Controlled Delivery of Biologics
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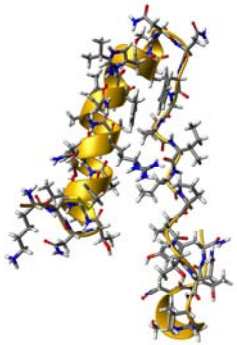
Controlled Delivery of Biologics

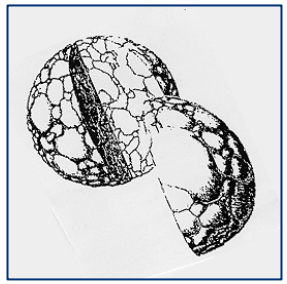
- Introduction
- Biologics Properties
- Why Not Oral Delivery?
- What Are Non-invasive Alternatives?
- Modified Release Formulations
- Sustained Circulation Strategies

Common Goals of Delivery Systems

- Improve patient convenience, compliance, ease of use, safety, efficacy
  - Must be a compelling reason to use the new product
- Change route or frequency of administration
- Improve safety / side effect profile
  - Target delivery or prevent systemic exposure to drug

What is Product Presentation for Biologics?
What Factors Influence It?





Molecule
- Efficacy / side effects
- Continuous or pulsatile
- Cost per gram
- Physicochemical properties

Biology & Chemistry

Delivery System
- Process complexity
- Bioavailability
- Cost per unit
- Compatibility with molecule

