Preliminary Competitive Intelligence Landscape Report for Duchenne Muscular Dystrophy

By

Abhay Gupta

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2017-2019

The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Sanganer, Airport
Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

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IIHMR UNIVERSITY

TO WHOMSOEVER IT MAY CONCERN

This is to certify that **Mr. Abhay Gupta,** student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone dissertation at **PharmaACE Innovations LLP, Pune, from 3rd Feb 2019- 4th May 2019.**

The Candidate has successfully carried out the study designated to him during dissertation and his approach to the study has been sincere, scientific and analytical.

The Internship is in partial fulfilment of the course requirements.

I wish his all success in all his future endeavours.

Dean of Pharmaceutical Management

The IIHMR University, Jaipur

Professor

The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141- 3924700, 2791431- 32, Fax: 0141 3924738, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

PharmaACE

The certificate is awarded to

Mr. Abhay Gupta

In recognition of having successfully completed his internship in the department of

Market Research

And has successfully completed his project on

"Preliminary Competitive Intelligence landscape report for Duchenne Muscular Dystrophy (DMD)"

3rd May 2019

He comes across as a committed, sincere and diligent person who has a strong drive and zeal for learning.

We wish him all the best for his future endeavors!

For PharmaACE Innovations LLP

Rashi Chawla

HR Lead

Blueridge Qubix, SEZ, IT-5, Ground Floor, Phase 1, Hinjewadi, Pune - 411057

The IIHMR University, Jaipur

CERTIFICATE BY SCHOLAR

This is to certify that the Dissertation Project titled Preliminary Competitive Intelligence Landscape report for Duchenne Muscular Dystrophy (DMD), submitted by **Mr. Abhay Gupta** Enrolment No. **MBA-PM-0089** under the supervision of **Mr. Dinesh Pandey (Project Head)and Mr. Amit Pharande (Engagement Manager)** for award of MBA in Pharmaceutical Management of the University carried out during the period from **4th Feb 2019 to 4th May 2019**embodies my original work and has not formed the basis for the award of any degree, diploma associateship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Signature: Abhay Gupta

14/05/2019

Acknowledgement

The satisfaction and euphoria that accompany the successful completion of the project would be incomplete without mentioning of the people who made it possible.

I Humbly owe the completion of summer intern work to the almighty and my family whose love and blessings will be with me in every moment of my life.

I would like to extend my sincere and heartfelt thanks to Mr. Dinesh Pandey, Business Project Head for providing me an opportunity to learn and develop professionally.

I would like to thank Mr. Amit Pharande, Engagement Manager at PharmaACE Innovations LLPfor constant support and guidance in every step which helped me to understand pharma market easily.

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I would like to thank all those who directly or indirectly helped me to complete this project work.

At last but not the least, most importantly I am thankful to the god who is the creator and director of all that initial and final modes to reach the destiny.

ABHAY GUPTA

List of Abbreviations

DMD	Duchenne Muscular Dystrophy
MOA	Mechanism of Action
ROA	Route of Administration
i.e.	That is
USA	United States of America
Ex-NA	Other than North America
ROW	Rest of the world
EU	Europe
FDA	Food & Drug Administration
IV	Intravenous
CRL	Complete Response Letter
Q1,Q2…	Quarter 1, Quarter 2….So on
H1, H2	First half year, Second half year
KDa	Kilo Daltons

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Executive Summary

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive genetic disease, mostly affecting boys characterized by progressive muscle degeneration and weakness, caused by an absence of dystrophin, a protein that keeps muscle cells intact.

- **Prevalence:**It is estimated that ~12k boys in the U.S. and >300k worldwideare living with the disease
- **Incidence**: ~1: 5000 males at birth

Boys with DMD usuallydidn't survive beyond their teen years but due to advances in treatment and care, survival into early 30s has become commonwith the average life expectancy of ~26 years.

Inline Marketed Products:

U.S.: Emflaza and Exondys 51 are the only two FDA approvedproducts, however prednisone is used as SOC for the treatment

- Emflazawas FDA approved in Feb 2017 inpatients 5yrs and above, regardless of genetic mutation
- Exondys 51 received FDA approval in Sep 2016 as the first disease-modifying drug for DMD. It is an 'exon-skipping' therapy approved for patients with Exon 51 mutations (~13% of DMD patients)
    - FDA exercised "*flexibility*" in granting accelerated approval for Exondys 51, solely based on a surrogate endpoint, increased muscular dystrophin expression in limited treated patients

Europe: Translarna received conditional approval from EMA in Aug 2014 for DMD patients with non-sense mutation aged 7-18 years. In 2018, Translarna received pediatric expansion for aged 2-5 years. Currently, Translarna is under review by the EMA for a label expansion to include non-ambulatory patients

- DMD patients with non-sense mutation (est. to comprise ~15% of total DMD patients, or ~2,000 patients in the U.S. and 2,500 patients in EU)

- **U.S.:** In Oct 2017, FDA issued a CRL refusing approval (and reiterated their position in Feb 2018). The company has an ongoing Phase 3 trial to provide additional data towards an NDA resubmission, potentially in Q1-2020

Part B:

Novel technologies to deliver Proteins and Peptides

Delivery Technologies

Parameters for Consideration	Implantable Pumps	Injectors	Transdermal	Pulmonary	Sublingual	Oral
MNK-1411 formulation change would be required	✗	✗	✗	✓	✓	✓
Suitable Drug Carriers for MNK-1411	Microparticles, Nanoparticles, Hydrogels	Microparticles, Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels
Delivery route	Implants or patch	SC, IM, ID	Transdermal patches	Inhalation	Buccal (sublingual)	Oral
Controlled/ sustained release	✓	✓	✓	✗	✗	✓
Developmental Cost	$ ↑	$ ↑	$ ↓	$ ↑	$ ↓	$ ↓
Patient Compliance	High	Medium	High	High	High	High
Examples	DUROS device	Bydureon BCise	Viador	Technosphere technology platform has also been used to deliver salmon calcitonin	Exenatide (under development)	Robotic pill of insulin (under development)

Use of new delivery route alone may not give it a required edge over other cosyntropin, but combining it with the novel drug carriers might help in obtaining a long-term patent protection (due to increase in complexity of the technology)

Research Objectives

- Part A: To identify the marketed and Pipeline products for Duchenne muscular products and based on their attributes to identify the impact of entry of product in market
- Part B: To suggest the novel delivery technologies options available to deliver proteins and peptides having 24 or more amino acids and can be given to DMD patients.

Research Methodology

Study Design

The research Conducted was Descriptive Research.

Study Selection

The selection area of sample is throughout the world for clinical trial, but focus is restricted to USA market.

