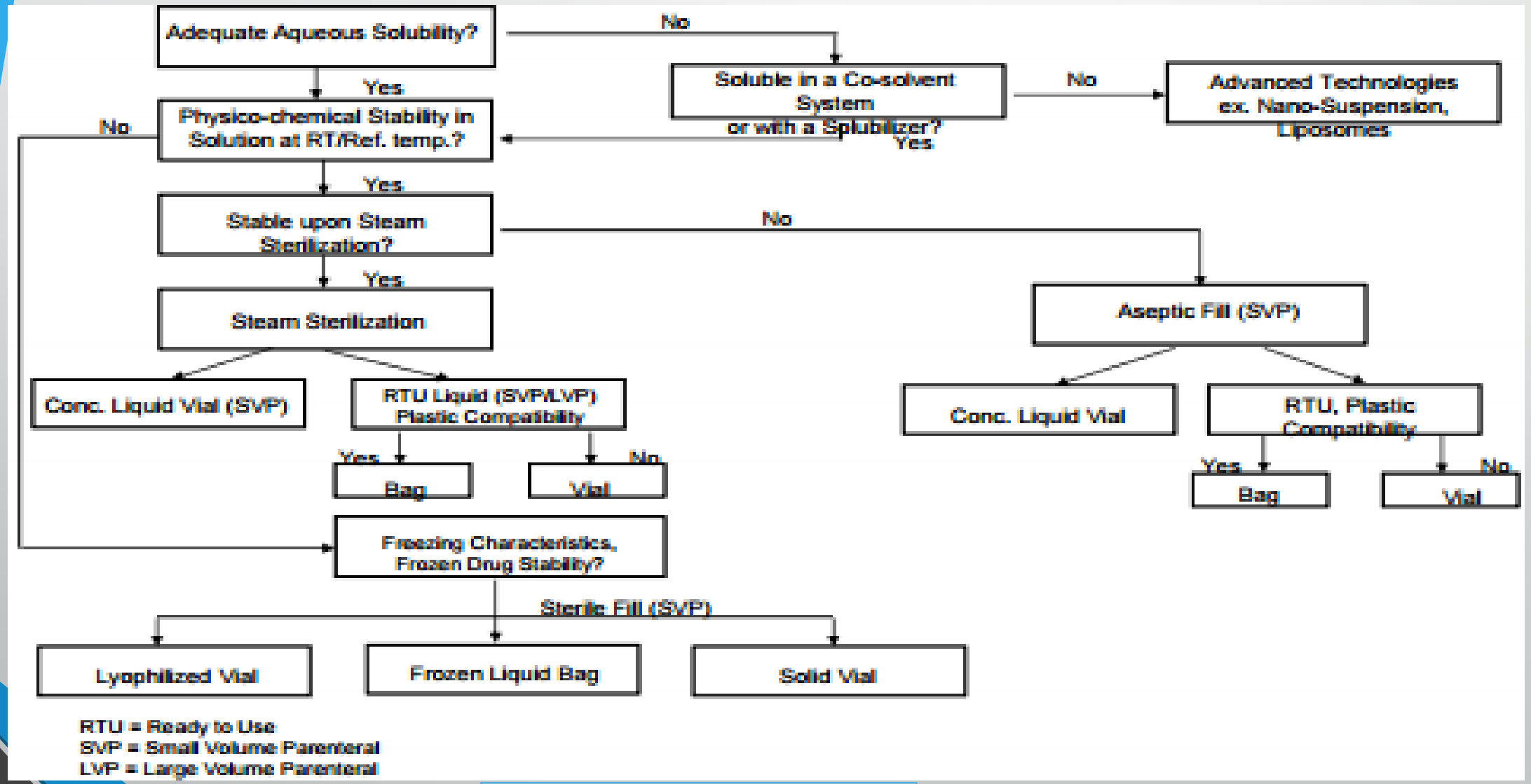
PARENTAL DOSAGE FORMS- ENHANCED PACKAGING CONT'D.

