Transdermal delivery of macromolecules using Macroflux® technology

System requirements with emphasis on microfabrication, surface chemical properties, drug-specific requirements, and the interaction with human skin and systemic biology

NCCAVS – Thin Film Users Group

Bio-Nano-MEMS Technology

June 17, 2009

Russell Ford, PhD

ZOSANO PHARMA

Better products with innovative delivery

Common routes of drug delivery

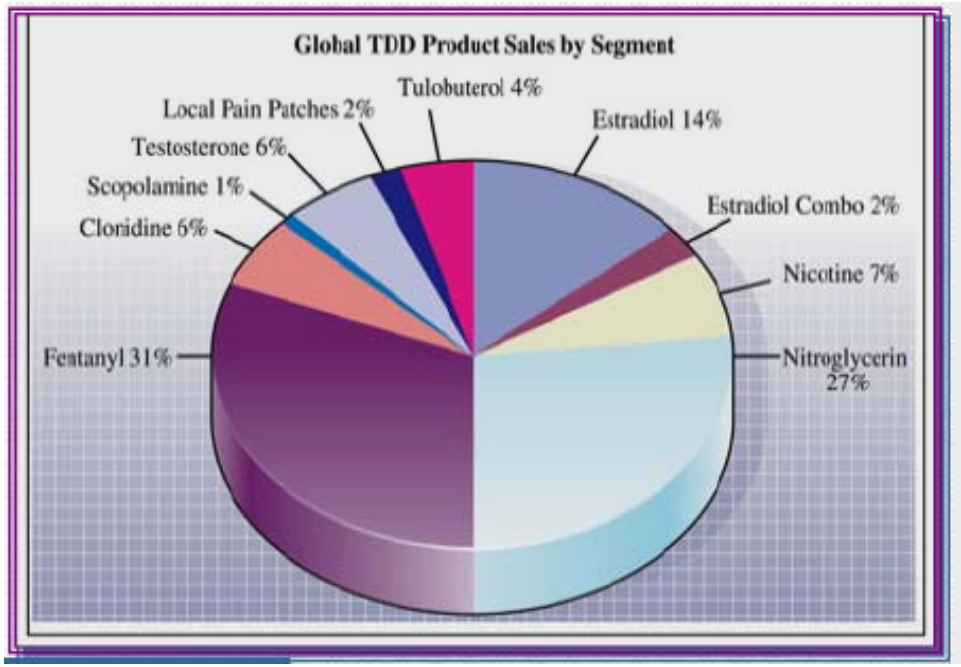
- Topical
- Oral
- Inhalation
- Injections
  - Intravenous
  - Intramuscular
  - Subcutaneous
  - Intradermal
- Transdermal
  - Passive
  - Active

Advantages of transdermal drug delivery

- Oral delivery is generally preferred but not always possible
  - May be degraded or not be absorbed by the gut
  - Can be irritating
  - Slow uptake
- Injection provides high bioavailability, but …
  - Often requires trained personnel to administer
  - More risk of infection, contaminants / particulates, air boluses
  - Rapid onset can be more addictive
  - Pain and/or phobia
- Transdermal drug delivery
  - Sustained or rapid onset
  - Possible diminished side effects due to reduced metabolites
  - Convenient and flexible dosing without pain
  - Dry formulations possible improving shelf-life and storage
  - Trend is towards faster onset and additional drug candidates

Passive transdermals are well-established

- Most people have used them or know someone who has
- Designed for daily or multi day wear
- Continuous steady state drug delivery profile



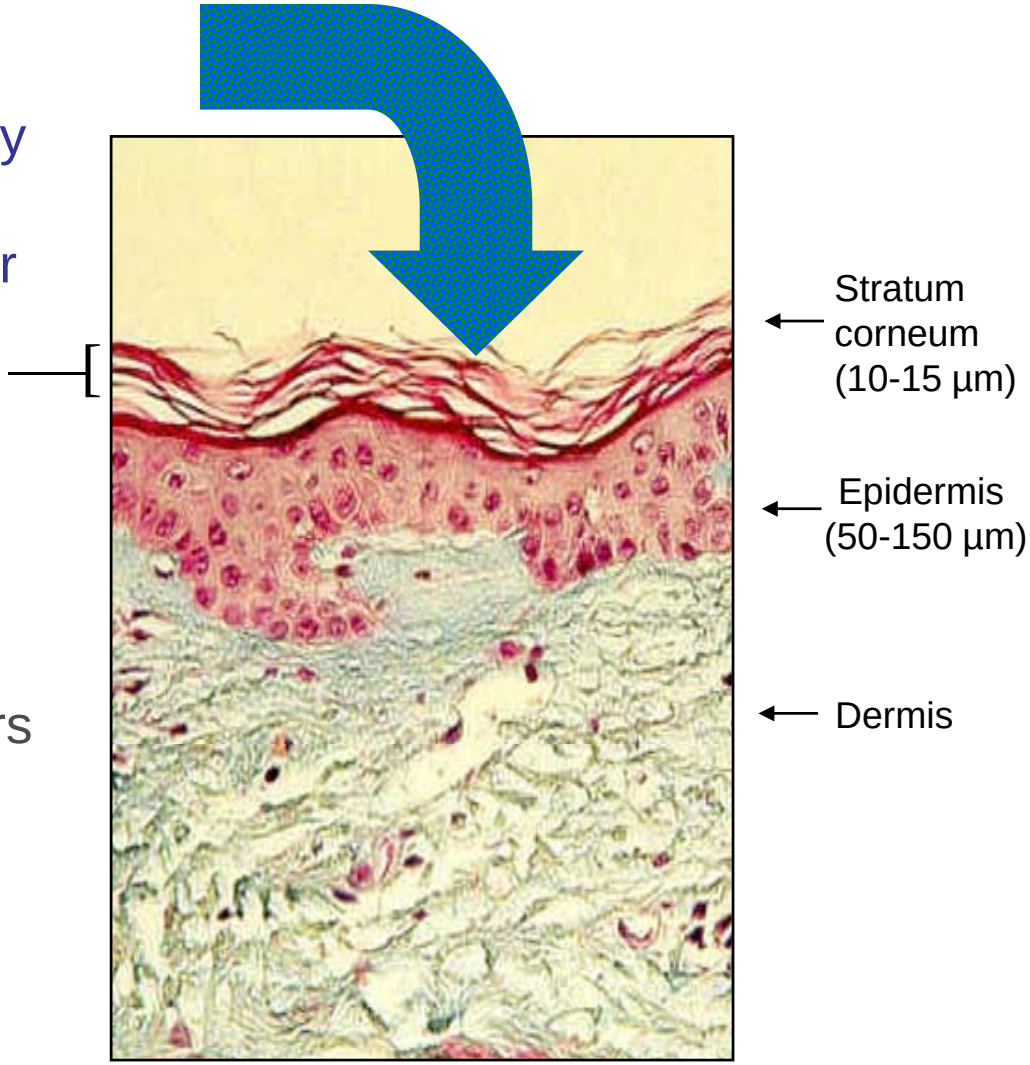
- Contain drug reservoir
- Passive, concentration dependent flux
- Slow delivery start up (hours)
- Steady state delivery, 1-7 days continuous
- Small hydrophobic drugs with molecular weights, <500 Da
- Small doses, <10mg/day
- Acceptable skin tolerability