Data Collection

All the data was collected from secondary sources

1. Clinical Trials.gov
2. AdisInsights
3. Company Websites
4. SEC filings and Presentations
5. Published Articles, Associations
6. Journals, Review Articles, Clinical Studies
7. PubMed

Time Period

Data was collected and interpreted between 3rd February 2019 to 3rd May 2019.

Consideration: No Article and clinical trial is considered prior to 2014.

Research Instrument (Tool & Techniques)

Research Instruments was Excel consisting of model if Impact analysis based on attributes. The information was collected through secondary sources and referred sources like Clinical trials.gov Adis Insights, company websites, Sec filing etc.

Data Analysis

The gathered data was entered into a form Presentation. Impact analysis on basis of different attributes was calculated on the Excel based model and interpretations are entered in final report.

Part A: Disease Overview

Duchenne Muscular Dystrophy

- Inherited X-linked, muscle-wasting disorder
- Characterized by progressive loss of mobility, pulmonary insufficiency, cardiomyopathy and premature death
- Patients with DMD are usually diagnosed before age of 5
- By the age of 12 they start using wheelchair and most don't survive their mid-20's with average life expectancy of ~26yrs

Causes and Symptoms

- Duchenne muscular dystrophy (DMD) is caused by mutations in the DMD gene
    - The DMD gene provides instructions for making a dystrophin protein
    - Because of an error in the genetic instructions, production of dystrophin protein is disrupted, which can result in DMD
    - Without dystrophin, muscle cells are damaged, and over time, are replaced with scar tissue and fat in a process called fibrosis
- **Inheritance**: The DMD gene is located on the X-chromosome, since males only have one X chromosome, they also only have one copy of DMD gene
- If this copy has a genetic change that causes DMD, the male will have DMD
- **Symptoms**:
    - Calf muscle hypertrophy
    - Cardiomyopathy
    - Cognitive impairment
    - Delayed speech and language development
    - Elevated serum creatine phosphokinase

FIGURE 1: INTRODUCTION TO DMD

Exon Skipping

Exon Skipping is a potential treatment approach to correct and restore production of dystrophin

- For specific genetic mutations it allows the body to make a shorter, usable dystrophin
- Exon skipping is not a cure for Duchenne, but it may make the effects less severe
- No single drug is believed to rescue all mutations
- It is estimated that 13% of Duchenne patients have a mutation amenable to skipping exon 51
- Exon skipping may eventually apply to 60-80% of Duchenne patients

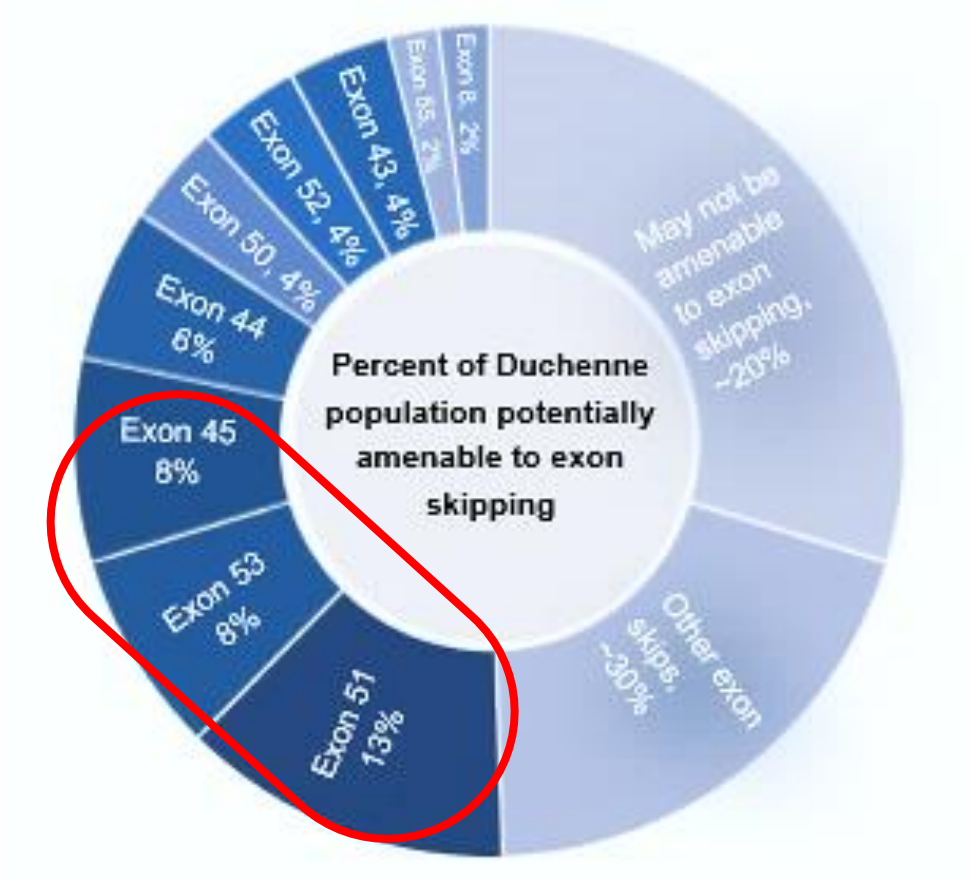


FIGURE 2: PERCENTAGE OF DMD POPULATION POTENTIAL AMENABLE TO EXON SKIPPING

Treatment Paradigm

- **1st line**: Prednisone and Emflaza
- **2nd line**:
  - Exon Skipping: Exondys 51
  - Nonsense mutation: Translarna

Epidemiology

- **Incidence:**1 in 5,000 boys, which are 200 per million male births
- Nearly 12,000 boys are living with the disease in the U.S. alone and >300,000 worldwide

Strategic Insights

- **Unmet Need:**

➢ Current steroid therapies are associated with severe side effects: Need for therapies that show less side effects than steroids

➢ Outcome measures specific to the muscular dystrophy population

Marketed Products

Product	Company	MOA	Price	Annual Cost
Emfalza	Marathon/ PTC Therap.	Steroid receptor agonist	$1,500 (6mg, 30 tab)	~$54,000
Exondys 51	Sarepta Therapeutics	Dystrophin expression stimulants	$1,678 (50mg/ml, 2mL)	~$523,536

