Drug Delivery Devices
A Market Perspective and Technology Discussion

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Outline

1. The Incumbents
2. What are the Value Drivers?
3. The Evolving Landscape – how to explore it
4. Novel Drug Delivery Technologies Discussion
5. Concluding Remarks

Prefilled Syringes and Cartridges In Auto-injectors and Pens Dominated the Recent Past

Since the mid-2000s: over 80+ launches of PFS based fixed dose single use auto-injectors

Cartridge based systems growing mainly through Insulin, but also other TAs (typically multiple doses per container)

Rise of biologics in many new therapeutic areas provided impressive growth

Communalities: standard primary containers, mainly self-injecting patients, a spring or the user delivers the dose, clear regulatory pathway, existing fill/finish and device assembly infrastructure (equipment, CMOs)

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PFS Based Auto-injectors Have Grown Tremendously Over the Last 1.5 Decades

- First US launches in 2006 for Enbrel and Humira
- Since 2006 many new therapeutic areas embraced the technology
  - RA
  - Dermatology (Psoriasis & atopic Dermitis)
  - MS
  - GI (UC and Crohn’s)
  - Dyslipidemia
  - Anti-migraine
  - GLP-1
  - Anti-obesity

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Cartridge Based Pen Injectors Showed Significant Growth Driven By Diabetes, Other TAs and Geographic Expansion

- Usually multiple doses per cartridge/device
- Market keeps transitioning to pen injectors for Insulin and other indications like
  - GLP-1s for diabetes or weight management
  - Fertility treatments
  - Human growth hormones
  - Osteoporosis
  - Hep C

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Note: So-called Wearable or On-body Injectors Are Evolving as a Device Solution For SC Delivery Of Large Volumes

- Some biologics feature high doses and volumes
- Supported by trend to move IV infusions to SC administrations
- Less mature technology but features a few product launches
  - Repatha (Amgen)
  - Neulasta (Amgen)
  - Furosemide (SC Pharmaceuticals)
  - Ultomiris (Alexion)

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Proven Technologies Have Advantages, but What's Next?

- We established the advantages of beforementioned systems, but where could they possibly fall short? Examples:
  - Little genuine differentiation among auto- or pen injectors
  - Not all users are comfortable self-injecting with needles
  - Limited enabling capabilities, i.e., non-invasive routes of delivery, high viscosity drugs, suspensions, targeted delivery, large volumes….
- Hypothesis: those devices may just not always be sufficient to reap the full potential of an asset

