# Manufacturing Considerations for Liposomal Drug Products

## Nanotechnology Workshop
## January 2014

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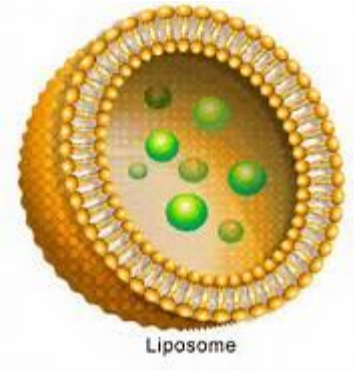
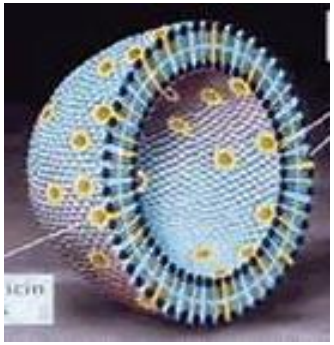
# Applications of Nano-Scale Drug Delivery Systems

- Wide range of carrier types
  - Liposomes
  - Solid core nanoparticles
  - Polymer-drug conjugates
- Historically have been applied primarily to generic drugs
- More recently, increased interest in:
  - New chemical entities
  - DNA/siRNA
  - Drug combinations
- Ultimate goal is to increase the therapeutic index via:
  - Altered drug biodistribution
  - Increased in vivo drug stability
  - Decreased drug toxicity
  - Increased drug therapeutic potency

# Types of Liposomal Products

- Route of administration
  - Inhalation
  - Intravenous
  - Localized injection
- Manufacturing method
  - Microfluidization
  - Emulsion/extrusion
  - Ethanol injection
- Location of Active substance
  - In the bilayer membrane
  - Encapsulated into the internal aqueous environment



images from encapsula, rxlist

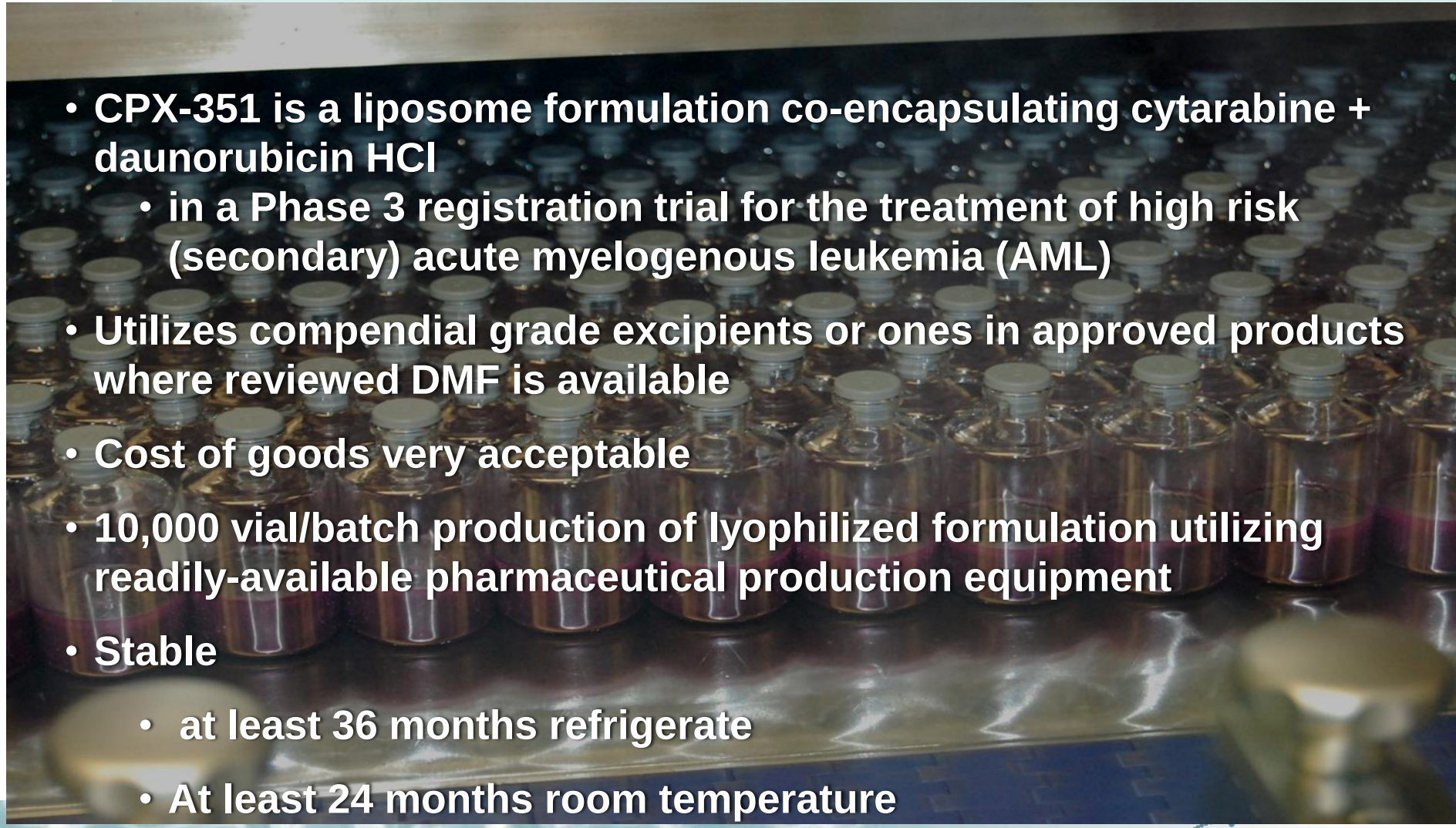
# Scale-up and Manufacturing Considerations for Liposomal Drug Delivery Systems