Review of Literature

- Straub V., Strehle EM. (2015) conducted a study on topic "Recent advances in the management of Duchenne Muscular Dystrophy". Duchenne muscular dystrophy (DMD) is the commonest inherited neuromuscular disorder of childhood and mainly affects males. Over the course of the last century, the average life expectancy of these patients has doubled and now stands at ~25 years. This progress has been made possible through advances in the diagnosis, treatment and long-term care of patients with DMD. Basic and clinical research, national and international scientific networks, and parent and patient support groups have all contributed to achieving this goal. The advent of molecular genetic therapies and personalised medicine has opened up new avenues and raised hopes that one day a cure for this debilitating orphan disease will be found. The main purpose of this short review is to enable paediatricians to have informed discussions with parents of boys with DMD about recent scientific advances affecting their child's clinical care.
- Mah JK. (2016) titled as "Current and emerging treatment strategies for Duchenne muscular dystrophy" explained as Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy in childhood. It is caused by mutations of the DMD gene, leading to progressive muscle weakness, loss of independent ambulation by early teens, and premature death due to cardiorespiratory complications. The diagnosis can usually be made after careful review of the history and examination of affected boys presenting with developmental delay, proximal weakness, and elevated serum creatine kinase, plus confirmation by muscle biopsy or genetic testing. Precise characterization of the DMD mutation is important for genetic counselling and individualized treatment. Current standard of care includes the use of corticosteroids to prolong ambulation and to delay the onset of secondary complications. Early use of cardioprotective agents, non-invasive positive pressure ventilation, and other supportive strategies has improved the life expectancy and health-related quality of life for many young adults with DMD. New emerging treatment includes viral-mediated micro dystrophin gene replacement, exon skipping to restore the reading frame, and nonsense suppression therapy to allow translation and production of a modified dystrophin protein. Other potential therapeutic targets involve upregulation of compensatory proteins, reduction of the inflammatory cascade, and enhancement of muscle regeneration. So far, data from DMD clinical trials have shown limited success in delaying disease progression; unforeseen obstacles included immune response against the generated mini-dystrophin, inconsistent evidence of dystrophin production in muscle biopsies, and

failure to demonstrate a significant improvement in the primary outcome measure, as defined by the 6-minute walk test in some studies. The long-term safety and efficacy of emerging treatments will depend on the selection of appropriate clinical end points and sensitive biomarkers to detect meaningful changes in disease progression. Correction of the underlying mutations using new gene-editing technologies and corticosteroid analogs with better safety profiles offers renewed hope for many individuals with DMD and their families.

- Leadley RM., Armstrong N. et.all (2017 titled as "The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review" defined the abstract as Duchenne Muscular Dystrophy (DMD) is a rapidly progressive, lethal neuromuscular disorder, present from birth, which occurs almost exclusively in males. We have reviewed contemporary evidence of burden, epidemiology, illness costs and treatment patterns of DMD. This systematic review adhered to published methods with information also sought from the web and contacting registries. The population of interest was individuals with clearly defined DMD or their careers.

Competitive Landscape of Marketed Products

Logo	Company Name	Brand Name	Mechanism of Action	Route of Administration	Location
PTC THERAPEUTICS	PTC Therapeutics	Translarna	Protein Synthesis stimulant	Oral	Europe
SAREPTA THERAPEUTICS	Sarepta Therapeutics	Exondys 51	Exon Skipping	Intravenous	USA
PTC THERAPEUTICS	PTC Therapeutics	Emflaza	Steriod Receptor Agonist	Oral	USA

Attribute Analysis of Marketed Products

Unlike Exondys 51 and Translarna which are targeted towards a sub-population of DMD patients with confirmed mutations (13-15%), Emflaza offers treatment option for the entire DMD patients, at a much lower annual cost

Attributes	Emflaza (deflazacort) 6 mg | 18 mg | 30 mg | 36 mg tablets 22.75 mg/mL oral suspension	EXONDYS 51 (eteplirsen) Inject	translarna ataluren
Company	Marathon/PTC Therapeutics	Sarepta Therapeutics	PTC Therapeutics
Molecule	Deflazacort	Eteplirsen	Ataluren
Mechanism of Action	Steroid receptor agonist	Dystrophin expression stimulants (Gene Therapy)	Protein synthesis stimulants (Gene Therapy)
Target Population	Age: 5 and older Treatment targeted for the entire DMD population	Age: 7 to 16 Patients with confirmed mutation amenable to Exon 51 skipping (~13% of total DMD patients)	Patients (7-18 years) with genetic disorders due to a nonsense mutation (expected to be ~15% of total DMD patients. Pediatric expansion (2-5 year) approved in 2018 in EU Label expansion in EU to include non-ambulatory pts is currently under review
U.S. Approval	2017	2016	Not FDA Approved (in Phase 3) Oct 2017: PTC received CRL from FDA for NDA of ataluren for which PTC filed FDRR 20 Feb 2018: FDA reiterated the it's prior position and denied PTC's

			appeal of the CRL in relation to the NDA for ataluren Ongoing Ph-3: To gather more data towards a potential FDA resubmission in Q1-2020
Price	$1,500 (6mg 30 tab), $3,286 (1 bottle 13mL, 22.75mg/ml oral suspension	$1,678 (50mg/mL, 2mL)	N.A.
Est. Annual Cost	~$54,000	$523,526	N.A.
ROA	Oral	IV	Oral
Frequency and Dosing	QD (0.9 mg/kg/day)	QW (30mg/kg/week)	TID (40 mg/kg/day)
Efficacy	The change in average muscle strength score was significantly greater for the deflazacort (0.9 mg/kg/day dose) group than for the placebo group between baseline and week-12	No significant difference in change in 6MWD between patients treated with EXONDYS 51 vs. placebo, at 24 week In 12 patients with evaluable results, there was a significant increase in dystrophin level (from pre-treatment of 0.16% ±0.12% to 0.44% ±0.43% after 48 weeks of treatment, p < 0.05) The median increase in dystrophin was 0.1% after 48 weeks	There was aimprovement in mean change in 6MWD of 31.3 meters from baseline to week 48 in the ataluren vs. placebo arm (p=0.056) But primary endpoint was NOT met,as didn't reach statistical significance (p≤0.05) Improvements in 'timed function tests' vs. placebo, from baseline to week 48 Time to run/walk 10 meters (better by 1.5 seconds) Time to climb 4 stairs (better by 2.4 seconds) Time to descend 4 stairs (better by 1.6 seconds)

Safety	The most common adverse reactions (≥ 10% for EMFLAZA and >placebo) are: Cushingoid appearance, Weight increased and Central obesity Increased appetite Upper respiratory tract infection Pollakiuria Hirsutism Nasopharyngitis	The most common adverse reactions (incidence ≥35% and >placebo) are: Balance disorder Vomiting	The most common side effects (seen in >5% of patients) are: Nausea and Vomiting Diarrhoea Headache stomach ache Flatulence Side effects were considered as usually mild to moderate in severity