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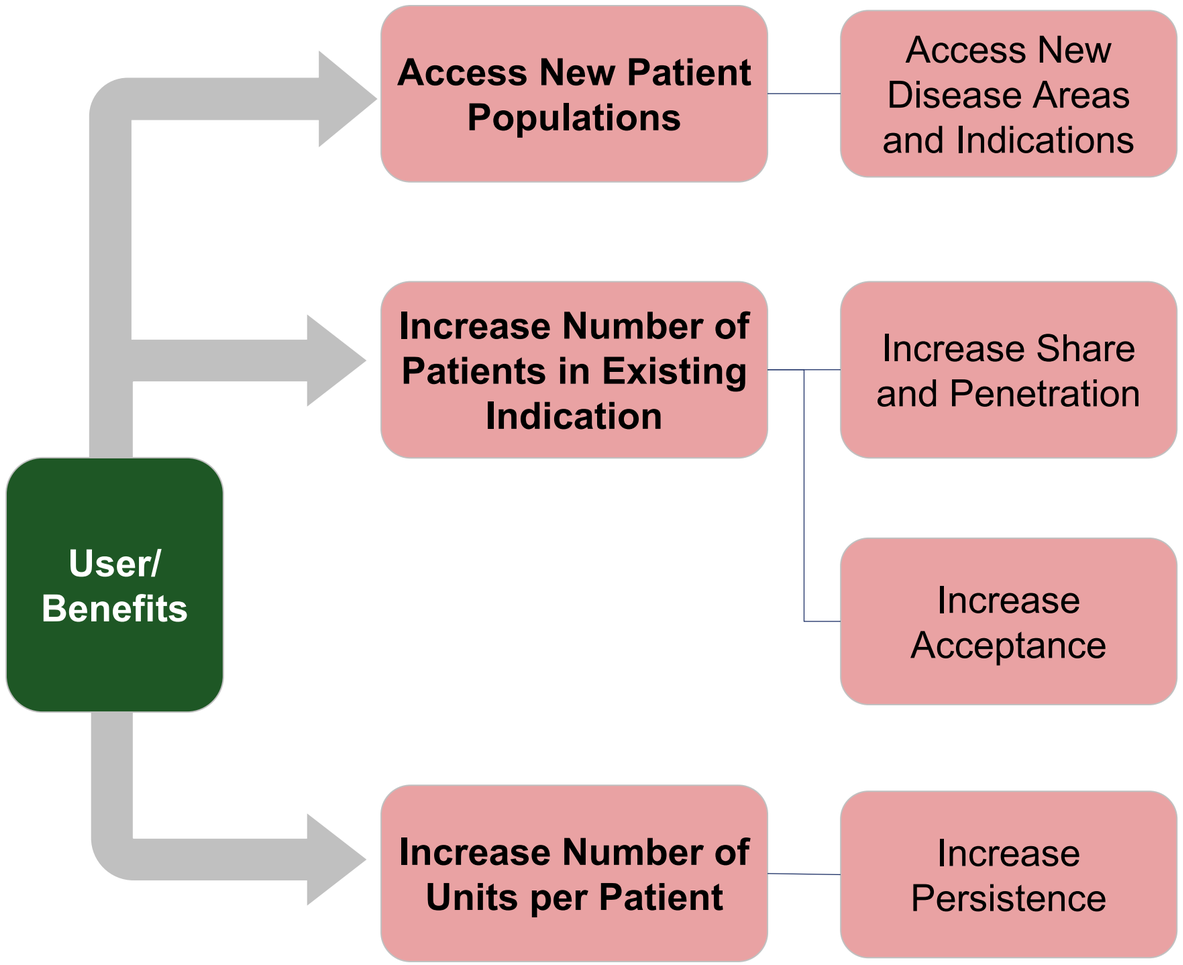
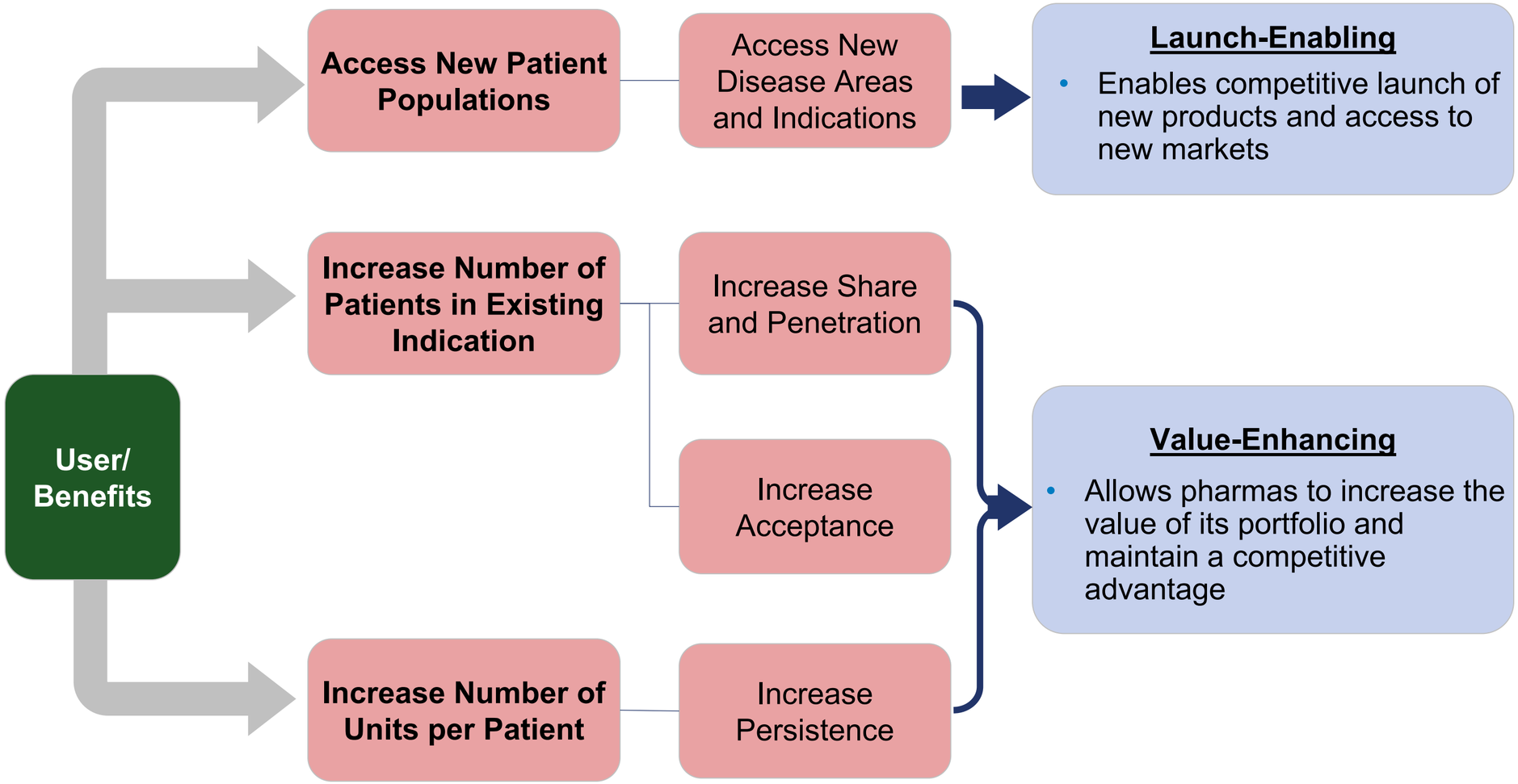
Value Drivers of Drug Delivery