	Dosage Form	Fill Volume	Application
	Double Chambered Syringes with lyophilized drug and liquid diluent •Lyo-ject® (Arzneimittel Gmbh Vetter)	25 mg	Intravenous or intramuscular after activation to mix powder drug and liquid diluent
	Dual Syringe System • DUPLOJECT (Baxter) for TISSEEL (Fibrin Sealant)	2, 4 and 10 mL	In Biosurgery for Hemostatis

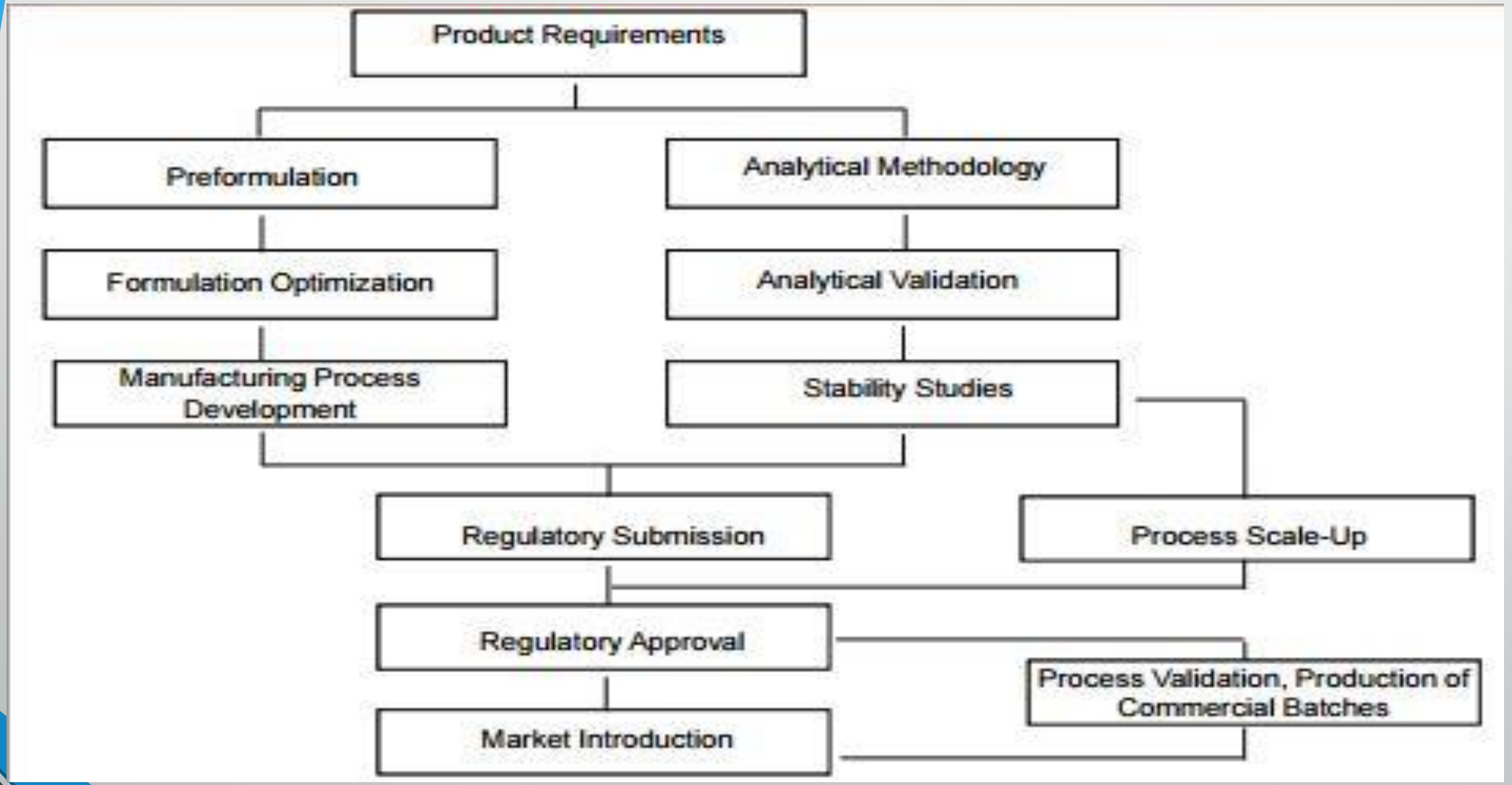
PARENTERAL PRODUCT CATEGORIES



DOSAGE FORM DECISION TREE FOR A NEW PARENTERAL DRUG



DEVELOPMENT CYCLE FOR A TYPICAL PARENTERAL DRUG PRODUCT



SCIENTIFIC CONSIDERATIONS IN DOSAGE FORM SELECTION

- *Proposed drug dose & concentration*
- *Type of Administration*
  - *Injection*
  - *Infusion*
- *Type of compound (e.g., quinolone)*
- *Aqueous Solubility (pH effects)*
- *Aqueous stability (pH effects)*
- *Oxidation*
- *Light Stability*
- *Buffer effect*
- *Container Compatibility*
  - *Absorption*
  - *Leachables*
- *Drug safety/handling*