High Impact	Medium Impact	Low Impact

Competitive Landscape of Pipeline Products

Preregistration

Logo	Company	Molecule	Mechanism	Route of	Location

	Name	Name	of Action	Administration	
	Sarepta Therapeutics	Exondys 51	Exon Skipping	Intravenous	Europe
	Sarepta Therapeutics	SRP-4053	Exon Skipping	Intravenous	USA

Phase III

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location
	Catabasis Pharma	CAT-1004 Edasalonexent	NF-kappa B inhibitors	Oral	USA, Canada, Ex-NA
	PTC Therapeutics	Translarna	Protein Synthesis stimulant	Oral	USA, Canada
	University Hospital	Tamoxifen	Estrogen receptor antagonists	Unknown	Switzerland
	Assistance Publique - Hôpitaux de	Nebivolol	Beta 1 adrenergic receptor antagonists	Unknown	Paris, France
	Italfarmaco	ITF 2357	Histone deacetylase inhibitor	Oral	USA, Canada, Ex-NA
	Sarepta Therapeutics	SRP-4045	Exon Skipping	Intravenous	USA, Canada, Ex-NA
	Sarepta Therapeutics	SRP-4053	Exon Skipping	Intravenous	Canada, Ex-NA
	Santhera	Idebenone	Reactive oxygen species inhibitors	Oral	USA, Ex-NA
	University Hospital, Switzerland	L-citrulline and Metformin	AMP activated protein kinase stimulants/ Amino Acis replacements	Oral	Switzerland

Phase II/ Phase III

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location
	Roche	RG6206	Myostatin inhibitors	Subcutaneous	USA, Canada, Ex-NA
	Charite University	Epigallocatechin-Gallate	AMP activated protein kinase stimulants	Unknown	Berlin, Germany
	Peking Union Medical College	Bisoprolol Fumarate with ACE inhibitors	Beta 1 adrenergic receptor antagonists	Unknown	China

	Hospital				
WAVE LIFE SCIENCES	WaVe life Sciences	Suvodirsen (WVE-210201)	Exon Skipping	Intravenous	USA, Canada, Ex-NA

Phase II

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location
NIPPON SHINYAKU CO., LTD.	Nippon Shinyaku	NS-065	Exon Skipping	Intravenous	USA, Canada
TAIHO PHARMA	Taiho Japan	TAS 205	Prostaglandin synthase inhibitors	Oral	Japan
Capricor	Capricor	CAP 1002	Cell Replacements	Intravenous	USA
antisense THERAPEUTICS	Antisense Therapeutics	ATL1102	Antisense inhibitor of CD49d	Subcutaneous	Australia
CUMBERLAND PHARMACEUTICALS	Cumberland Pharmaceuticals	Ifetroban	Thromboxane A2 receptor antagonists	Oral	Unknown
FibroGen	FibroGen	FG-3019	Connective tissue GH inhibitors	Intravenous	USA
	Washington University School of Medicine	Prednisolone	Glucocorticoid receptor antagonist	Oral	USA
Mallinckrodt	Mallinckrodt	MNK-1411	Melanocortin receptor agonist	Intravenous	USA, Ex-NA
ReveraGen BioPharma	ReveraGenBioPharma	VBP-15	Glucocorticoid receptor antagonist	Oral	USA, Canada, Ex-NA
SAREPTA THERAPEUTICS	Sarepta Therapeutics	SRP-9001	Dystrophin expression stimulants	Intravenous	USA
PHRIXUS Pharmaceuticals Inc.	Phrixus Pharmaceuticals	P-188	Blood Cell modulators	Subcutaneous	USA

Phase I/Phase II

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location

	Daiichi Sankyo	DS-5141	Dystrophin expression stimulants	Subcutaneous	Japan
	Cardero Therapeutics	Epicatechin	Mitochondrial protein modulators	Oral	USA
	Milo Biotechnology	AAV1-Follistatin	Myostatin inhibitors	Intramuscular	USA
	CHU de Quebec-Universite Laval	Myoblast transplantation	Cell Replacements	Intravenous	Canada
	Stem Cells Arabia	Bone Marrow-Derived Autologous Stem Cells	Cell Replacements	Unknown	Unknown
	Sarepta Therapeutics	rAAVrh74.MCK.GALGT2	Gene delivery	Intravenous	USA
	Solid Biosciences	SGT-001	Gene delivery	Intravenous	USA
	Sarepta Therapeutics	SRP-5051	Exon Skipping	Intravenous	USA

Phase I

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location
	ARMGO Pharma	ARM 210	Ryanodine receptor Ca release channel modulators	Oral	USA, Ex-NA
	Merck Serono	Rimeporide	Sodium hydrogen antiporter inhibitor	Oral	Europe
	Hadassah Medical Organization	Tamoxifen	Estrogen receptor antagonists	Unknown	Israel
	Nationwide Children's Hospital	Spironolactone	Aldosterone antagonist	Oral	USA
	Medical University of Bialystok	G-CSF/Filgrastim	Granulocyte colony factor stimulant	Subcutaneous	Poland
	Mitobridge	MA-0211	PPAR delta	Oral	USA
	Pfizer	PF-06939926	Gene delivery	Intravenous	USA, Ex-NA

BioLeaders	BioLeaders Corp.	BLS-M22	Anti-myotatin	Oral	Korea

Preclinical

Logo	Company Name	Molecule Name	Mechanism of Action	Route of Administration	Location
TARIX ORPHAN	Tarix Pharmaceuticals	TXA127	Proto-oncogene protein c-mas-1 agonists	Oral	Unknown
akashi therapeutics	Akashi Therapeutics	AT-300	Calcium channel inhibitor	Unknown	USA
Fulcrum Therapeutics	Fulcrum Therapeutics	DMD Therapy	Unknown	Unknown	Unknown
	University of Minnesota Medical School	Muscle stem/progenitor cells	cell replacements	Unknown	Unknown
AUDENTES	Audentes Therapeutics	AT702	Exon Skipping	Unknown	Unknown
AUDENTES	Audentes Therapeutics	AT751	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	SRP-5053	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	SRP-5050	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	SRP-5044	Exon Skipping	Unknown	Unknown
WAVE	Wave Life Sciences	WVE-N531	Exon Skipping	Unknown	Unknown
WAVE	Wave Life Sciences	DMD therapies	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	CRISPR/CAS9	Gene therapy	Unknown	USA
AUDENTES	Audentes Therapeutics	AT753	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	SRP-5045	Exon Skipping	Unknown	Unknown
SAREPTA	Sarepta Therapeutics	SRP-5052	Exon Skipping	Unknown	Unknown
exonics THERAPEUTICS	Exonics Therapeutics	CRISPR gene editing	Gene therapy	Unknown	Unknown
Novo Biosciences Unlocking Our Regenerative Power	Novo Biosciences	MSI-1436	Protein tyrosine phosphatase	Intravenous	USA