- Access new disease areas and new indications
- Increase penetration into an existing on-label indication (physician driven)
- Increase pharmas' share of the class
- Increase acceptance in existing on-label indication (patient driven)
- Increase in the number of doses for the existing and new patients on pharmas' products through:
  - Increased adherence
  - Increased compliance

Addressing Needs Will Enable Pharmas to Launch New Products or Enhance the Value of Existing Products



Drug Delivery Technologies Can Address Patient Needs Through Device and / or Product-Enhancement Solutions

Device Solutions	Product-Enhancement Solutions	Combination Device / Formulation Solutions
• Broaden volume capacity • Broaden viscosity capacity • Reduce needle size/ remove needle • Reconstitute lyophilized therapeutics • Enable patient self-administration	• Increase concentration • Improve half-life and stability • Advance therapeutic index • Achieve the desired distribution (e.g., organ vs. systemic)	• Deliver to the desired location (e.g., organ, cell) • Adjust delivery timing (e.g., sustained release vs. fast delivery)

Insights Generated During "Proof of Concept and Value" Will Either Drive Investment or Help Refine Perspective

INSIGHT

Evolving Tech Landscape Perspective

- Prioritize technology based on:
  - Ability of technology to drive value for pharma
  - Maturity of technology

Qualify for POC & V

Proof of Concept and Value (POC&V)

- Assess technology based on:
  - Value proposition
  - Technical feasibility
  - Manufacturability
  - Clinical feasibility (if appropriate)

STRATEGIC ACTIONS

Implementation Investment

Implementation for specific Asset(s)

- Technology is ready for implementation; clear business case

Development Investment

Pharma allocates funding / resources to technology development

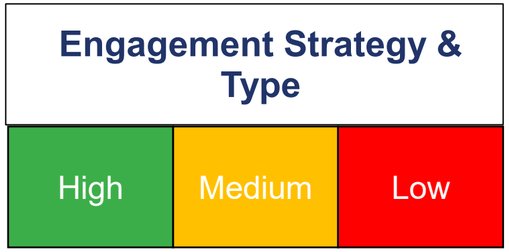
- Technology not mature enough to implement, but highly compelling, and pharma can drive development

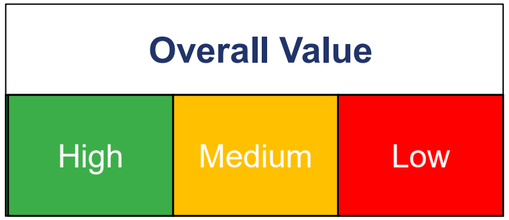
Refine Perspective

No immediate investment

- Insight gained from POC&V incorporated into evolving technology landscape perspective