- Establish process that can be scaled from bench (<1L) to pilot scale (10-20L), to commercial scale (≥200L) without major changes
- Minimize hazardous conditions
  - Use of solvents
  - High pressure methods in the presence of cytotoxic or other toxic active agents
- Standard methods for sterilization
  - Sterile filtration vs. total aseptic process
- Final dosage form based on stability and shelf life
  - Suspension, kit, lyophilate
- Extensive characterization for content, physicochemical characteristics and performance attributes

# Development and Validation

- Determine the product critical quality attributes and the critical process parameters to meet those attributes
- Development studies to determine or verify ranges
  - Large number of components and multiple processing steps makes the QbD approach challenging
  - Design space would be very complex
- Science-based, process based
  - Determine CPP for each processing step
    - Liposome preparation
    - Active agent encapsulation
    - Feasibility for reworking
- Validation based on variability of data from development and clinical batch manufacture and characterization

# Example of a Stable Liposome Product Manufactured at Commercial Scale: CPX-351



- CPX-351 is a liposome formulation co-encapsulating cytarabine + daunorubicin HCl
  - in a Phase 3 registration trial for the treatment of high risk (secondary) acute myelogenous leukemia (AML)
- Utilizes compendial grade excipients or ones in approved products where reviewed DMF is available
- Cost of goods very acceptable
- 10,000 vial/batch production of lyophilized formulation utilizing readily-available pharmaceutical production equipment
- Stable
  - at least 36 months refrigerate
  - At least 24 months room temperature

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# Characterization

- **Characterization is a regulatory requirement:**

> ***"The physicochemical characterization tests, which are critical to ensuring product quality of each batch of liposome drug product, should be identified."***
>
> ***"Rigorous characterization of the physicochemical properties can also be beneficial in evaluating subsequent changes in manufacturing."***

- **Types of characterization activities:**
  - Common to all liposome drug products: "Core"
  - Product-specific

Source: 2002 Draft Guidance Document, Center for Drug Evaluation and Research (CDER), FDA: "Liposome Drug Products: Chemistry, Manufacturing and Controls; Human Pharmacokinetics and Bioavailability; and Labelling Documentation"