			inhibitor		
	Children's Hospital	Jagged1 protein	Utrophin activator	Unknown	USA
	Genethon	DMD Program	Gene therapy	Unknown	Unknown
	Tivorsan Pharma	TVN-102	Utrophin activators	Unknown	Unknown
	InnoBioscience	IB-DMD	NF-kappa B inhibitors	Oral	USA
	Wyss Institute at Harvar	IL-4 nanoparticles	Anti-inflammatory cytokine	Intravenous	USA
	University of Ottawa	EGFR producing Gene	Gene therapy	Unknown	Canada
	MyoGene Bio	SPY-DYS	Gene therapy	Unknown	Unknown
	Avidity Biosciences	DMD therapy for patients with mutations in exons 44 and 45	Antibody oligonucleotide conjugate	Unknown	Unknown
	Evox Therapeutics	Engineered Exosomes	Unknown	Unknown	Unknown
	The University of Western Australia	Taurine	Amino acid	Oral	Australia
	Binghamton University	Exon skipping or micro-dystrophin gene therapy	Exon Skipping	Unknown	Ex-NA
	University of Missouri School of Medicine	CRISPR gene editing	Gene therapy	Intravenous	USA
	UT Southwestern Medical Centre	CRISPR gene editing	Gene therapy	Unknown	USA

Attribute Analysis of High Impact Pipeline Assets

Attributes	Mallinckrodt Pharmaceuticals	catabasis	ReveraGen BioPharma	SAREPTA THERAPEUTICS
Company	Mallinckrodt	Catabasis	ReveraGen	Sarepta
Molecule	MNK-1411	CAT-1004	VBP-15	rAAVrh74.MHCK7.GAGLT2
Mechanism of Action	Melanocortin receptor agonist	NF-kappa B inhibitors	Glucocorticoid receptor antagonist	Gene Delivery
Phase	**Phase 2** (NCT03400852) Recruiting, Dosed first patient in Aug 2018	Phase 3 PolarisDMD pivotal trial (NCT03703882) recruitment ongoing	**Phase 2b (NCT03439670)** (Registration trial, recruiting)	**Phase 1/2a** (NCT03375164). In 2019, Sarepta plans to commence a confirmatory trial with commercial material
Patient number (n)	132	125	120	24
Region	U.S., Ex-NA	U.S., Canada, Ex-NA	U.S., Canada, Ex-NA	U.S.
RoA	SC	Oral	Oral	IV
Dosing	Twice a week	Three times a day	QD	One-time therapy
Orphan Drug Designation	Yes (U.S., EU)	Yes (U.S., EU)	Yes (U.S., EU)	No
Fast track designation	Yes	Yes	Yes	No
Est. U.S. Launch	Q4-2024	Q3-2021	H2 2021	Q1-2022

