DRUG-DEVICE COMBINATION PRODUCTS SSF PERSPECTIVE AND CAPABILITIES

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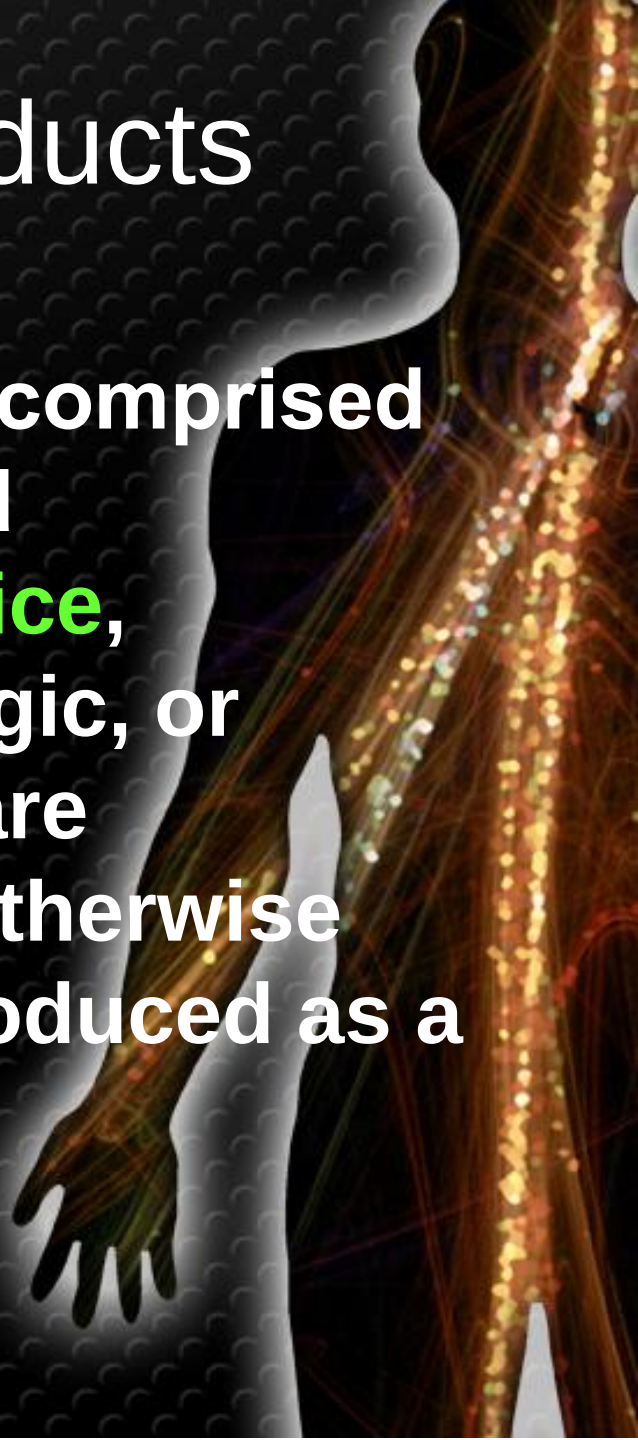
Combination Products

FDA defines as “a product comprised from two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity”.