The New Transdermal Delivery Opportunities

- Hydrophilic small drugs with poor or highly variable oral absorption, Class III drugs
- Small hydrophilic drugs requiring rapid delivery or sustained delivery (1 to ? Days)
- Injectables
  - Peptides
  - Biopharmaceuticals
    - (rec proteins, antibodies, RNAi….)
  - Vaccines
    - (protein, glycoconjugates, virus particles and DNA)

Approaches to overcoming skin barrier function

- Most drugs can not passively diffuse across the waxy stratum corneum skin barrier
- Especially:
  - Hydrophilic
  - Large molecular size
- Approaches:
  - Chemical enhancers
    - Ethanol, FA & esters
  - Electrotransport
  - Mechanical methods

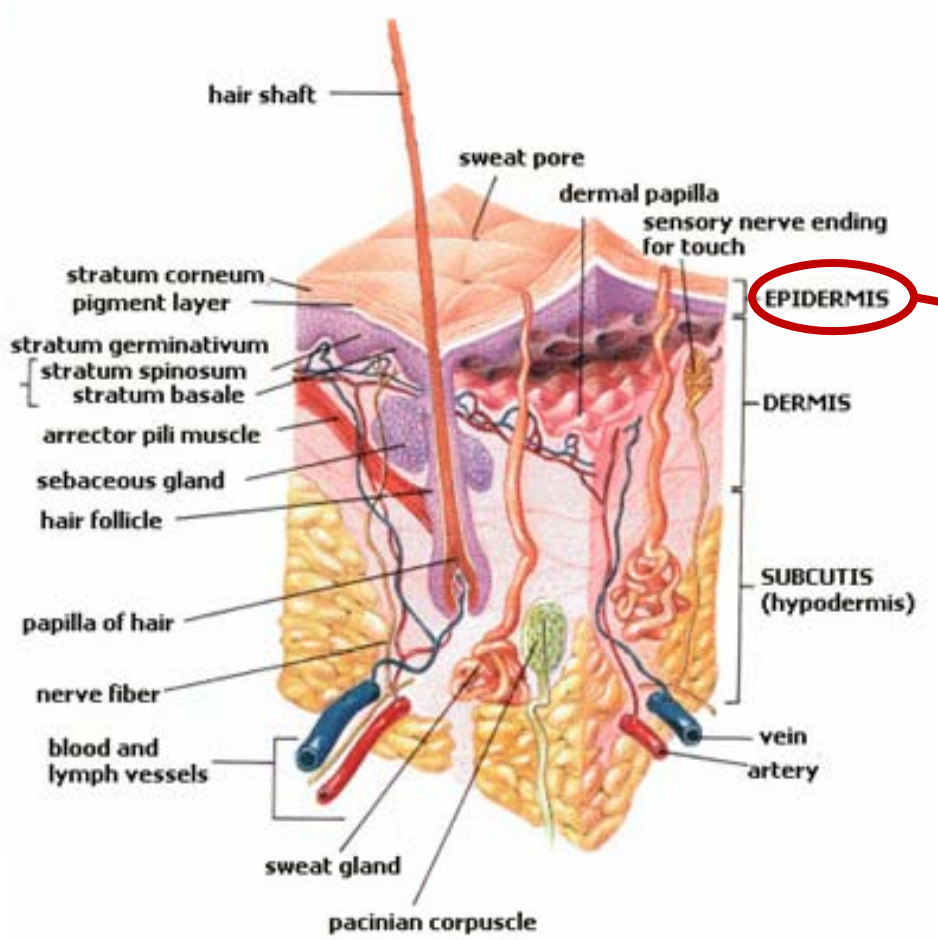


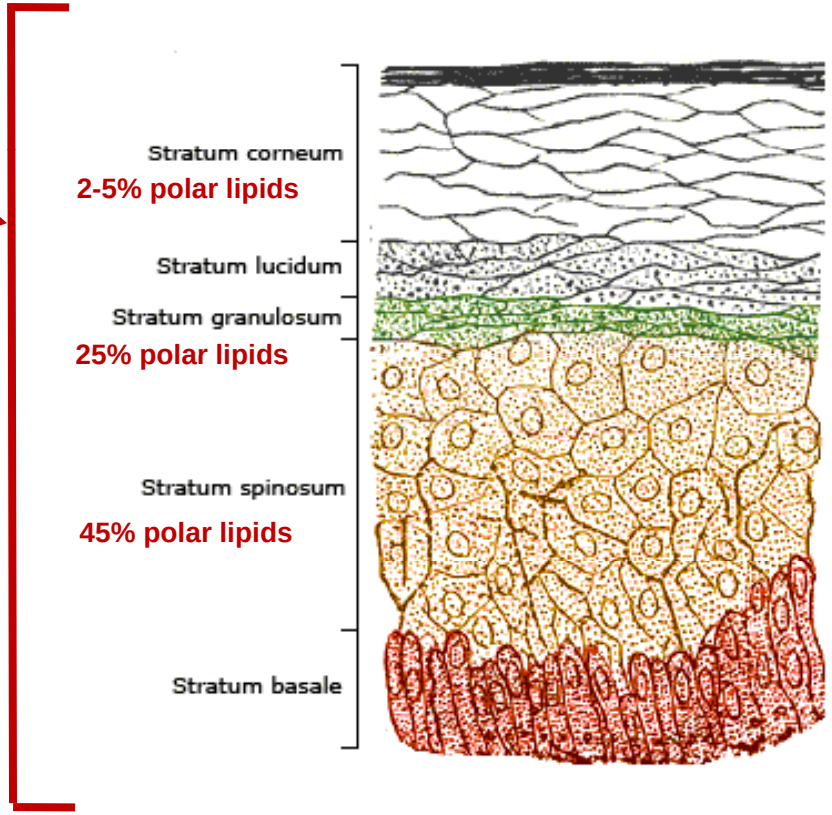
A number of micro mechanical approaches are in development