Assessment of Future Impacts to DMD Market

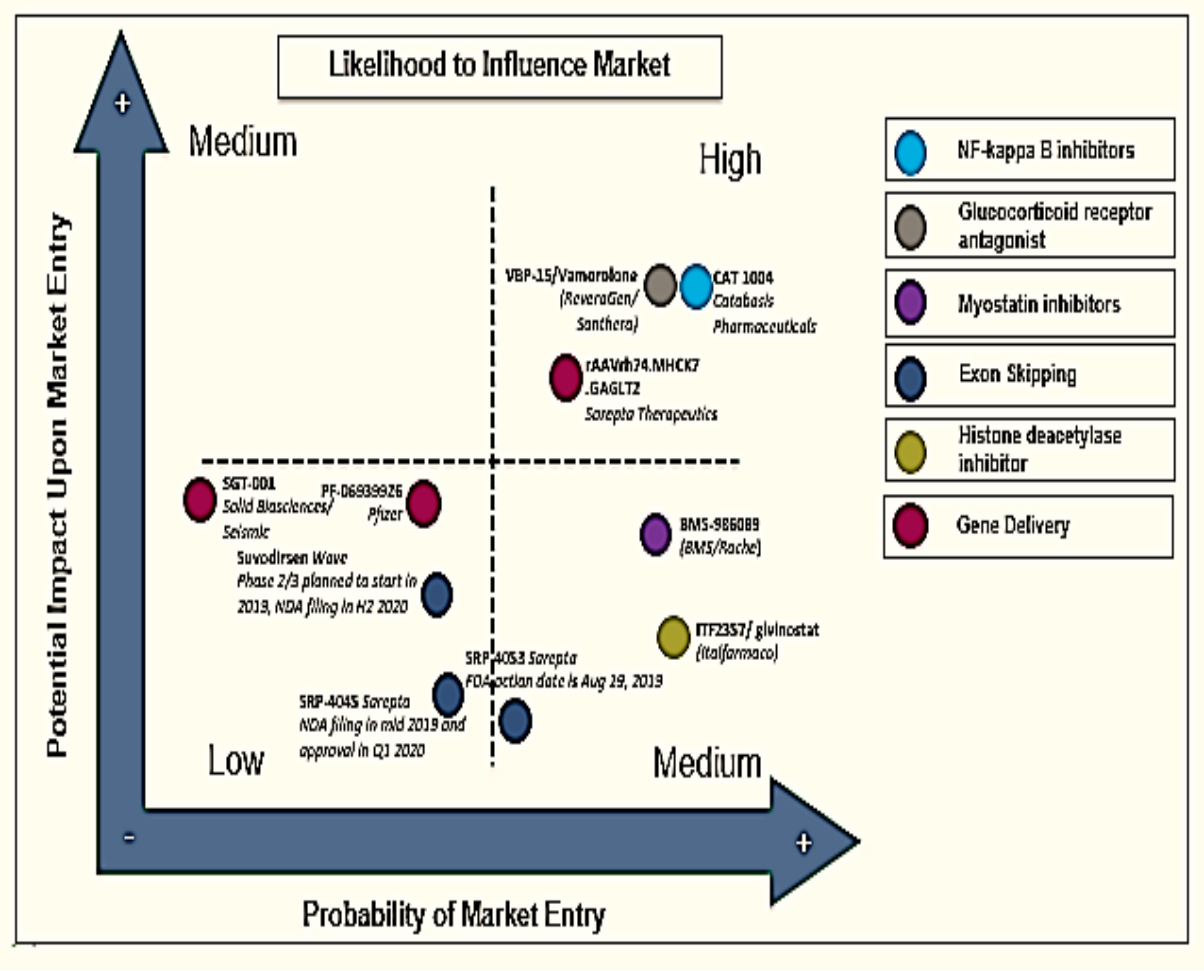


FIGURE 3: POTENTIAL IMPACT UPON MARKET ENTRY

Line of Therapy

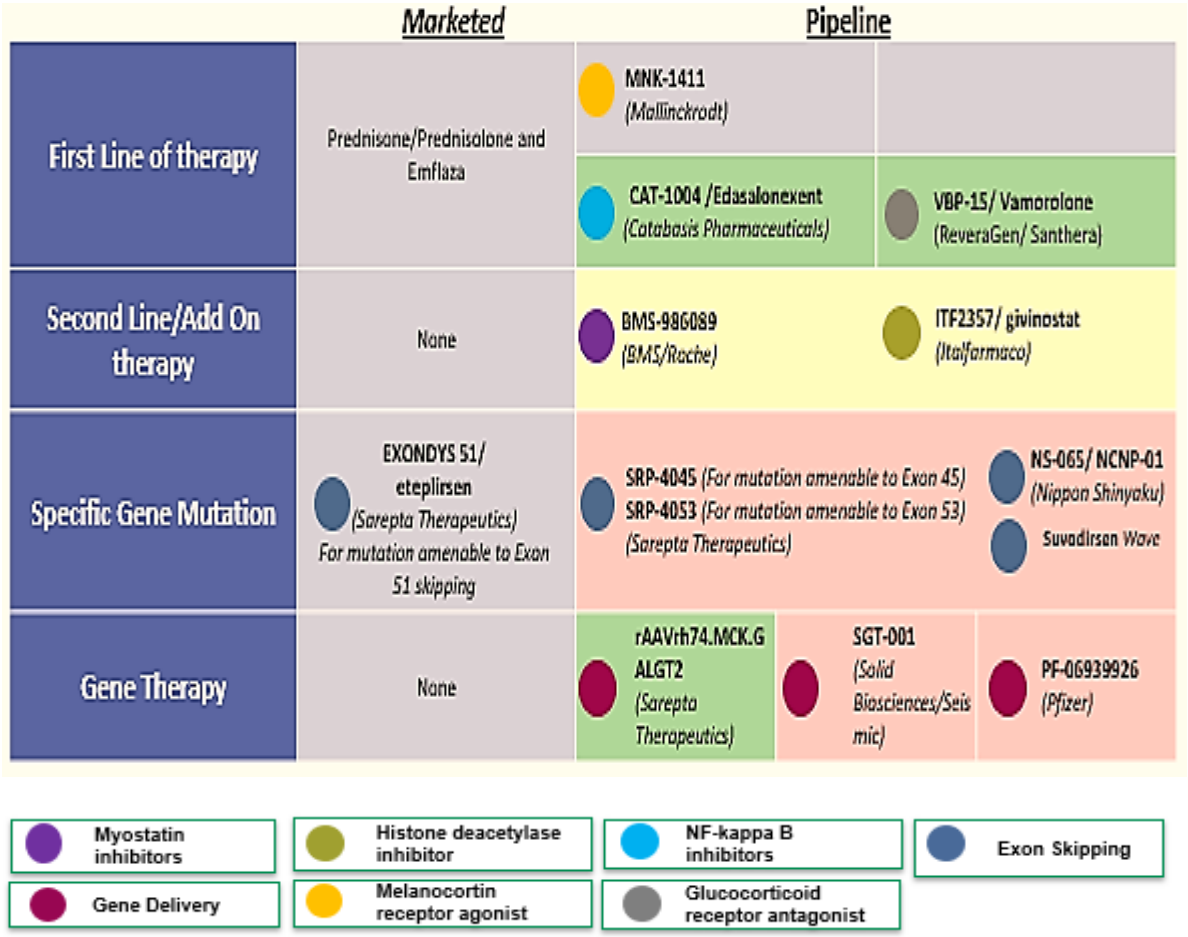


FIGURE 4: LINE OF THERAPY

Potential Order of Entry

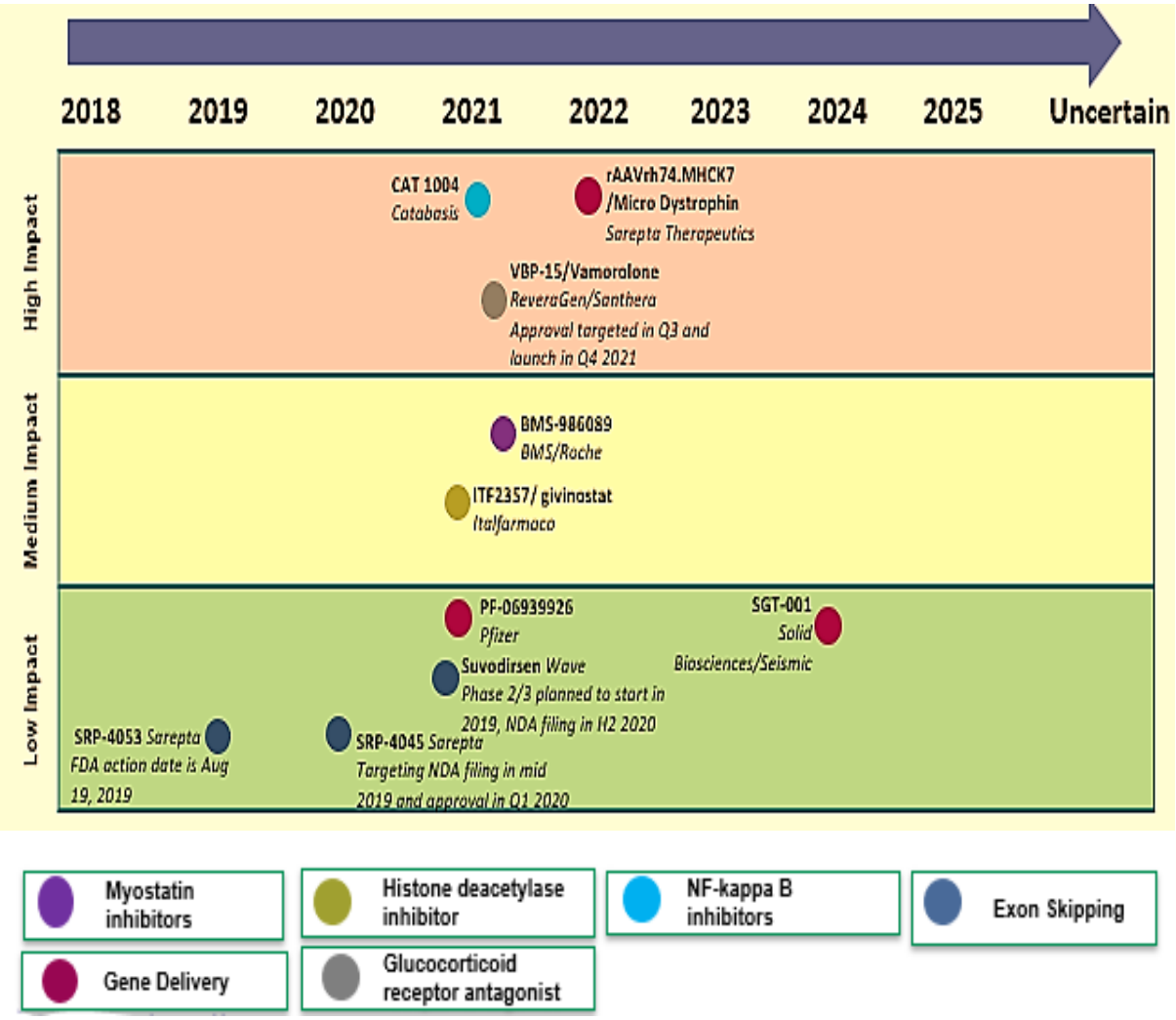


FIGURE 5: POTENTIAL ORDER OF ENT

Part B: Novel Delivery Technologies options to deliver proteins and peptides in DMD patients

Objective: To suggest the novel delivery technologies options available to deliver proteins and peptides having 24 or more amino acids and can be given to DMD patients.

Transdermal Drug Delivery

- A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream
- **Example:**Trivarion Buffered Iontophoretic Delivery Kit restricted to the delivery of molecules with a molecular weight of ~10–15 kDa
- Basic components of transdermal system: Polymer matrix or matrices (Natural and Synthetic polymers and Synthetic elastomers), release liners, backing laminate, drug, penetration enhancers and other excipients (Plasticizers and solvents)