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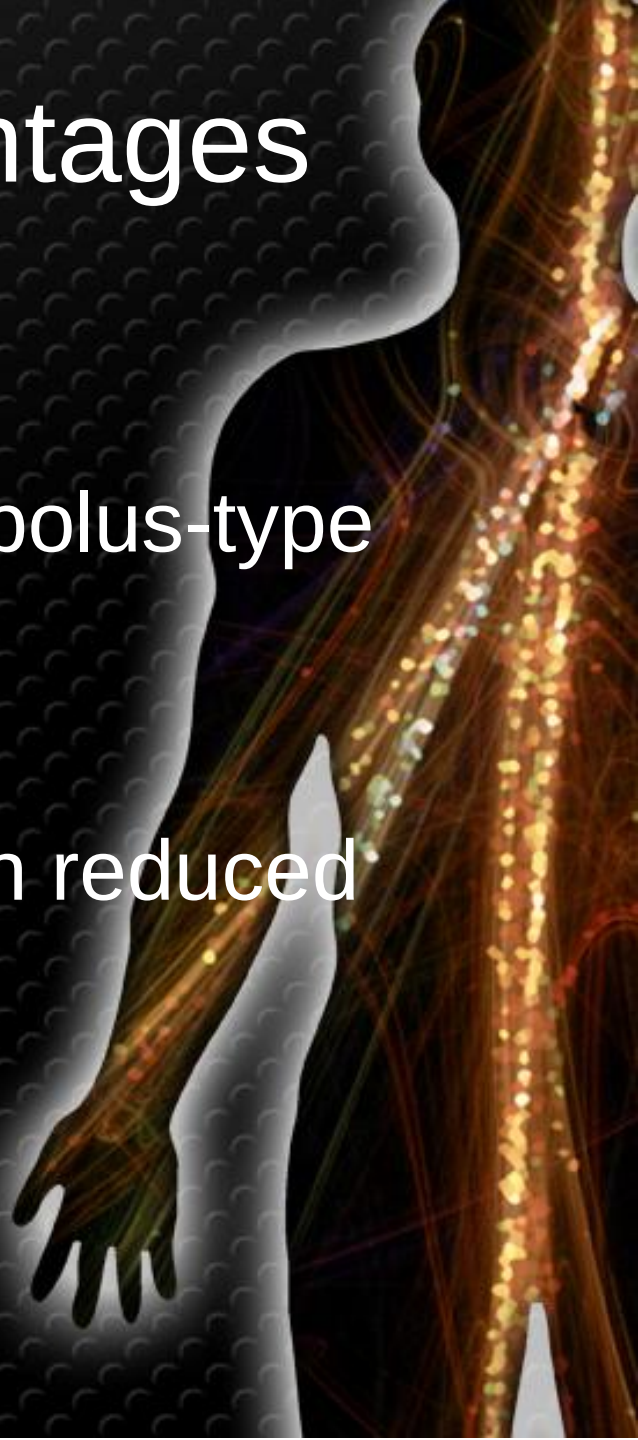
Therapeutic Advantages

- Implanted or transdermal
- Controlled release of API vs bolus-type delivery
- Targeted delivery
- Higher therapeutic doses with reduced systemic toxicity
- Improved patient compliance