PREFORMULATION

PREFORMULATION ACTIVITIES FOR PARENTERAL SOLUTIONS

- Aqueous Drug Solubility
- Aqueous Drug Stability

PREFORMULATION ACTIVITIES FOR PARENTERAL SOLUTIONS

- Aqueous Drug Solubility
  - pH- solubility profiles
  - Solubility-temperature profile-heat of solution
  - Co-solvents, other solubilizers
  - Partition coefficient

PREFORMULATION OF PARENTERAL SOLUTIONS

- *pH- Solubility Profiles*
  - *Many drug substances are either acidic or basic in nature and show differences in aqueous solubility as a function of pH depending on their ionization constants*
  - *The relationship between solubility and pH can be defined as follows:*
    pH = pKa + log [Cs] /[Ca]

    Where

    pKa = negative logarithm of the ionization constant of the acid

    {Cs } = molar concentration of salt form in water

    [Ca]= molar concentration of free acid in water
  - *Experimentally generated pH- solubility profile is essential to ensure solubility of the drug in the formulation at specified dose and formulation pH*

PREFORMULATION OF PARENTERAL SOLUTIONS

- Co-Solvents
  - Examples: Ethanol, Propylene Glycol, Polyethylene Glycol
- Acid Solubilizers
  - Examples: Hydrochloric acid, lactic acid, methane sulfonic acid
- Surfactants
  - Examples: Polysorbate 80, Cremaphor®
- Complexation Agents
  - Examples: Cyclodextrin

PREFORMULATION OF PARENTERAL SOLUTIONS

- ***References on Solubilizers and other Parenteral Excipients***
  - Excipients and their use in injectable products. Sandeep Nema, R.J. Washkuhn, and R.J. Brendel. PDA Journal of Pharmaceutical Science and Technology. Vol. 51, No. 4. July August 1997
  - Solubilizing Excipients in Oral and Injectable Formulations. Robert G. Strickley. Pharmaceutical Research. Vol. 21, No. 2, February 2004
  - Compendium of excipients for Parenteral Formulations. Michael F. Powell, Tue Nguyen, and Lisa Baloian. PDA Journal of Pharmaceutical Science and Technology. Vol. 52, No. 5. September – October 1998.

PREFORMULATION ACTIVITIES FOR PARENTERAL SOLUTIONS

- *Aqueous Drug Stability*
  - *Chemical kinetics*
  - *Degradation pathways*
  - *Identification and monitoring of degradation products*

PREFORMULATION ACTIVITIES FOR PARENTERAL SOLUTIONS

- *Aqueous Drug Stability – Chemical kinetics*
  - *Arrhenius plots*
  - *Micellar effects on kinetics*
  - *Impact of excipients*