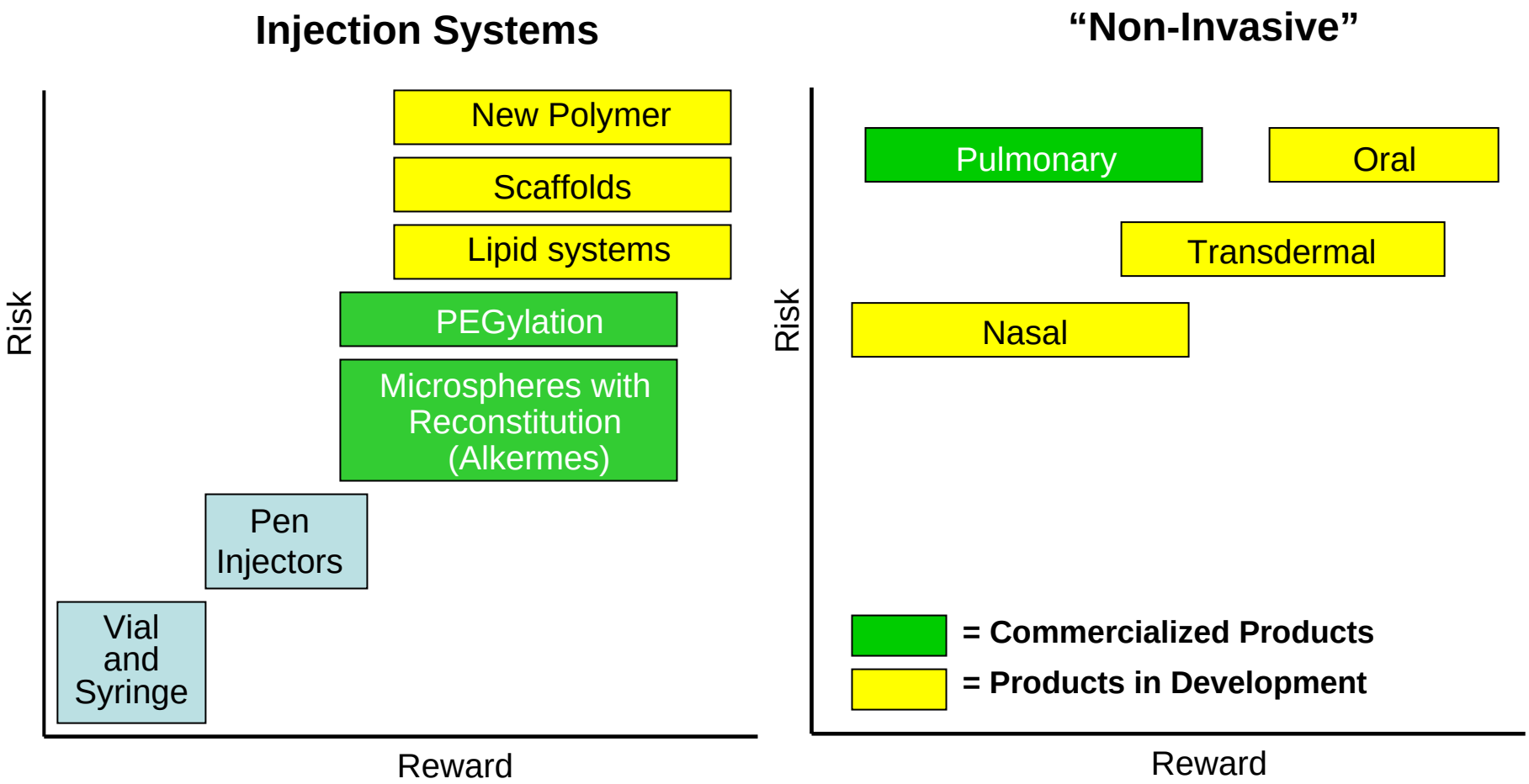
PK & Formulation

Device
- Device complexity
- Ease of use / acceptance
- Cost per unit
- Formulation compatibility

Device & Handling

Product Presentation is how patient and physician interact with and experience the product

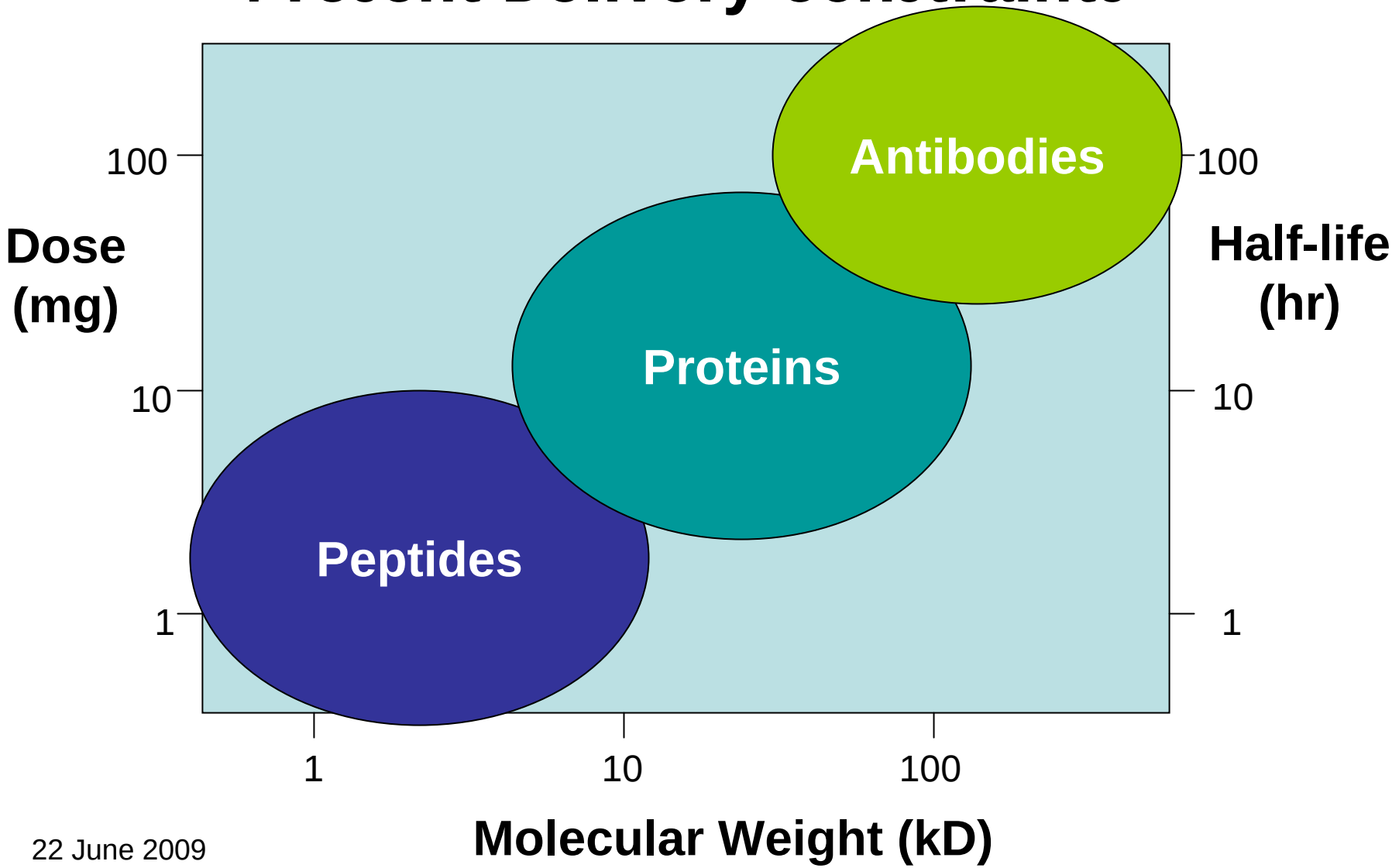
Significant Challenges and Limited Options for Biologics Product Presentations