- Radio- frequency- Transpharma- ViaDerm
  - RF pulse to skin
- Thermal ablation- Altea- PassPort
  - “Hot wire” elements applied topically vaporize lipids in stratum corneum to create defects- rapid & local heating
- Laser Ablation- Pantec Bio
  - Excimer laser
- Electroporation- Genetronic Biomedical-MedPulser
  - Pulse voltage- 10-100 volts/ pulsed for micro-milli secs.
- Acoustical Waves- Encapsulation Systems-U-Strip, Sontra Medical- SonoPrep
  - Low frequency ultrasound (<100 kHz)
- Microneedles…….

Skin Biology

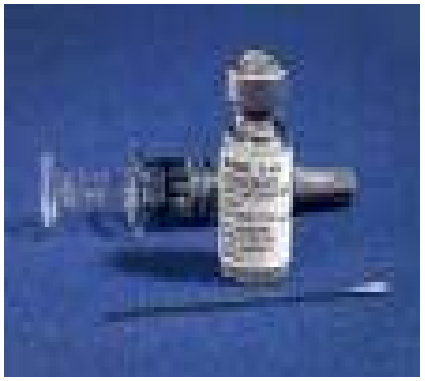
Shallow delivery to epidermis avoids vascular bed and majority of pain nerves, reaching stratum spinoseum crosses the hydrophobic / hydrophyllic gradient

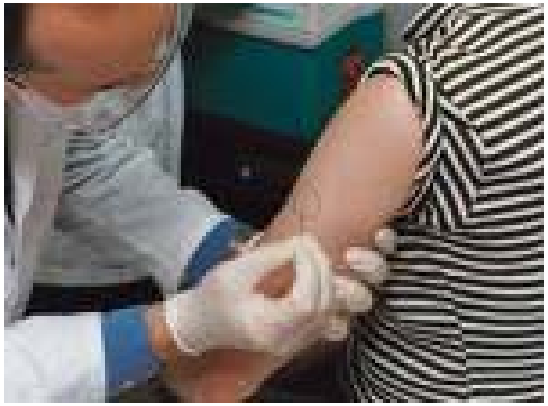


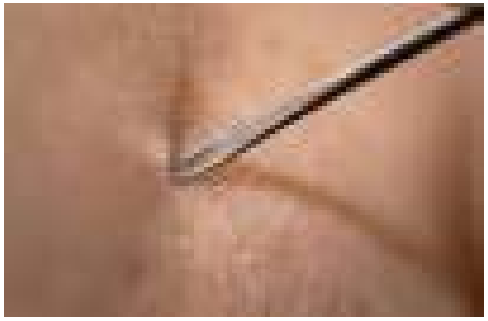


Short Needles Have Been Known for Decades

- **Smallpox vaccination**





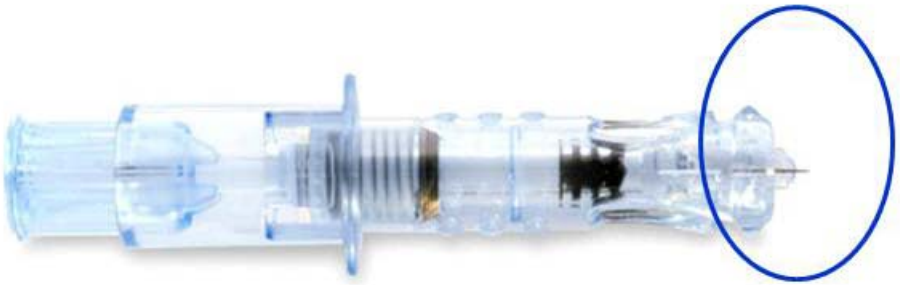


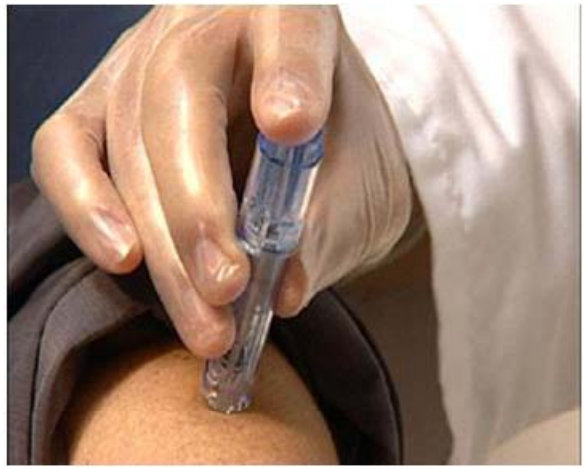
TB Tine Test

Hollow microneedles are more traditional looking and designed for ID injection (mm length needles)

BD-Microneedle ID injector,

- Soluviä microinjection system a prefilled syringe with 1.5 mm needle





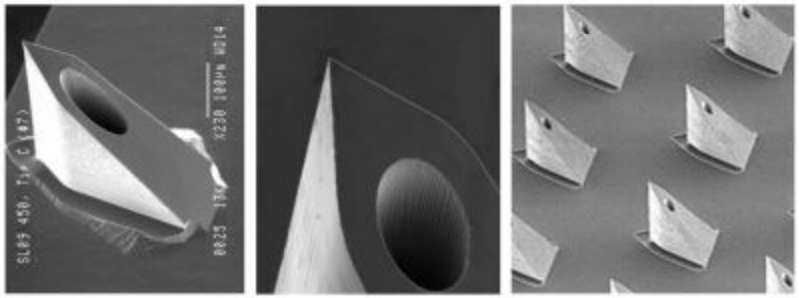
1st EMEA application for intradermal influenza vaccine delivery
Announced Feb 13, 2008 by Sanofi Pasteur