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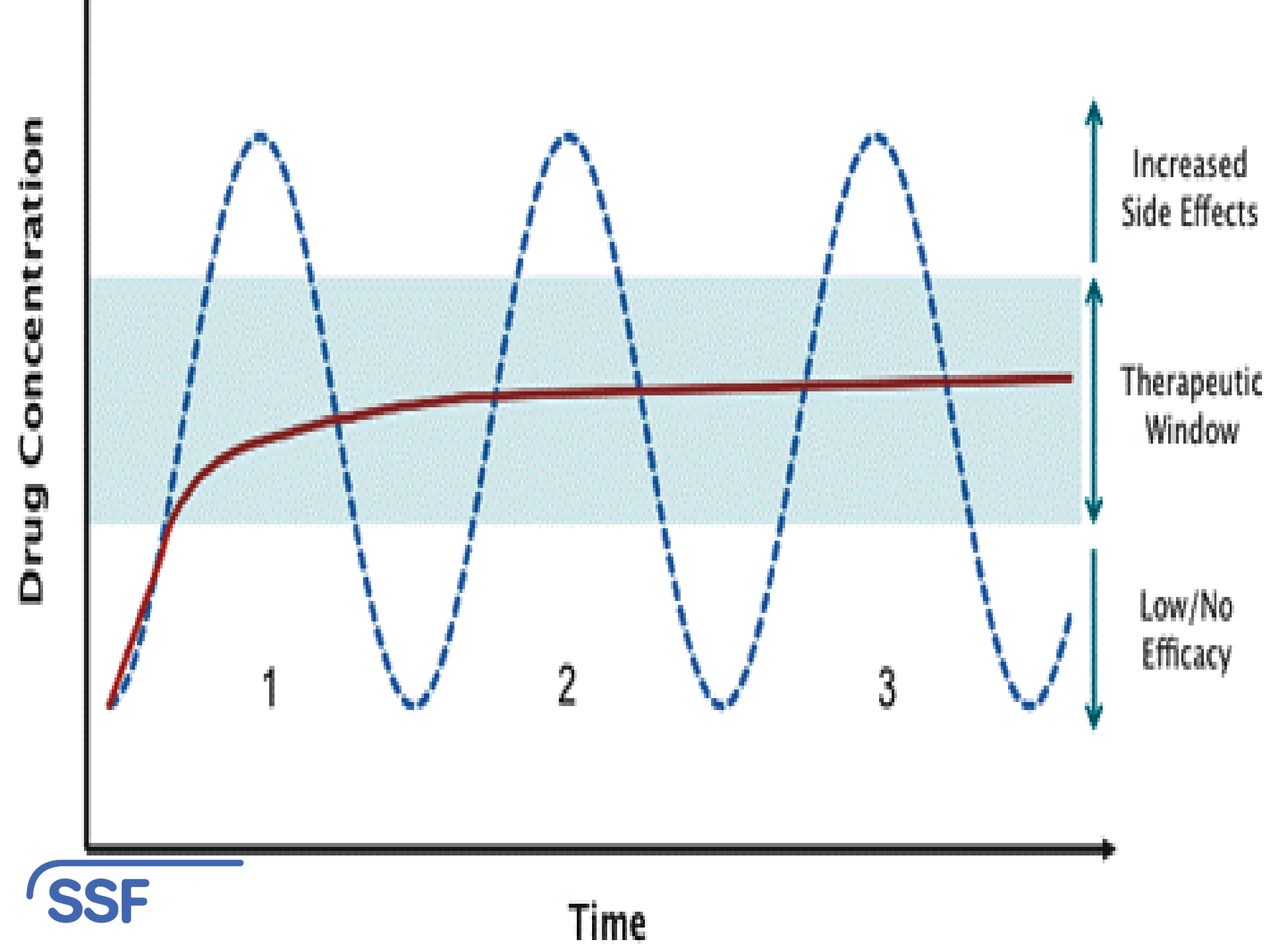
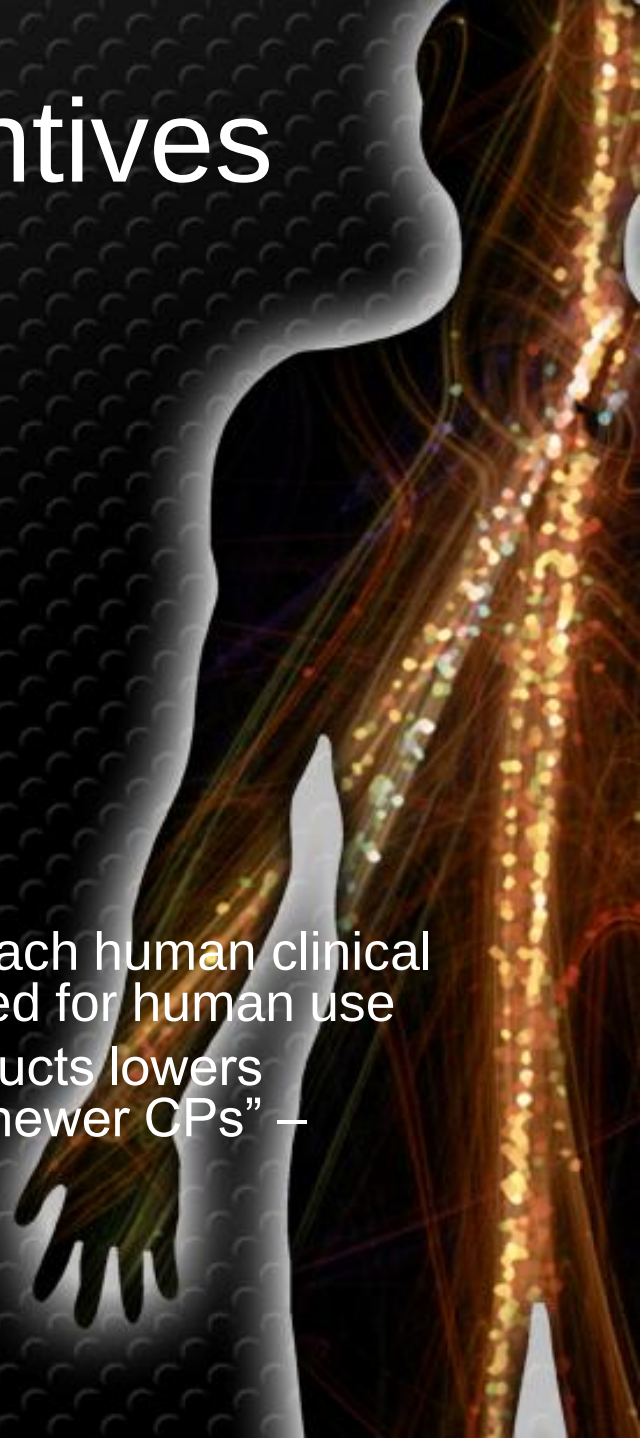