Common Challenges of Delivery Systems

- Extended exposure systems more variable than immediate release
- Clinical development more complicated than immediate release delivery system
- Daily cost of goods often higher
  - Bioavailability, device and formulation cost
- CMC Development often rate-limiting

Peptide and Protein Therapeutics Properties Present Delivery Constraints



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Delivery System Choice is Often Dictated by Drug, Technology, or Market Constraints

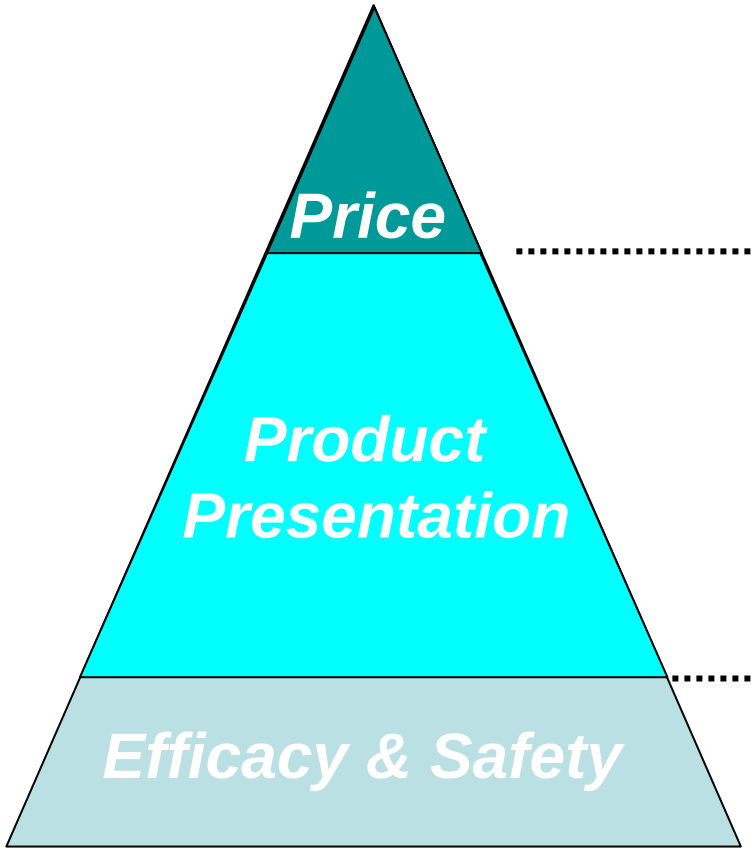
- Marketplace constraints
  - Patient population and reimbursement will have impact on price
  - Competitive products set bar for ease of use
- Drug / delivery system constraints
  - Preclinical / clinical PK and PD needs
  - Compatibility with delivery system
  - Cost of delivery system (drug and device)

Who are our customers? What do they want and need?

- **Patients, physicians, payors desire products that are …**
  - **Safe and effective**
  - **Easy and painless to use**
  - **Easy to train patient to use**
  - **Cost effective and cost competitive**
- **An oral tablet is a highly preferred delivery system**
  - **90% of pharmaceutical products are oral**

Why is Product Presentation Important?