Example – Microneedle patch skin pretreatment enhances Naltrexone delivery in clinical study

- 50 ss microneedles 620 micrometers in length
- Skin Pretreatment followed by hydrogel drug patch

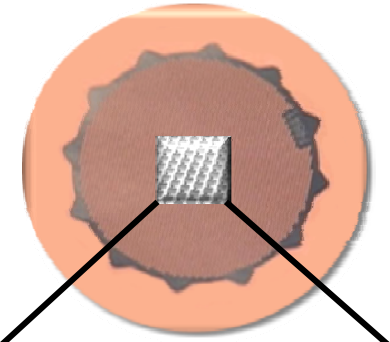
Wermeling, DP et al PNAS 105, 2058, 2008

Nanopass



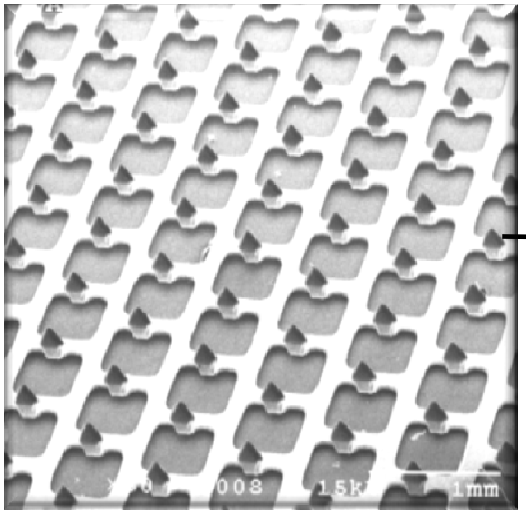
Debiotech

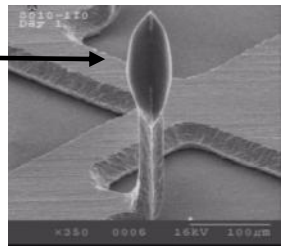
Zosano Patch Delivery System



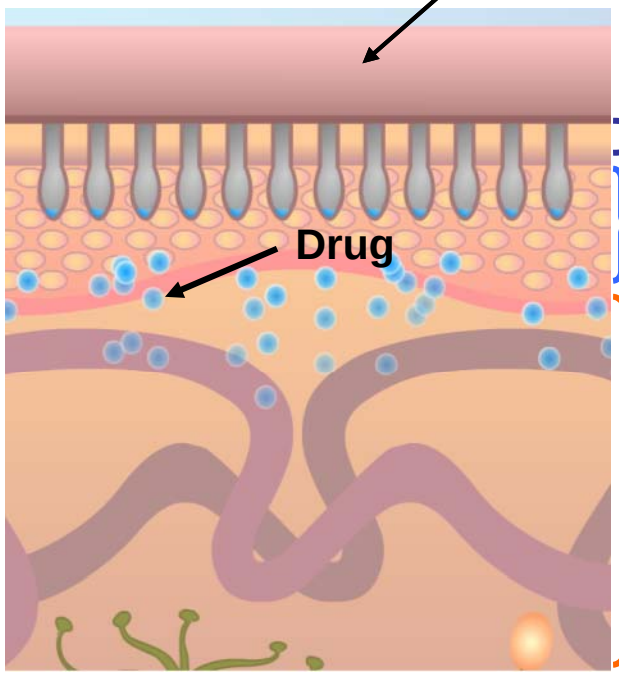
Drug-coated patch
(size of a US quarter)