Advantages

- Transdermal medication provides safe, convenient and pain-free self-administration for patients
- Transdermal drug delivery provide a constant rate of release of medicine to maintain concentration level of drug for a longer period of time
- Transdermal patches improved therapeutic effect of various drugs by avoiding specific problems associated with drugs such as pre-systemic metabolism, formation of toxic metabolites, low absorption, etc
- Transdermal systems are generally inexpensive and economic when compared with other therapies
- The general acceptability of transdermal products by patients is very high
- Provide relatively large area of application in comparison with the buccal or nasal cavity

Types of transdermal delivery systems

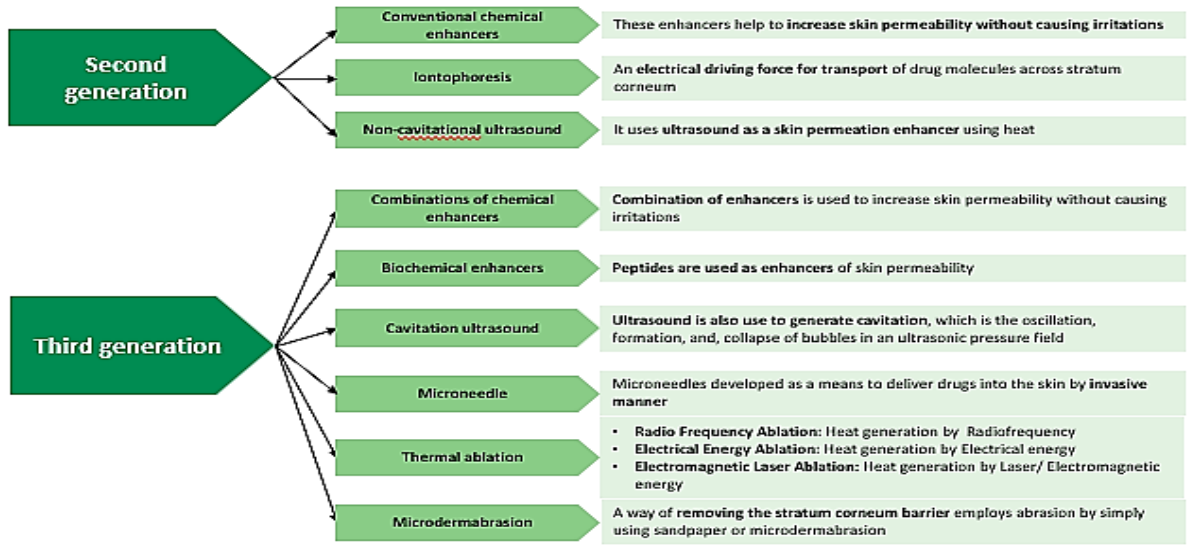


FIGURE 6: TYPES OF TRANSDERMAL DRUG DELIVERY TECHNOLOGIES

Thermal ablation: Technology works on the principle of creating micropores using different forms of energies to deliver the drug