Patient / physician experience is paramount



Customer & Market Influence

- ***Invasive/Non-Invasive***
- ***Simplicity of Administration***
- ***Frequency***
- ***Annoying Side Effects***
- ***Storage/refrigeration***
- ***Cost of Goods***

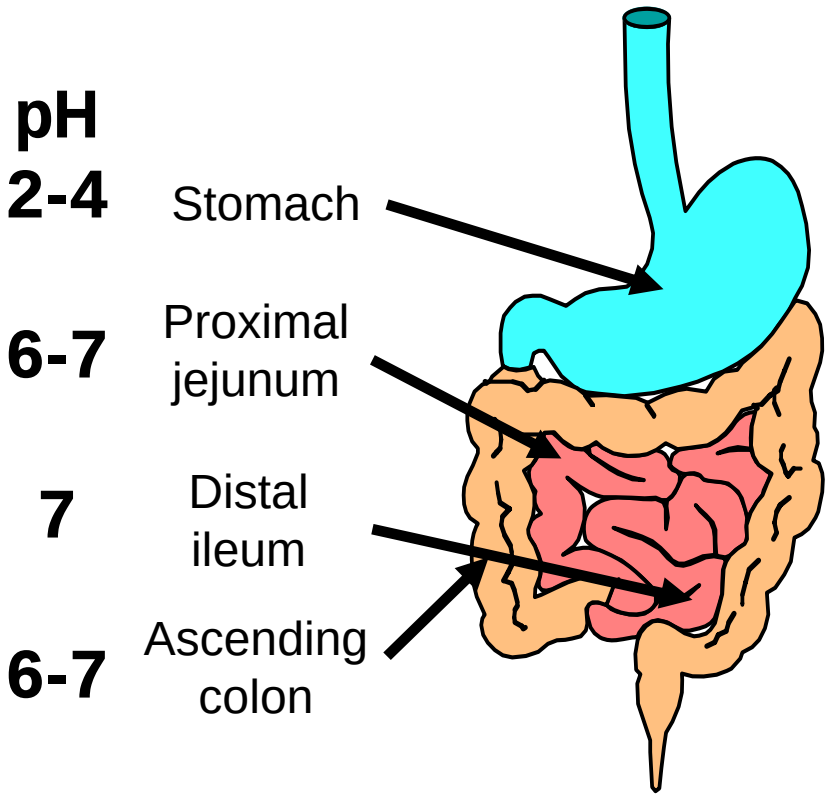
Biology & Chemistry

Attributes must be in balance to provide overall value to patient and physician

Injectable and Non-Injectable Delivery Technologies for Peptides and Proteins

- Modified Release Injectables
  - Depot injection formulations
  - Patch / pump / transdermal
  - Implantable systems
- Sustained Circulation Injectables
  - PEGylation and related covalent strategies
- Non-Injectable Delivery Systems
  - Nasal spray or pulmonary inhalation
  - Oral / Sublingual / Buccal

Gastro-intestinal tract is a challenging environment for biologics



GI system designed to break down nutrients for absorption (acidic pH, enzymes)

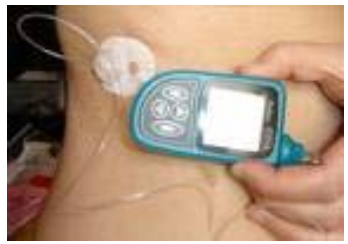
Nutrient absorption occurs mostly in the small intestine

Absorption requires transport across a lipid bilayer membrane

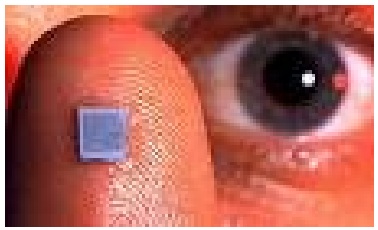
Several factors work against oral:
Instability to acidic pH and enzymatic systems
Low absorption due to poor membrane permeation