Magnified drug-coated microprojections

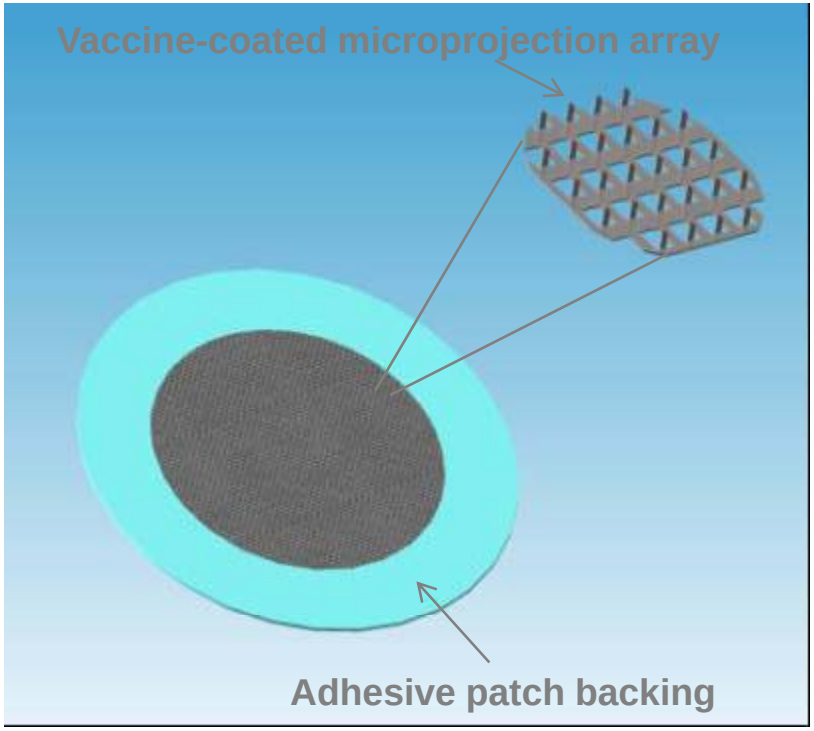




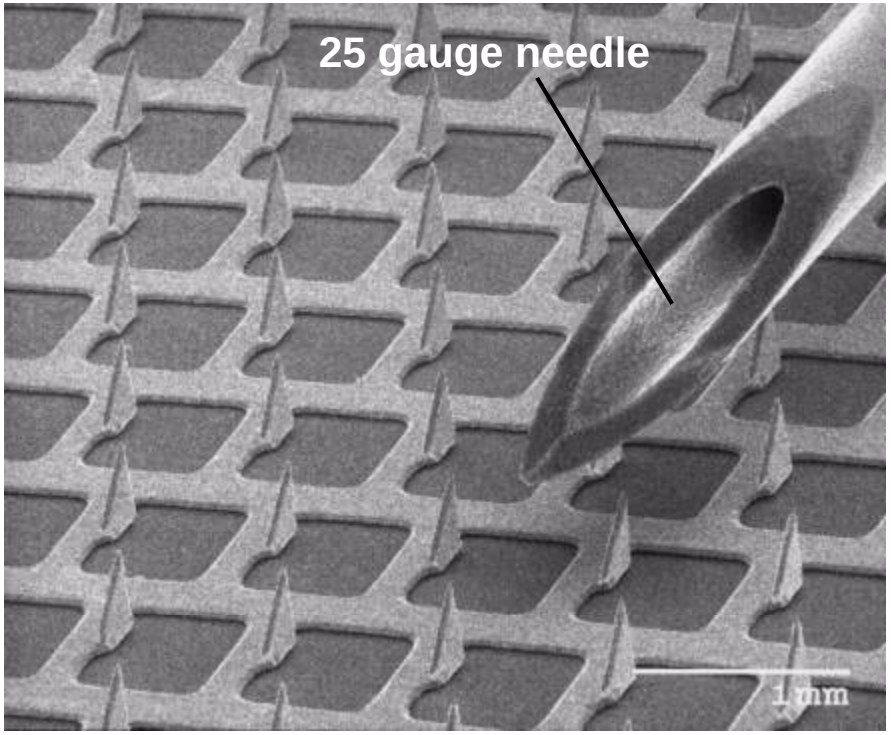
Individual microprojection



Zosano Patch: Comparison to 25 g Needle



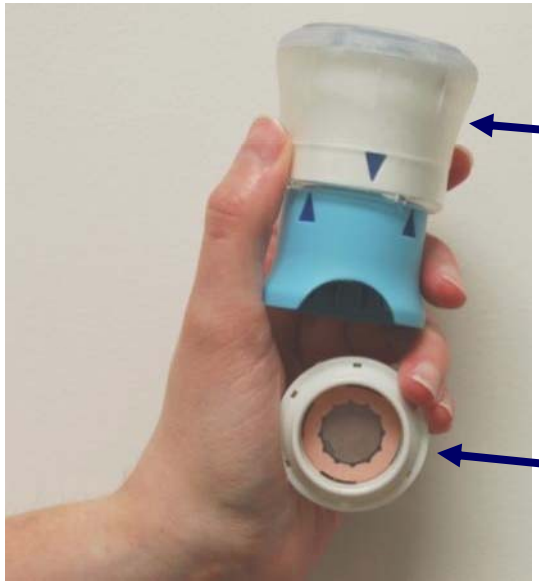
Microprojection array



System Requirements

- Self-administration
  - Simple
  - Minimal required dexterity
  - Robust to user variability
  - Room-temperature storage

- Minimal topical effects
  - Relatively short pathway patency
  - Visibly clear in 24 – 48 hours
  - Average stratum corneum turnover time is 14 days, epidermis 26-42 days