Drug Delivery Technology Profile: Definitions





Value to Pharma

- **Value Proposition:** Driver for potential pharma investment given the technology:
  - Overcomes key challenges with current therapies
  - Enables a competitive commercial presentation for launch or LCM
- **Potential Range of Impact:** Potential $ impact for pharma if the technology was able to meet the value proposition perfectly; analysis is based on:
  - Number of assets that may benefit from the technology from the visible and / or early-stage portfolio
  - Impact based on risk-adjusted projected **global sales** for the visible portfolio
  - Comparable products where appropriate
  - Impact based on **global revenue estimates for comparable products**
- **Imperatives:** Drug Delivery imperatives that the technology can address
- **Applicability:** Assets from drug portfolio that may benefit from the technology

Key Technology Barriers

- Barriers that may prevent the full capture of the $ impact and / or applicability of the technology

Promising Solutions / Companies, Timing and Investment

- **Solution / Suppliers:** Companies / institutions with promising platforms
- **Investment:** Relative level of investment (e.g., low, moderate, high) in addressing the technical barriers

Examples

Definitions of Imperatives

Imperative	Description	Example Solution
Localize delivery when there is an efficacy or safety benefit	Use new technology to reach effective concentrations without systemic administration	Intraocular or pulmonary delivery
Support flexibility for site of care	Simplify administration so that it can move from hospital to clinic, clinic to office, and/or office to home	Allow for SC delivery for previously IV administered drugs
Improve cost-effectiveness of therapy delivery	Reduce cost with new device or lower payload through optimized RoA	Use higher volume handheld device vs. wearable injector
Minimize preparation requirements	Simplify use for HCP or patient to reduce time required and chance of errors	Use dual chamber device instead of reconstitution kit for lyo drug
Make administration portable	Reduce product size and/or simplify travel with room temperature stability	Room temperature stability available for XX weeks
Consider monthly dosing for self-admin SC injectables	Reduce frequency for Q2W dosing, without increasing the payload required for Q2M+ dosing	Monthly dosing vs. weekly or bi-weekly
Limit injectables to single administration event per dose	Eliminate use of more than one device during self-administration	Use 2 or 3 mL autoinjector for higher dose
Reduce pain and intimidation of administration	Improve administration experience to increase patient acceptance and extend patient persistence	Reduce “sting” of formulations; i.e., microneedles to address perception of pain
Minimize dosing duration while maximizing tolerability	Limit patient’s time required during administration without increasing pain of administration	Reduce duration large volume delivery using wearable injectors

To Meet The Growing Complexities of The Portfolio, Pharma Should Address Several Imperatives Across the **Drug Delivery Value Continuum**

Broaden Range of Targets and Modalities	Enable Dose Administration by Intended User	Drive Efficiency	Improve access & Increase new patient starts	Improve Persistence
	Minimize preparation requirements			
Localize delivery when there is an efficacy or safety benefit for the portfolio, e.g.: • Solid tumor • Intraocular • Pulmonary • Cardiac tissue		**Improve cost-effectiveness** of therapy delivery	**Optimize dosing/administration** • Consider less frequent ***dosing*** for self-administered SC injectables • Achieve ***competitive dosing schedule*** for non SC products • Limit injectables to ***single administration*** event per dose • ***Minimize dosing duration*** while maximizing tolerability	
	Support flexibility for site of care			• **Reduce pain** and intimidation of administration • Make administration **portable** • Enable patient to **independently administer therapy**, when appropriate

Launch-Enabling → **Value-Enhancing**

Assess A Broad Range of Device Technology Segments for Ability to Meet Needs / Gaps in Pharma's Portfolio

Example Device Technology Segments

Subcutaneous Injectors

- Disposable & reusable handheld
- Multi-dose pens
- Wearable injectors
- Dual phase reconstitution
- Continuous infusion

Subcutaneous Injector Components / Add-ons

- Actuator technology (drive mechanism)
- Primary container (rigid & non-rigid)
- Needle, i.e., thin wall, safety needle
- Temperature control / lockout
- Dose viability indicator
- Sensed feedback
- Connectivity