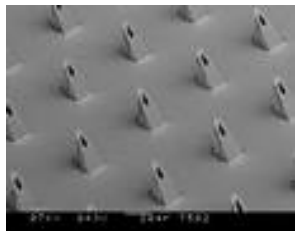
Alternatives to Daily Injection

- Pumps

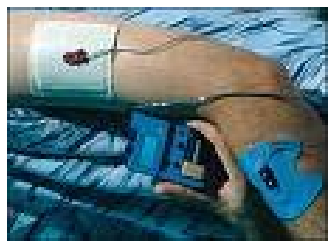


- Micro Needle Arrays





- Transdermal Systems

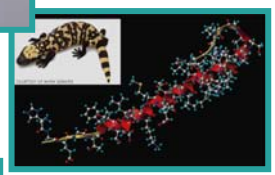


Sustained Release Injectable Systems

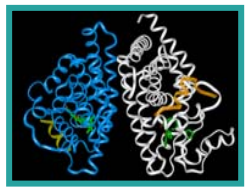
- Polymer or lipid excipients
- Formulations are microparticle or form gels with temperature transition
- Biodegradable in days to weeks
- Depot administered or formed at injection site (subcutaneous)
- Drug release through diffusion and erosion of formulation depot

Diabetes Market – Many Injectable Insulins and Orals

Inhaled insulins
GLP-1 analogs DPP – 4



Detemir
Pramlintide
Exenatide
Aspart
Glargine
Glinides
Glitazones
Lispro
Metformin
Human insulin
Sulfonylurea
Animal insulin



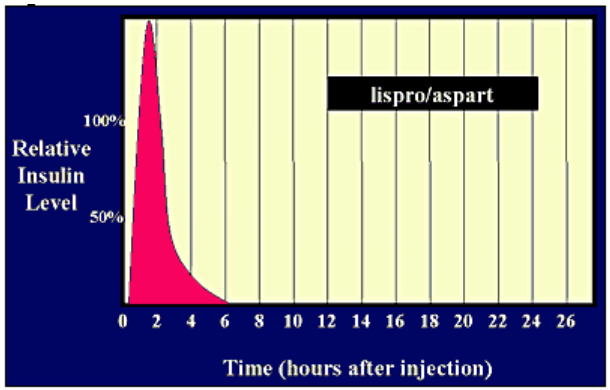
1922 1950's 1982-5 1995 1996 2001 2003 2005 2006

History of Insulin and Sustained Release

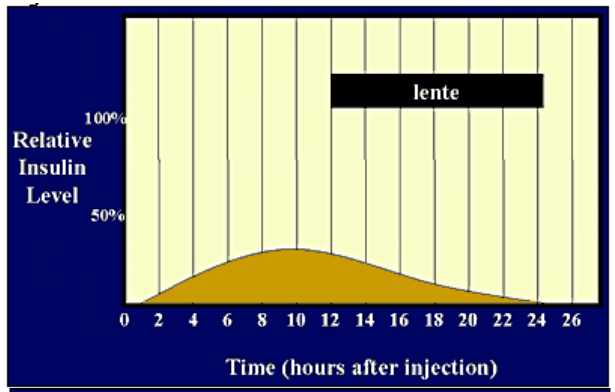
- 1920 - Banting and Best extract insulin from fetal calf pancreas
  - Jan 11, 1922 – first patient treated
- 1925 – Abel crystallizes insulin
- 1934 – Scott discovers insulin crystals contain Zinc
- 1930 to 1950 – Suspension formulations marketed (PZI, NPH, Lente)
- 2004 – Lantus (insulin glargine) approved

Time Activity Profiles for Insulins

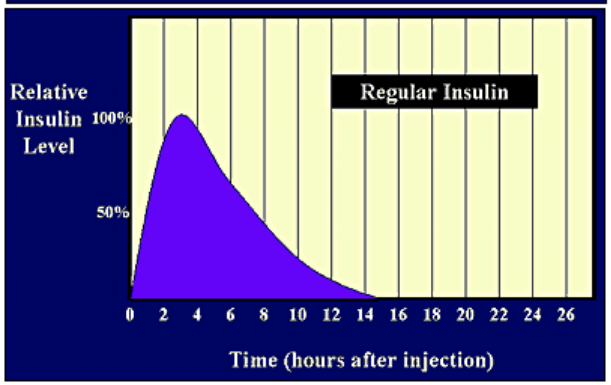
Rapid-acting (solution)