Drug Concentration
Increased Side Effects
Therapeutic Window
Low/No Efficacy
1
2
3
Time

Commercial Incentives

- **Medical device sector**
  - Build a better mousetrap
    - DEX steroid collars on cardiac leads
    - Drug eluting stents
    - Drug eluting punctal plugs
    - Antimicrobial catheters/wound drains
- **Pharmaceutical sector**
  - Reinvestigate “dry holes”
    - 5 of 10,000 compounds investigated reach human clinical studies; historically 1 of 10,000 approved for human use
    - “Reviving of failed pharmaceutical products lowers development time and costs to launch newer CPs” – Mindbranch Research, Jan 2010
    - Extend IP protection



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Sector Growth

- "Spurred by an aging population, the U.S. medical devices industry is expected to demonstrate a healthy growth rate of 9.0 percent for the period 2006-2013." – Frost & Sullivan, March 2008
- "US pharmaceuticals market to expand at just 1.8% CAGR in next five years." - Business Monitor Intl, Oct. 2010
- "Overall sales of drug device combination products were $12 billion in 2008 and $13.7 billion in 2009. This is projected to reach $27 billion in 2014 at a compound annual growth rate (CAGR) of 14.5%." -BCC Research, Jan 2010

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Silicone as Drug Matrix

- 50 year implant history, inert and biostable
- PDMS - helical conformation, weak intermolecular forces, high free volume, exceptional permeability
- PDMS elastomers are 1000X more permeable to progesterone than polyethylene
- Formulated as elastomers and gels
- Multiple fabrication techniques
  - Molded components, extrusion (tubing or rod), thin film membrane, dipped/sprayed coatings
- Various vulcanization mechanisms

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Silicone Cure Systems

- **RTV - acetoxy, alkoxy, oxime**
  - Tin catalyzed
  - Room temperature vulcanization, various leaving groups
  - H_2O generally required for hydrolysis/condensation crosslinking, limits fabrication methods
  - Generally very slow reaction
  - Cured physical properties are marginal
- **Peroxide - bis 2,4 dichlorobenzoyl peroxide**
  - High temperature initiation
  - High temperature post cure to eliminate 2,4 dichlorobenzoic acid
- **Platinum**
  - Electrophillic addition of H to vinyl
  - Relatively rapid cure at elevated temperatures
  - No leaving group
  - Good cured physical properties
  - Numerous fabrication techniques; molding, extrusion, thin films, coatings
- **UV**
  - JDA with Momentive Performance Materials - May 18, 2011