Non-hypodermic

- Microneedle
- Needle-free

Non-subcutaneous RoA

- Pulmonary
- Pericardial
- Intrathecal
- Intraocular
- Buccal
- Oral
- Intranasal
- Transdermal

Implantable

- Eluting polymers
- Micromachine / microchip

Example Needs Addressed

Intuitive Use

- Minimize complexity
- Augment patient's intuitive understanding with IFUs

Enabling Proper And Consistent Execution

- Administer therapy in safe and effective manner
- Enable a consistent experience every time

Confident Completion

- Confirm dose delivery
- Provide clarity around device removal (if required), and disposal or storage post-use

Patient Perceptions of Pain, Discomfort, Intimidation

Minimal Disruption to Activities Of Daily Living

How Will We Prioritize Technology Categories?

Segment
- Category

EXAMPLE TECHNOLOGY SEGMENTS

Subcutaneous Injectors

- Disposable handheld
- Multi-dose pens
- Dry drug reconstitution
- Continuous infusion

SC injector components / add-ons

- Actuator (drive mechanism)
- Primary container
- Needle
- Temperature control / lockout
- Dose viability indicator
- Sensed feedback
- Connectivity

"Non-hypodermic" Delivery Device

- Microneedle
- Needle-free/jet stream

Implantable

- Eluting polymers
- Solid dose implantable device
- Micromachine/ micro-chip (implantable)
- Actively implantable delivery system

Non-SC RoA

- Pulmonary
- Pericardial
- Intrathecal
- Intraocular
- Buccal
- Oral delivery for biologics
- Intranasal
- Transdermal

Nanoparticle

- Drug-encapsulating nanoparticles (polymeric micelles, block copolymers, liposomes, solid lipid, nucleic acids)
- Drug-coated Inorganic nanoparticle
- Nanocrystal (e.g., fluorescence) / Q-dots
- Nanotube
- Micro-molding

Protein Crystallization

- Crystallizations (including tech scale-ups)
- Crystal Suspensions

Complexes/ Excipients

- Novel Non-covalent
- Covalent modification/ targeting
  - Antibody-drug
  - Antibody-Antibody
  - Peptide-Antibody
  - Stapled Peptides

Polymeric

- Eluting Polymer
- Hydrogels
- Prodrugs/PEGylation

Other

- Microspheres
- Hydrophobic salt excipients
- Novel dry powders
- Edible electronics

Device Focused → **Formulation-Focused**

Different Technology Categories Represent Value to Pharma with Different Potential Likelihood of Success (1)

Technology Segment	Technology Benefits	Imperative(s) Addressed	POS**
Crystallization (incl. tech scale)	• Concentrates product (e.g., 3 mL Q1M dose to <2 mL)	• Minimize dosing duration while maximizing tolerability; minimize preparation requirements • Limit injectables to single administration event per dose • Consider monthly dosing for self-administered SC injectables	High
Drug-encapsulating nanoparticles	• Extend half-life • Potentially enable localized delivery	• Achieve competitive dosing schedule for non SC products	*Moderate*
Novel non-covalent complexes/ excipients	• Enhances solubility/ stability to support increased concentrations	• Make administration portable • Limit injectables to single administration event per dose	*Moderate*

** POS defined as likelihood of technology to capture value

Different Technology Categories Represent Value to Pharma with Different Potential Likelihood of Success (2)

Technology Segment	Technology Benefits	Imperative(s) Addressed	POS
Hollow microneedles	• Eliminate use of hypodermic needles	• Reduce pain & intimidation of administration	*High*
Actuator (drive mechanism)	• Support AI delivery of highly concentrated and/or viscous formulations	• Consider monthly dosing for self-administered SC injectables • Improve cost-effectiveness	*Moderate*
Resorbable drug-eluting polymers	• Sustained release at site of injection/delivery	• Localize delivery when there is an efficacy or safety benefit	*High*
Dry drug reconstitution	• Simplification of reconstitution by patient	• Minimize preparation requirements	*Moderate / High*
Pulmonary delivery	• Minimize systemic distribution while delivering to lung	• Localize delivery when there is an efficacy or safety benefit	*Moderate*
Intraocular delivery	• Launch intravitreal product with commercially attractive dosing regimen	• Localize delivery when there is an efficacy or safety benefit • Achieve competitive dosing schedule for non SC products	*Moderate*
Localized cardiac delivery	• Minimize systemic distribution while delivering to heart	• Localize delivery when there is an efficacy or safety benefit	*Moderate*