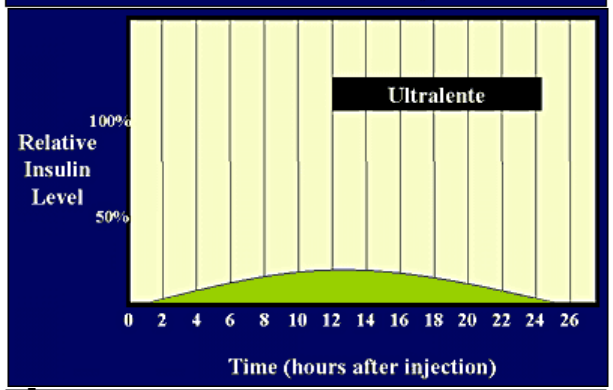
Intermediate-acting (suspension)



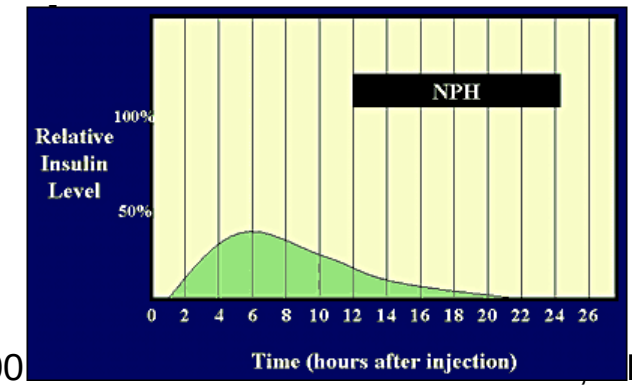
Short-acting (solution)



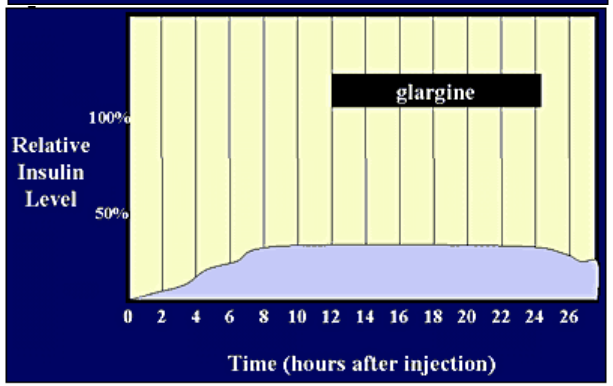
Long-acting (suspension)



Intermediate-acting (suspension)



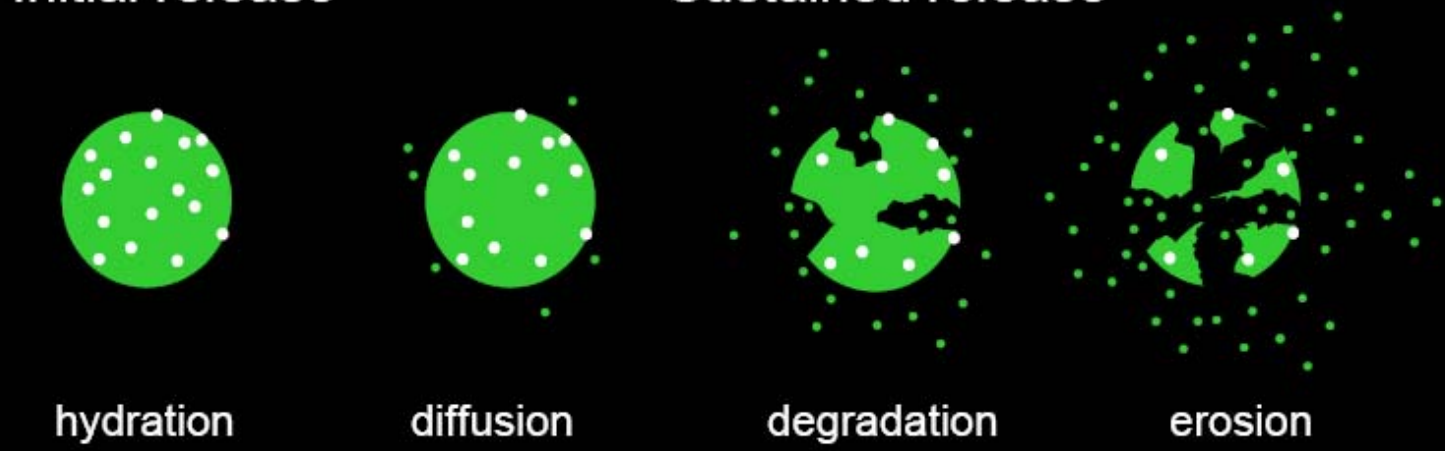
Long-acting (solution)