Reusable Patch Applicator

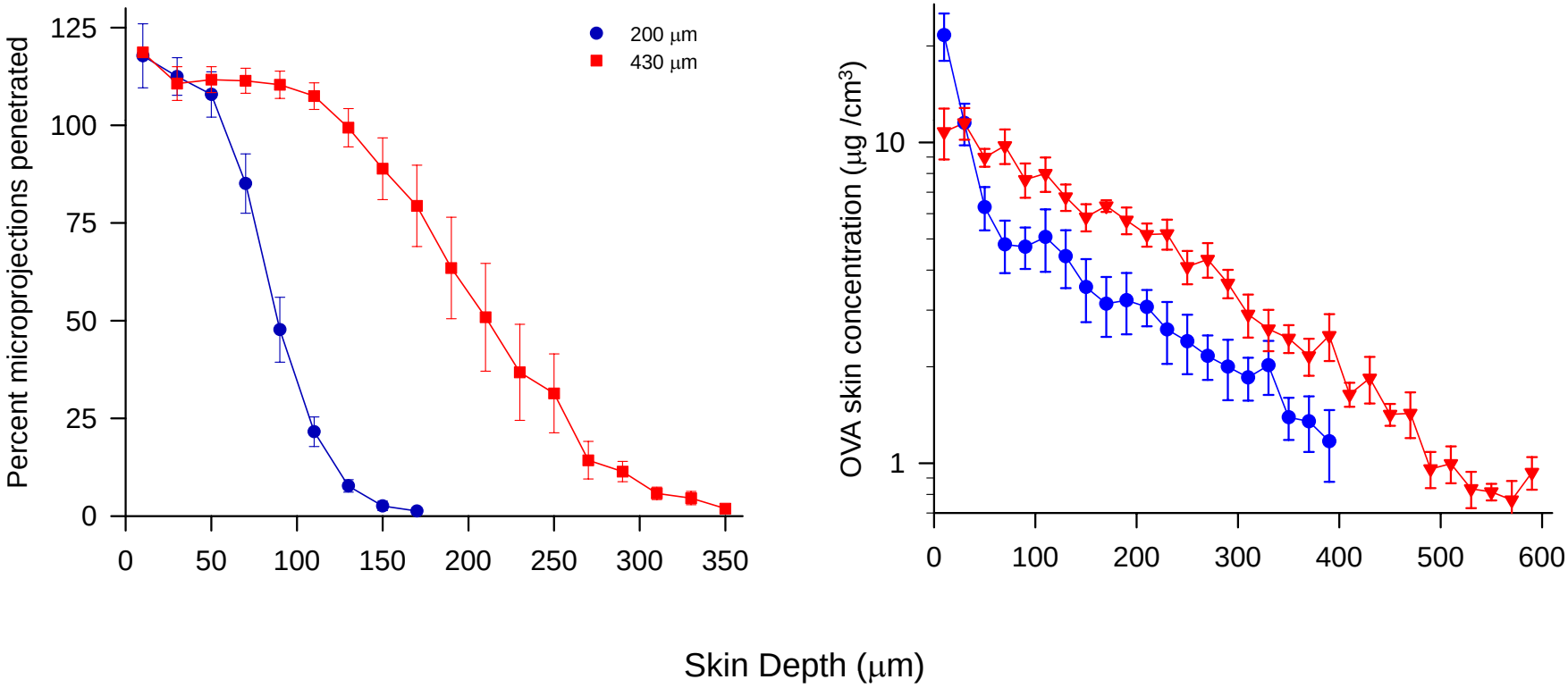
Disposable Patch Ring

Patch Applied

Short Patch Wear Time

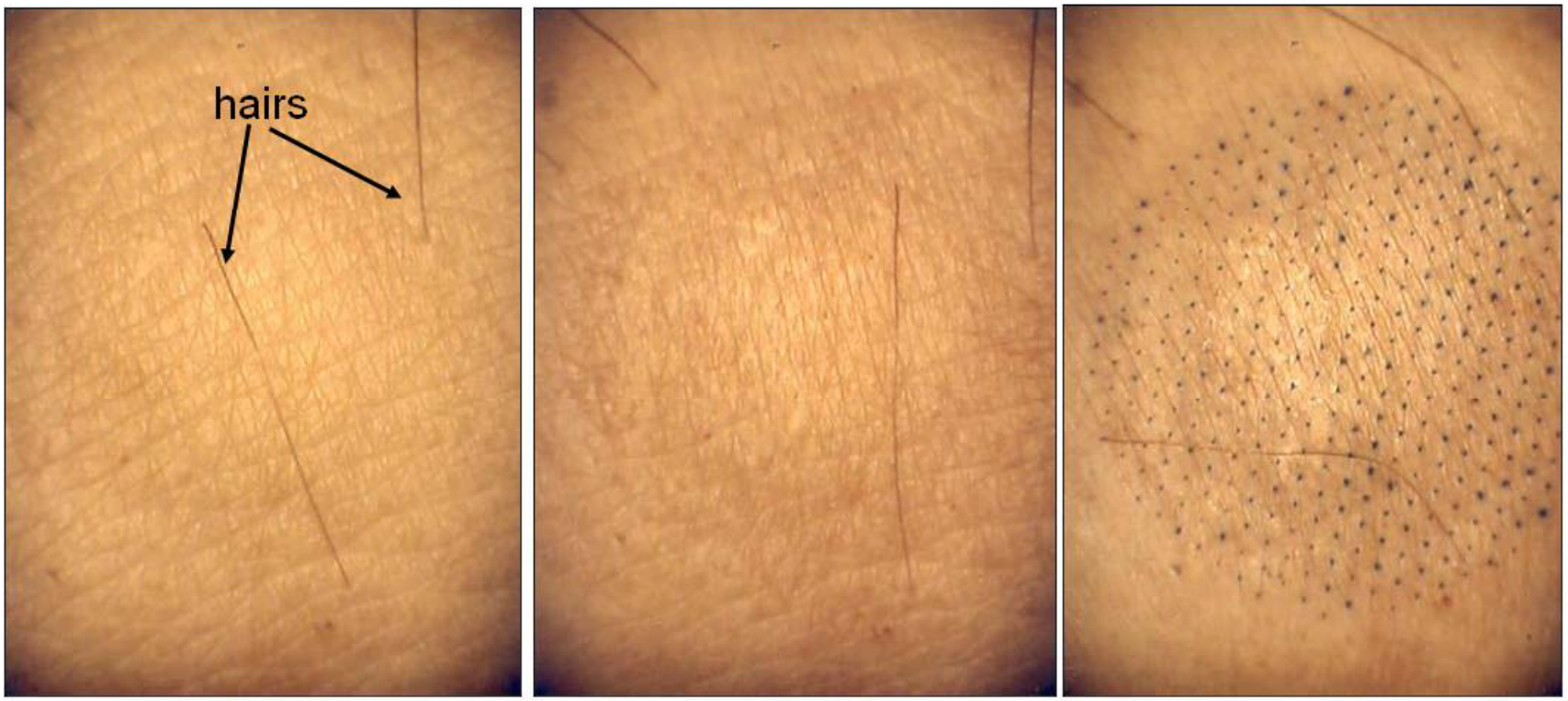
Patch in Applicator – Press to Apply

Skin Penetration is Controlled by Microprojection Length and Applicator System



5 s application from dip-coated ^{14}C-OVA microprojection arrays

Microneedle Patch Application on Human Subjects Is Well-tolerated and Efficient

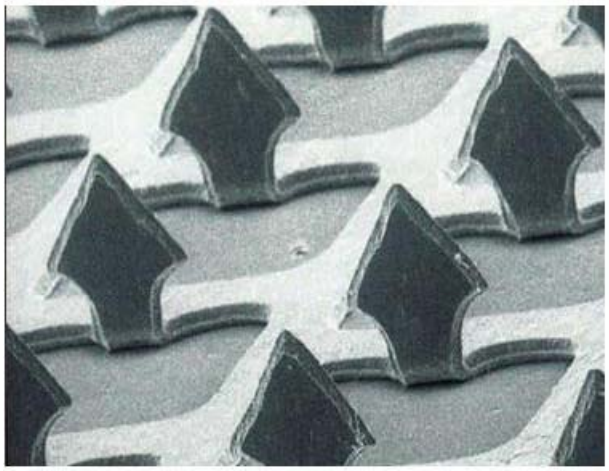


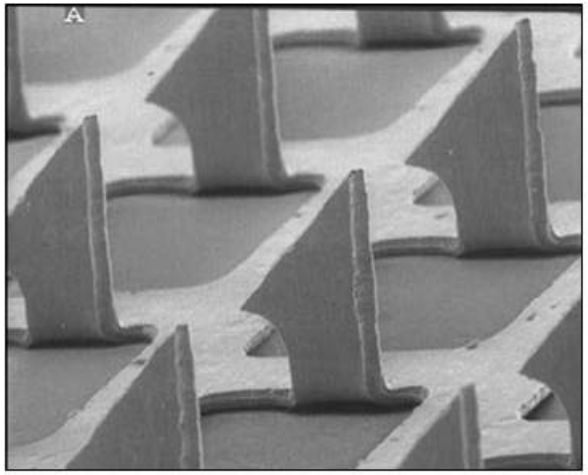
Pre-treatment | Post-treatment | Methylene blue stained