DISCUSSION

The Key Challenges addressed by Microneedle Technology includes Administration Pain and Anxiety associated with Needle Injections

Key Challenge: Pain and anxiety associated with needle injections

Description of Technology Solutions

Device technology that reduces administration pain and intimidation associated with needle injections by eliminating needles and / or reducing needle length

Scientific / Biological Barriers

Feasibility of non-hypodermic needle device to deliver drugs across the top layer of the epidermis (i.e., stratum corneum)

Investment to Address Barriers

Low-moderate given investment likely to focus on feasibility vs. new development activity

Clinical Timing of Solution

< 5 years

Microneedles

Example: Pharma may consider developing microneedle technology addressing the imperative intimidation of administration of self-injectables

Engagement Strategy
Qualify for PoC/V

Overall Value
High

Value to Pharma

- **Value Proposition:** Enhance value and maintain competitive advantage of self-injectable assets by overcoming administration pain and intimidation associated with needle-based injections
- **Potential Range of Impact:** ~$XXXm
- **Pharma Imperatives:** Reduce pain and intimidation of administration
- **Applicability:** any assets that are known to benefit from a technology that reduces self-administration pain and anxiety

Key Technology Barriers

- Variable kinetics / dynamics / bioavailability (vs. SC)
- Limited delivery volume (e.g., <2mL for hollow microneedles)
- Some degree of inability to deliver high viscosity
- Unknown wear-ability
- Potential for increased immunogenicity associated with intradermal vs. SC delivery
- May enhance pain assoc. with formulation
- Manufacturing concerns (e.g., primary container)

Promising Solutions / Companies, Timing and Investment

- **Solution / Company:** A handful of companies appear to have a promising platform that addresses many technical barriers associated with microneedles
- **Investment:** Low-moderate investment to overcome technical barriers

Microneedle Subtypes Include Hollow Microneedles and Novel Dissolving Microneedles

Technology Overview

Array of small needles (e.g., micrometers in length) that delivers a drug into the transdermal / intradermal space without penetrating the subcutaneous layer of the skin

Key Technical Attributes

Molecule type: Small and large molecule drugs (e.g., proteins, mAbs)

ROA: Intradermal

Delivery: Systemic and local

Volume: < 2mL (hollow microneedles)

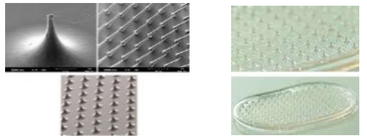
Sub-Types*

Hollow Microneedles
Delivers a liquid formulation through a single microneedle or multi-needle array; may use novel surface-modifications (e.g., nanotopography)

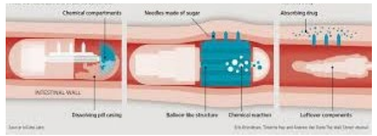
Kindeva - Hollow MTS with on body reservoir

KC – Nanotopography microneedle

Novel Dissolving Microneedles Introduces drug embedded within biodegradable polymer into the transdermal space and/or other anti-parenteral ROA (e.g., oral)



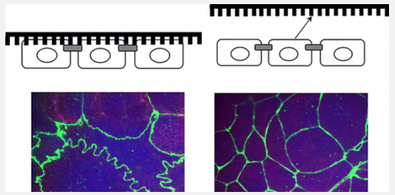
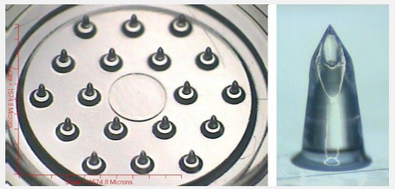
MicroHyala



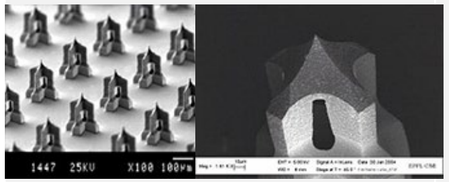
Rani Therapeutics

**Other microneedle subtypes exist, but have limited applicability for delivering large molecules*

Selection of Companies that may have Promising Technologies to enable Clinical and Commercial Use of Microneedles (1)