Microsphere system

Long-Acting Release Technology

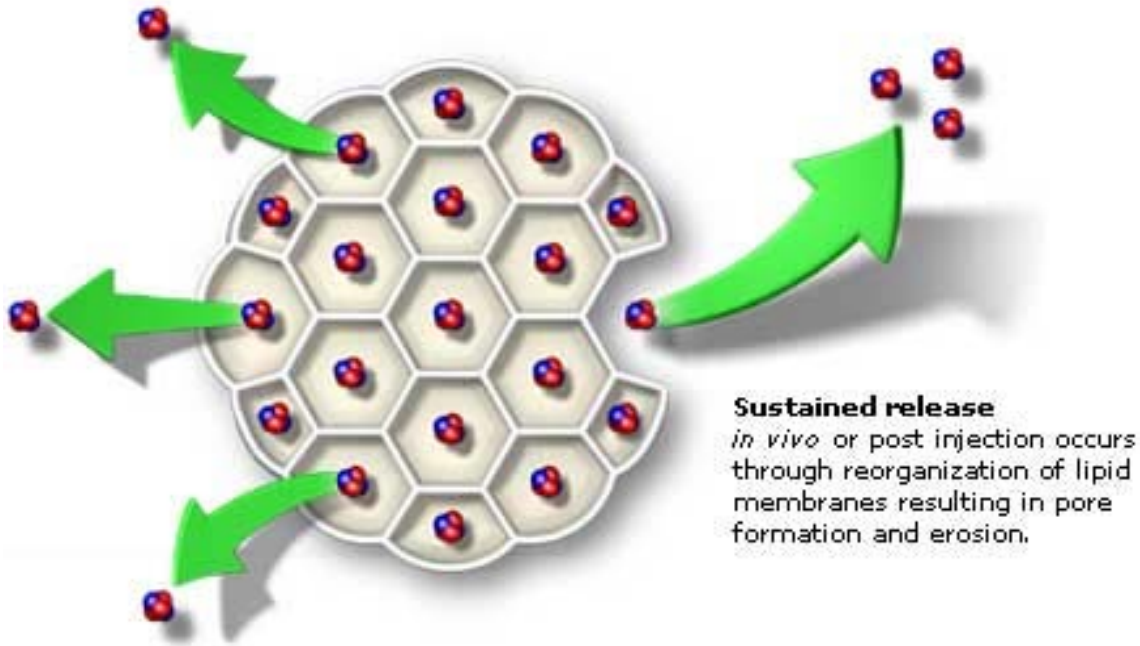
- Exenatide LAR:
  - biodegradable polymeric microspheres for extended release
  - detectable plasma concentrations of exenatide for weeks to months after a single dose



Bartus RT et al. Science. 1998;281:1161-1162

Liposomes release drugs as depot or from circulation in blood

- Liposome formulation excipients are lipids with limited water solubility
- The lipids gradually diffuse into bodily fluid
- The bilayer structure breaks up and releases drug



Schematic of drug release from a multivesicular liposome (DepoFoam®)

Sustained Circulation Injectables

- Scaffold covalently attached to therapeutic agent
- PEG or other construct to increase MW and hydrodynamic volume to reduce clearance rate
- Antibody and antibody fragments to promote albumin binding and reduce clearance
- Systems may be recombinant or synthetic

PEGylation as Product Precedent in Protein Therapeutics

PEGylation has demonstrated :

- Slowed clearance / maintained circulating concentrations / reduced dose frequency
- Increased solubility and stability
- Reduced aggregation / precipitation
- Reduced immunogenicity
- Accepted regulatory / safety profile

How do we choose drug delivery technologies and strategies?

- Technical constraints
  - Anticipated pharmacokinetic profile
  - Probability of technical success
    - Complexity of device
    - Difficulty of development
    - Proven in a marketed product
  - Cost of the system to the patient
- Patient and Physician experience
  - Training required, ease of use