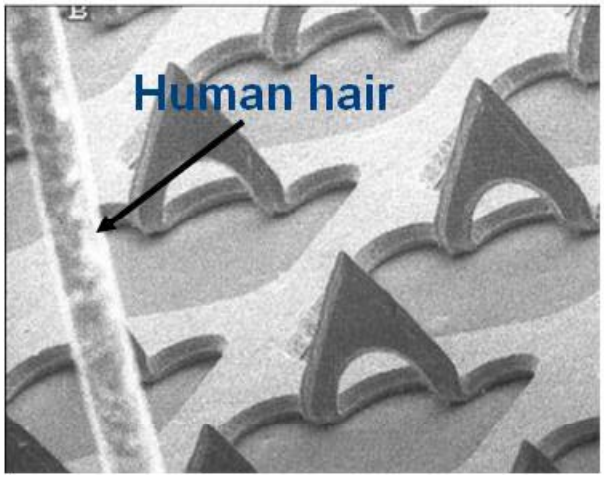
Solid Metal Microneedle Arrays can be Fabricated to Different Sizes, Shapes, and Densities

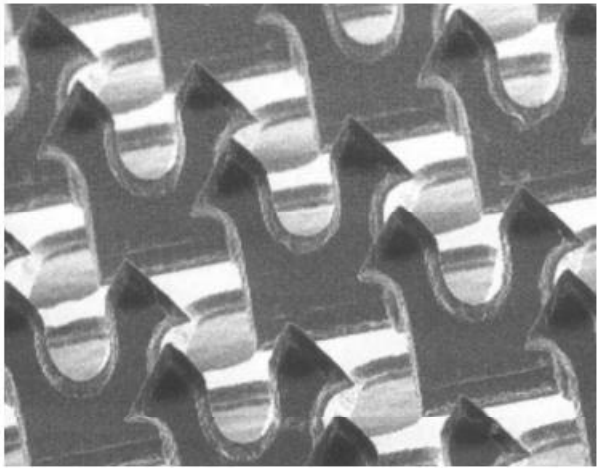
Process:

- Photochemical machining / contact lighography
- Can be scaled to continuous web
- Options for better dimensional control ??
- Options for improved forming tools ??





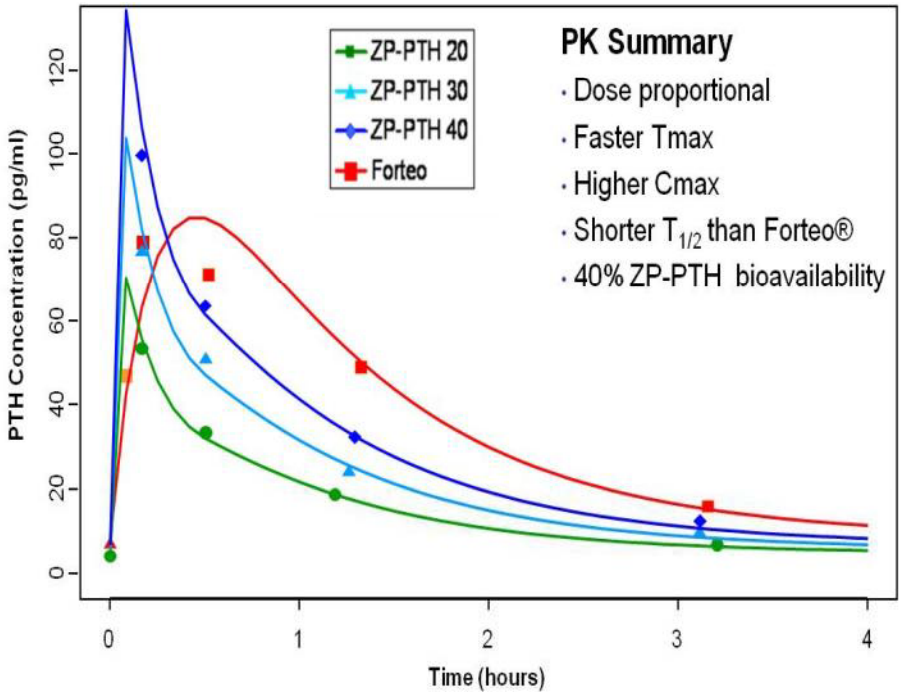


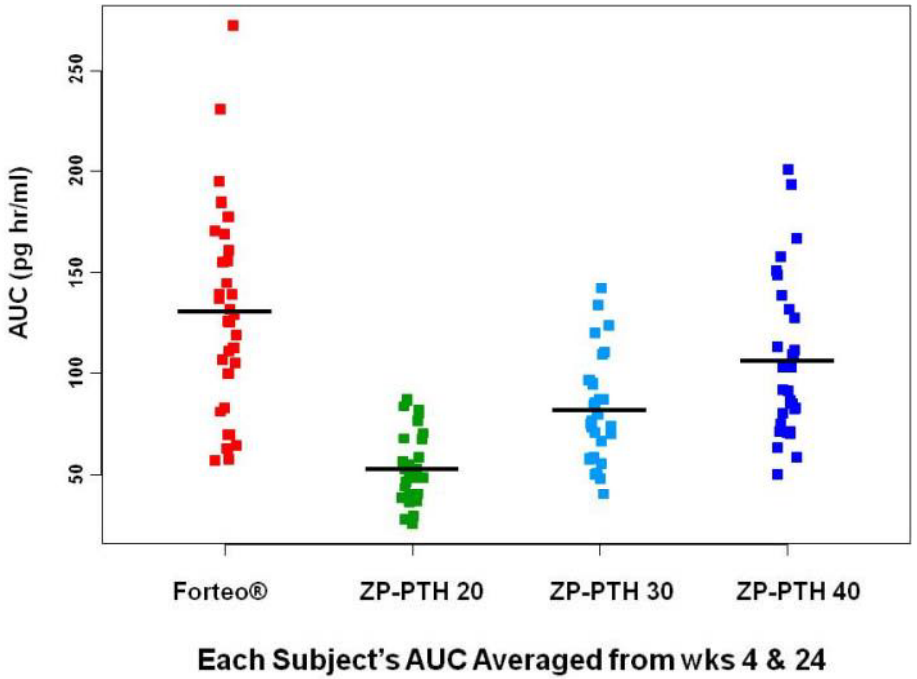


Zosano PTH Patch Clinical Program

- Extensive Phase 1 program completed to
  - Ensure tolerability
  - Investigate human PK
  - Optimize patch design (projection length & shape)
  - Select optimal patch application site
  - Select range of doses for Phase 2
- Successfully completed Phase 2, 6-month BMD study comparing 3 patch doses to both placebo and Forteo
- Phase 3 one-year BMD study planned for registration