Microneedle Technology Companies	Delivery Sub-type	Platform	Strengths	Weaknesses
Sorento Therapeutics 	Hollow microneedles	Sofusa nanotopography microneedles	• Novel nanotopography mechanism enabling drug delivery across opened tight junctions • Opening tight junctions may enable enhanced drug delivery via paracellular transport • Potential to deliver high drug volume (e.g., >2mL)	• May require long wear time (e.g., 60 – 90 min) • Does not use a standard primary container and may require redesign for manufacturability
Kindeva 	Hollow microneedles	Hollow microstructured transdermal system (hMTS)	• Hollow microneedle device with standard primary container that can deliver >1mL	• May still have meaningful administration pain (with select formulations); potential for reduced patient usability with size / shape of the device

Selection of Companies that may have Promising Technologies to enable Clinical and Commercial Use of Microneedles (2)

Microneedle Technology Companies	Delivery Sub-type	Platform	Strengths	Weaknesses
Debiotech 	Hollow microneedles	Debioject microneedle platform	• Novel microneedle with unique side protected delivery hole; sharp MEMs-fabricated needles that reduce pain associated with skin puncture and drug delivery; lumen efficiency for reduce driving pressure requirement	• Limited clinical validation and no commercial products
Rani Therapeutics 	Hollow microneedles	‘Robotic’ pill with dissolvable sugar microneedles	• Microneedle injection in the small intestine with minimal to no drug admin. pain	• Novel concept in earlier stages of development with limited scientific validation of feasibility
Nanopass 	Hollow microneedles	MicronJet needle array that attaches to the end of a syringe	• Low cost and can be used with any standard syringe	• Limited clinical validation and may introduce an incremental device preparation step (e.g., attaching the needle array to the syringe)

Additional Microneedle Subtypes include Solid Microneedle Arrays, Drug-coated, and Single Microneedle Platforms

Significant volume constraints; re-formulation may be required for these technologies

Microneedle Sub-Types

Device technology that reduces administration pain and intimidation associated with needle injections by eliminating needles and / or reducing needle length

540 Needle Microneedle roller

Solid microneedle array: Increases skin permeability before and / or during topical drug delivery

Zosano ZP patch

Drug-coated microneedles: Disperse drug molecules coated on the microneedle surface into the transdermal space

BD's Soluvia microneedle

Single microneedle platform: Prefillable microinjection system using a single microneedle to deliver drug or vaccine intradermally

An Example for established non-invasive Drug Delivery: Nasal Drug Delivery is such Technology with further Growth Potential

Aptar Pharma's Single Use Platform serves a variety of TAs

- Value Proposition: needle free and non-invasive drug delivery
- The Addresses multiple drug delivery imperatives
- Opportunity for device customization leveraging existing technology





Zomig ® | Imitrex™ | Tosymra™ | Nayzilam® | Nascobal® | Narcan® | Valtoco® | Spravato™ | Glucagon | Nasal Vaccines

ASTRAZENECA | gsk GlaxoSmithKline | UPSHER-SMITH Partners in Health Since 1919 | ucb | endo Pharmaceuticals | emergent biosolutions | NEURELIS | janssen

Concluding Remarks (1)

- Established drug delivery technology might be the existing standard, but pharmas may miss out across their portfolios if they don’t understand and introduce novel innovative technologies
- It is key to comprehend the value proposition of such technologies for a variety of stakeholders, their maturity and technology barriers – Pharma should categorize drug delivery technology on an on-going basis, and act accordingly on the insights generated
- A lot of such novel technologies are evolving, we could only discuss a few of them today. However, not all promising technologies will be commercialized

Concluding Remarks (2)

- Many of the reviewed technologies are regulated as combination products. It is mandatory to understand i.e., quality management requirements and design controls to operate in/enter that area
- For small or mid-sized pharmas this may mean to move into the world of combination products. Often it will be novel to adjust their quality management systems and manage design history files etc.
- Finally, the case is made here that it will be worth for pharmas to stay on top of new innovations that can be applied to maximize value for all stakeholders across the board

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