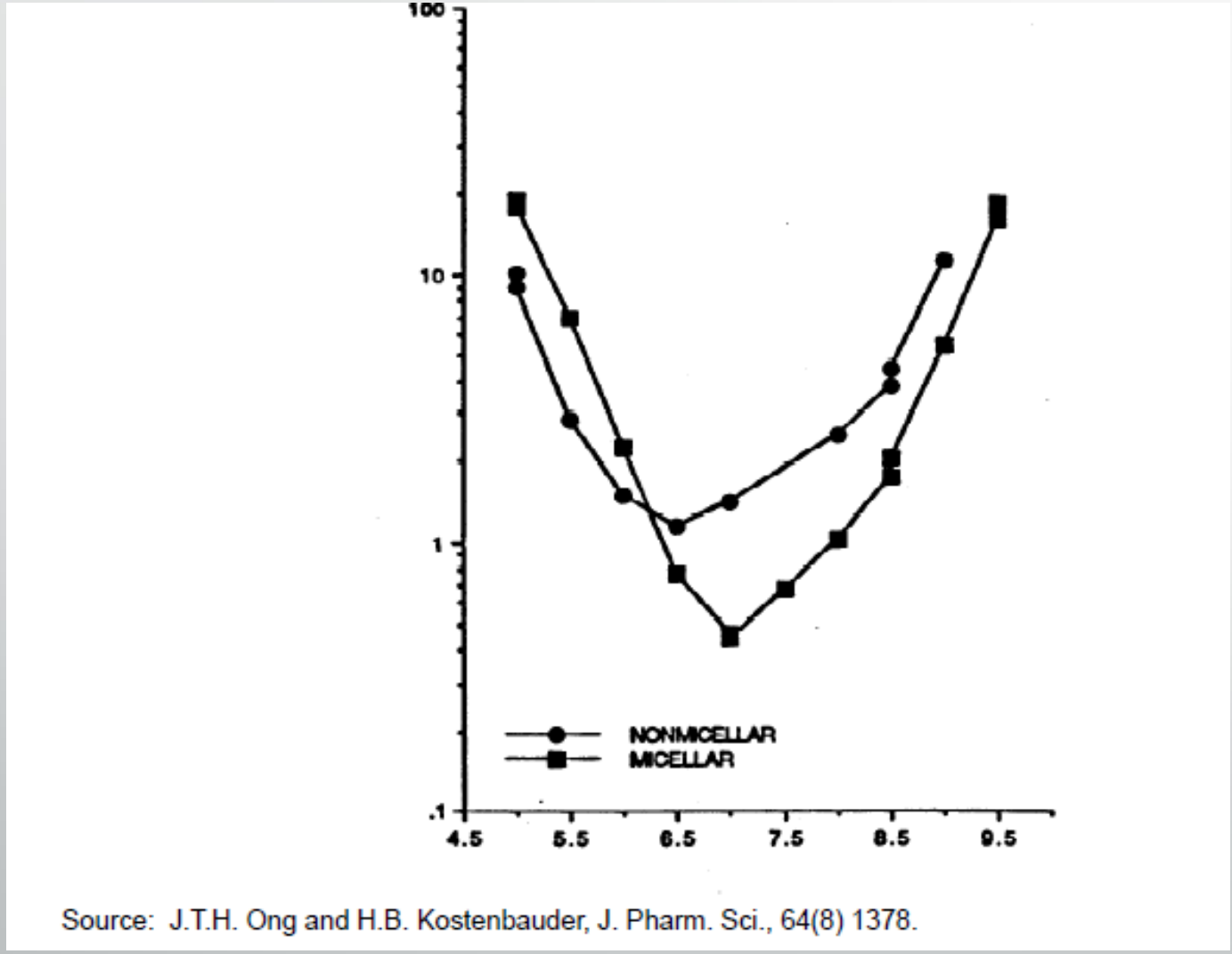
    Example
  - *pH- rate profiles*

ACCELERATED STUDIES & USE OF ARRHENIUS RELATIONSHIP

- *Drug degradation rate is a key factor in formulation development*
  - *Many drug degradation reactions are slow and it may take up to several months at room temperature to determine the degradation rate.*
  - *In order to expedite the formulation optimization, degradation studies may be carried out at elevated temperatures and rate constants of room temperature can be estimated through Arrhenius relationship between the reaction rate and temperature.*

pH – Rate Profiles of Penicillin G

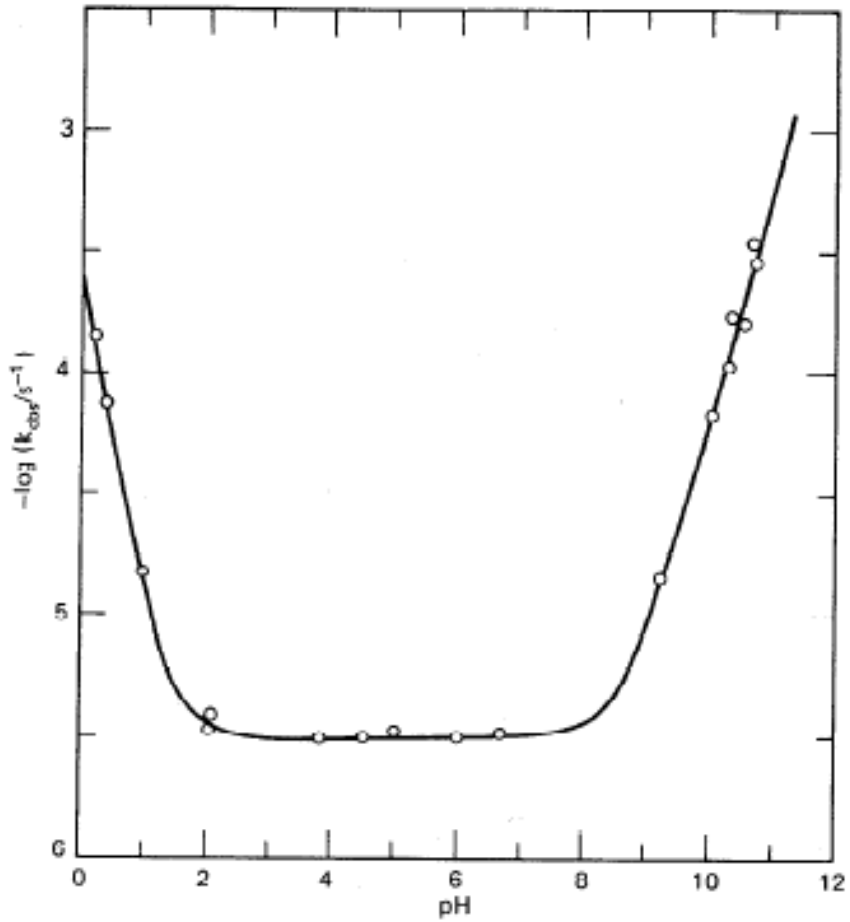
in 0.5% (w/v) Non-micellar & 30% Micellar Concentrations