Phase 2 Data in PMW with Osteoporosis Shows ZP-PTH Provides Rapid Pulse and Dose Proportional Delivery



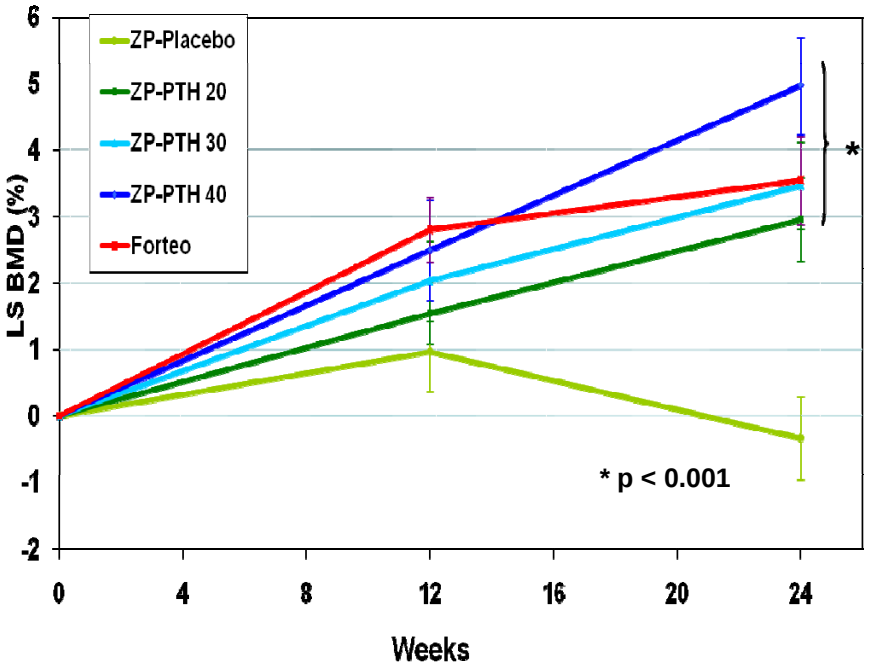


- Patch dose proportionality demonstrated
- Patch delivers faster Tmax, higher Cmax, shorter half life than Forteo injection
- AUC dose variability is comparable to Forteo
- Bioavailability of coated dose administered is ~40% = ~16mcg

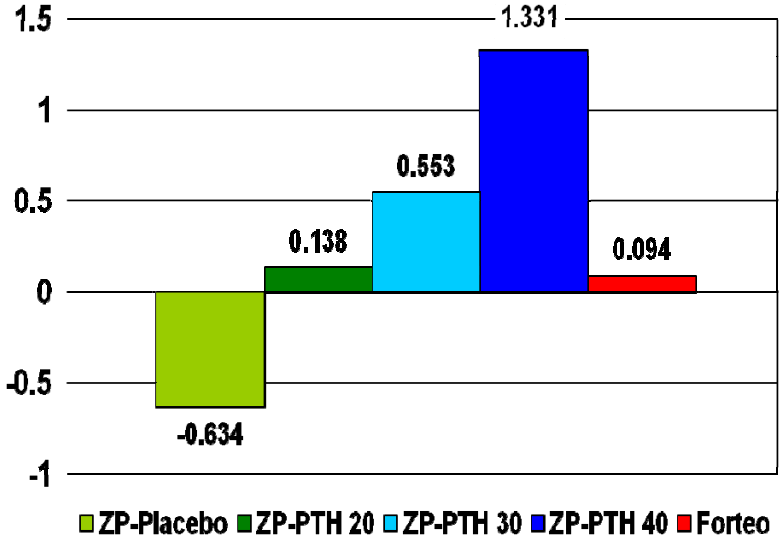
Lane et al, ACR/AHRP Ann Scientific Meeting, Oct 24-29, 2008

Following 24 weeks of treatment all active treatment groups increased BMD greater than placebo

Percent Change from Baseline in LS-BMD (Mean +/- SE)



Percent Change From Baseline Total Hip BMD



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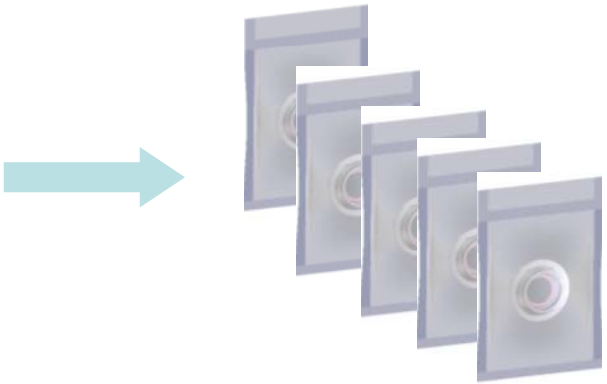
Volume Manufacturing Capability



- **Automated aseptic patch coating and packaging equipment**
- **Automated forming and assembly of patches subassemblies**
- **Phase 1-3 clinical supply production capacity**
- **Highly scalable process for commercial manufacturing**

Zosano Transdermal Patch Technology

- Ideal solution for delivery of large and small hydrophilic drugs
  - No molecular size limitation
- Change/improve PK profile / PD outcome
- Simple therapeutic drug delivery
  - High patient acceptance, user friendly, and travel friendly
- Cost effective, alternative to outpatient injection

<u>Additional benefits:</u>

- Ready-to-use drug-coated patch with reusable or disposable low cost patch applicators
- Life cycle management
- Potential elimination of cold-chain (no product refrigeration required)
- Short patch wear time (<1hr); Rapid drug delivery
- Band-Aid like patch removal and disposal