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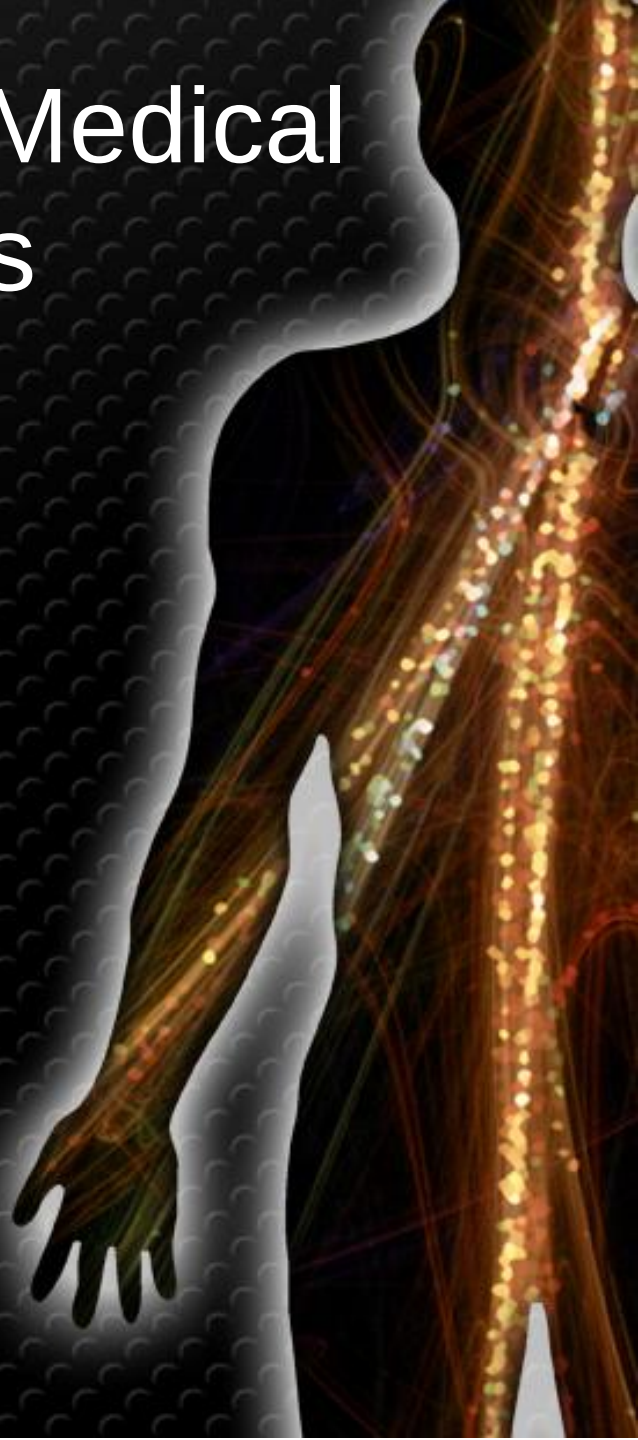
Pharmaceutical and Medical Device Sectors

- Cardiology
- Orthopedics
- Urology
- Ophthalmology
- Women’s Health
- Wound Management
- Antimicrobial Technology
- Veterinary Science



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API

COMPLETED

- Rifampin, Minocycline – antimicrobial technology
- Dexamethasone sodium phosphate – cardiology
- Cyclosporine – ophthalmics
- Chlorhexidine – urology, wound care