Source: J.T.H. Ong and H.B. Kostenbauder, J. Pharm. Sci., 64(8) 1378.

CEPHALOTHIN -

pH-Rate Profile for Hydrolysis of ß-lactam Ring in Cephalothin at 30°C



Source: Chemical Stability of Pharmaceuticals.
K.A. Connors, G. L. Amidon, and L. Kennon, John Wiley & Sons

PREFORMULATION ACTIVITIES FOR PARENTERAL

- *Aqueous Drug Stability – Degradation Pathways*
  - *Hydrolysis*
  - *Polymerization*
  - *Isomerization/epimerization*
  - *Oxidation*
  - *Photolysis*

PREFORMULATION OF PARENTERAL SOLUTIONS

- ***References on Drug Degradation Pathways***
  - Chemical Stability of Pharmaceuticals – A Hand Book for Pharmacists. Chapters 4 and 5. Second Edition. Editors: Kenneth A. Connors, Gordon L. Amidon, and Valentino J. Stella. John Wiley and Sons.
  - Pharmaceutical Dosage Forms, Parenteral Medications, Volume 1. Kenneth E. Avis, Leon Lachman, and Herbert A. Lieberman, Editors. Marcel Dekker, Inc.
  - Remington: The Science and Practice of Pharmacy. Loyd V. Allen, Editor-Chair. Pharmaceutical Press. 22nd Edition (2012).
  - Physical Pharmacy. Alfred martin, James Swarbrick, and Arthur Cammarata. Editors. Lea & Fiebiger.

FORMULATION OPTIMIZATION

FORMULATION OPTIMIZATION OF PARENTERAL SOLUTIONS

- *Approaches to minimize drug degradation*
- *Formulation considerations in frozen drug development*
- *Influence of container compatibility and enhanced packaging*

FORMULATION OPTIMIZATION-

FORMULATION APPROACHES TO MINMIZE DRUG DEGRADATION

- *Hydrolysis*
  - *Determine the optimum pH for pH- rate profiles*
  - *Calculate change in hydrogen/hydroxyl ion concentration*
  - *Select bugger if needed based on solution pH and buffer pKa*
  - *Estimate the buffer concentration based on change in hydrogen/hydroxide ion concentration and buffer capacity of the buffer*
  - *pKa of Commonly used Buffers for Parenterals*

Acetic acid	4.76
Citric acid	3.15, 4.78, 6.40
Phosphoric acid	2.12, 7.21, 12.67

INFLUENCE OF CONTAINER SYSTEM ON FORMULATION

- *Protection*
  - *Light*
  - *Water Loss*
  - *Oxygen Permeation*
  - *Microbial Ingress*