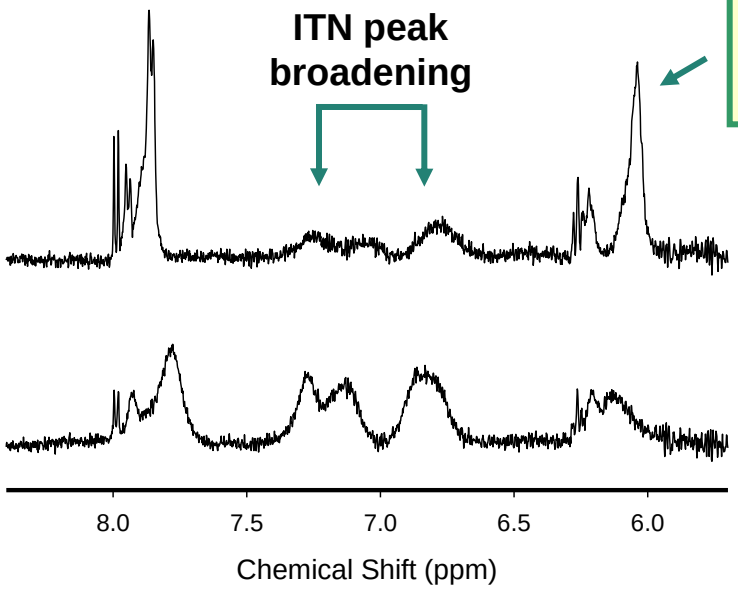
# Characterization

- **Core physicochemical parameters:**
  - Phase transition temperature (differential scanning calorimetry)
  - Trapped volume
  - Lamellarity and morphology (electron microscopy)
  - Surface charge (zeta potential)
- **Product specific:**
  - Drug-excipient interactions
  - Drug loading/stabilization mechanisms
  - Drug-drug interactions
- **Method examples:**
  - Mock drug encapsulation, in vitro release (IVR)
  - Spectroscopic characterization (NMR, UV-Vis, FT-IR, Fluoresc)
  - Calorimetry (ITC, DSC)

# Identifying Features Relate to Performance; CPX-1 (irinotecan:floxuridine)

- Spectroscopy reveals drug-excipient and intra-drug interactions influence drug release:

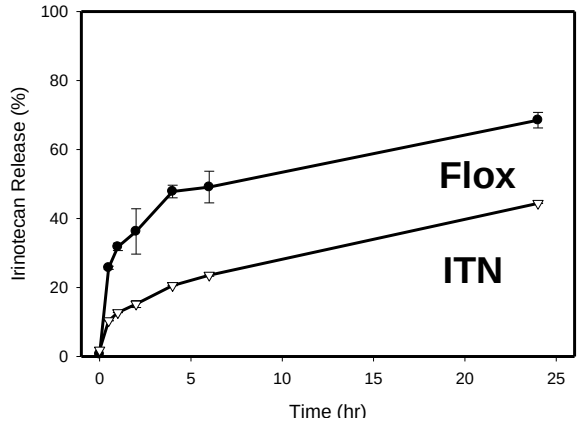
**$^1$H NMR, aromatic region**

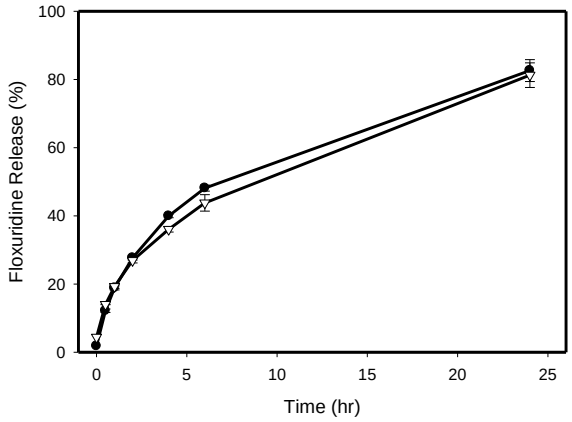



**Cu-free, gluconate-TEA buffer**

**Copper gluconate-TEA buffer**

**In vitro release assay:**




Ref: Dicko, et al. 2008, *Pharm. Res. 25*, 1702. Flox = floxuridine, ITN = irinotecan

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# Summary: Liposomes

- Most developed to date
  - Many approved and available commercially
- Formulation based on target product profile
- Robust, scalable manufacturing process
- Dosage form to maximize shelf life but still easy to use
  - Suspension
  - Lyophilate
- Product specifications can be lengthy
  - Active substances and membrane components: content, encapsulation, impurities
  - Particle size and ….more…
- Thorough physicochemical characterization
- Validation for multicomponent, multi-step manufacturing process