CURRENT

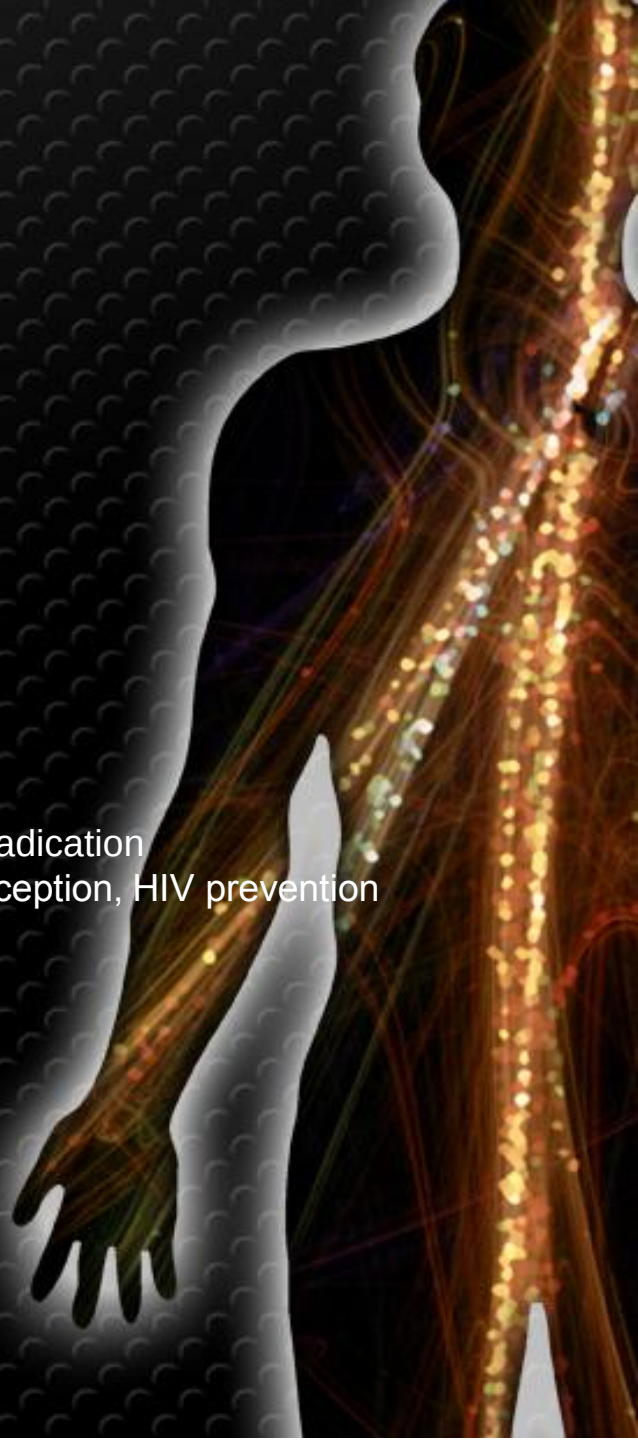
- Dexamethasone Acetate – glucose monitor
- Gentamcin - orthopedics
- Progesterone – veterinary science
- Xifaxin – urology
- Tenfovir Disoproxyl Fumerate – HIV prevention

PENDING

- Levonorgestrel – (proposals under review), women's health
- Ivermectin – (proposal under review), tropical medicine, malaria eradication
- LNG, Dapirivine – (proposal under review) women's health, contraception, HIV prevention
- Cefazolin – (proposal under review) orthopedics

UV VULCANIZATION STUDY

- Fluocinolone actetinide
- Doxycycline
- Diclofenac



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Manufacturing Process Overview

- Confirm API identity, FTIR
- Select optimal matrix material
  - API compatibility
  - Elution rate targeting
  - Fabrication method, scalability
- Cure test for inhibition/poisoning of crosslinking reaction
- Determine API temperature stability – DSC
- Optimize API-silicone mixing process
  - In process HPLC testing
- Optimize manufacturing process
  - Rheometry testing to determine time/temp parameters
- Develop lot acceptance criteria
  - Total drug content, HPLC
  - Determine acceptable elution rate range, HPLC

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About SSF

- Founded 1984 – Privately held
- 3 locations – 235 employees
- 190,000 sq ft – 100,000 sq ft manufacturing – 65,000 sq ft clean rooms
- 2012 – manufactured 1100+ components for 250+ customers in 17 countries
- CA Department of Public Health FDB (Food & Drug Branch):
  - Medical Device Manufacturing License
  - Drug Manufacturing License
- FDA Establishment Registration
- ISO 13485: 2003
- ISO 9001: 2008

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