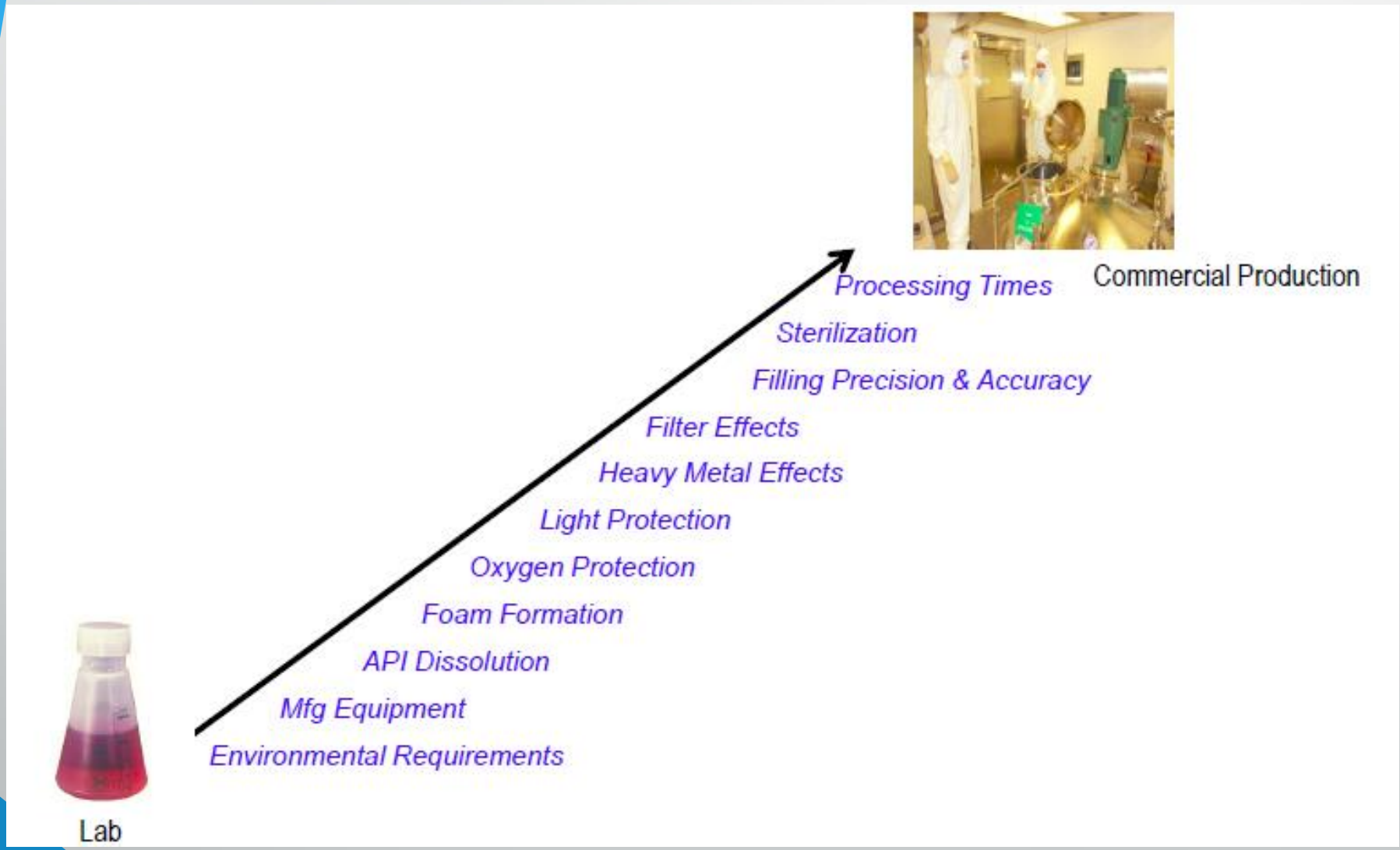
CONTAINER SYSTEM – DRUG FORMULATION COMPATIBILTY

- *Container Extractables*
  - *pH Changes" Extractables from the plastic container may migrate into the solution and alter the formulation pH affecting the drug stability*
  - *Excessive Levels of Extractables: Presence of solubilizers in the formulation may result in excessive levels of extractables*
  - *Precipitation: Extractable may precipitate die to formulation pH*

CONTAINER SYSTEM – DRUG FORMULATION COMPATIBILTY

- *Drug Adsorption/Sorption to the Plastic Container*
  - *Some drugs such as nitroglycerin adsorb to PVC*
  - *Some drugs may sorb into the plastic, particularly during autoclave sterilization (high temperature and pressure)*

FACTORS IN PROCESS SCALE UP



CONCLUSION

- *Product Requirements*
- *Product Development with Container & Closure System*

- *TEAM EFFORT*  *SUCCESS*

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2nd International Conference and Expo

on

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