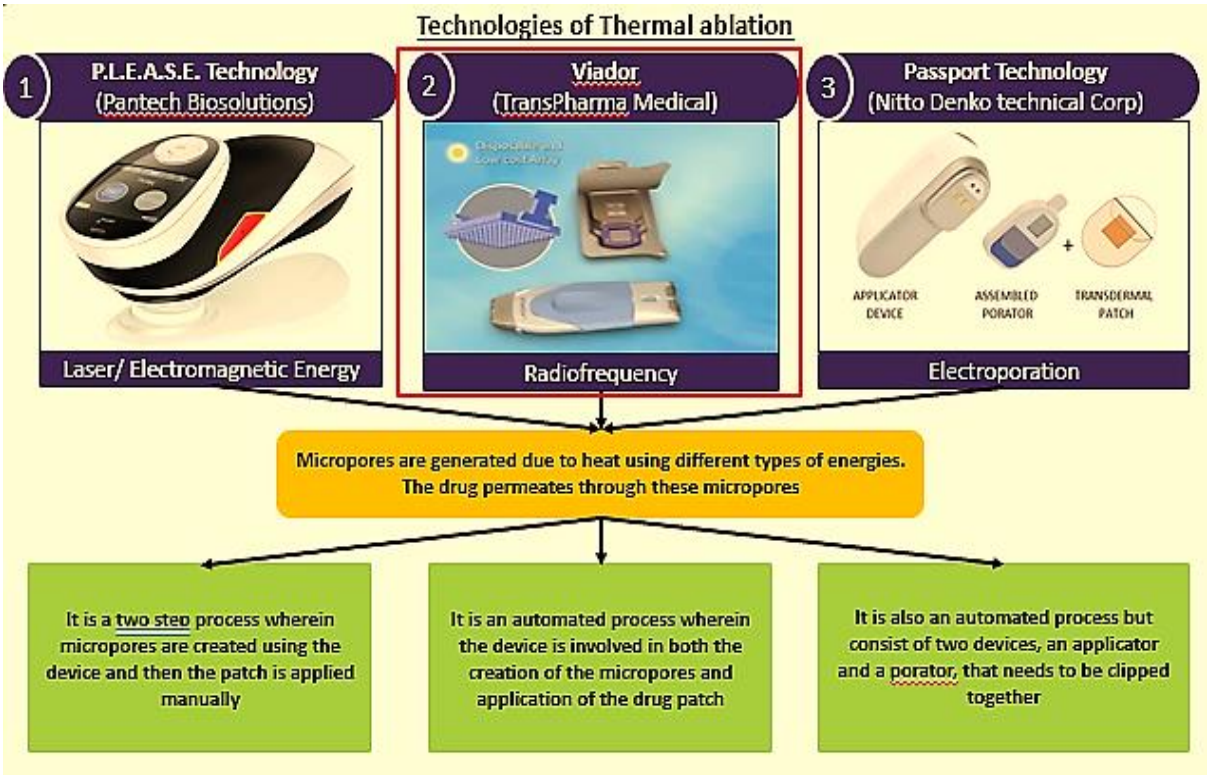


FIGURE 7: DIFFERENT TYPES OF THERMAL ABLATION TECHNIQUES WITH EXAMPLES

- **Iontophoresis:** ActivaPatchIntelliDose 2.5 is a highly intelligent, microprocessor controlled, self-powered iontophoresis patch. The flexible and low-profile ActivaPatch contours to multiple anatomical treatment sites, and a single patch can deliver a 40mAmp min or 80mAmp min treatment in approximately 2.5 hours
- Patented Shunt Technology: The ActivaPatch LED will automatically turn off at the end of 80mA minute treatment. The patch can then be removed from the skin

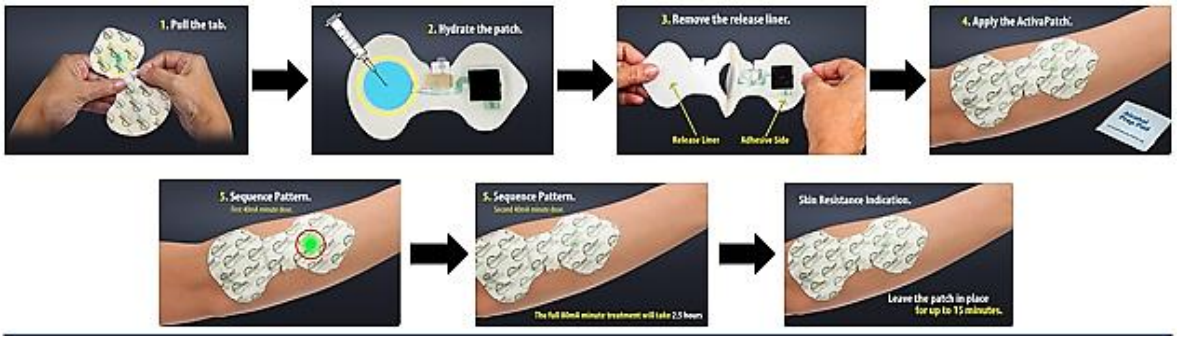


FIGURE 8: TECHNIQUE OF IONTOPHORESIS

If the LED begins to flash once every 30 seconds, then skin resistance has lowered to acceptable range and treatment has begin. If this does not occur within 15 minutes, skin resistance is too high to be treated with ActivaPatch. In these cases, the ActivaDose II Iontophoresis Delivery Unit and a quality wired Iontophoresis electrode such as the Trivarion should be used to treat the patient

Implantable Pumps

- Implanted infusion pumps are small devices placed under the skin during surgery
- The pump sends liquid medicine through a thin, flexible tube (catheter) to a specific part of the body
- It provides targeted and consistent delivery of the medicine and is used when patients need long-term medicines or fluids3
- **Example:DUROS device** is a subcutaneously implantable osmotic pump that has been shown to deliver uniform levels of therapeutic peptides and proteins. DUROS devices have successfully delivered therapeutic molecules as small as 1.2 kDa and as large as 25 kDa

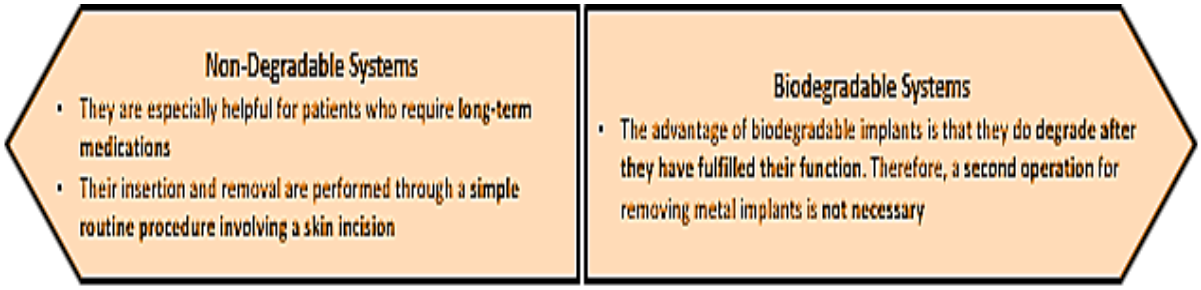
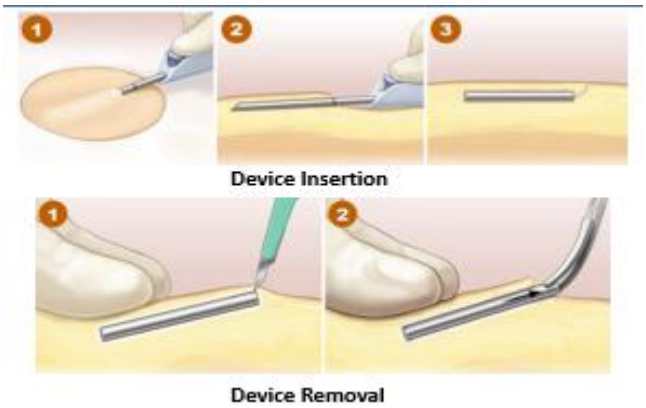


FIGURE 9: TYPES OF IMPLANTABLE PUMPS

Advantages

- Improved efficiency
- Small dose is sufficient to elicit the action. For example, progesterone 2–8 mg
- Reduced side effects
- On-spot delivery
- Provide linear delivery for long periods of time, from a few weeks to many months
- Plasma drug levels are continuously maintained in a therapeutically desirable range
- Continuous small amounts of drug may be less painful than several large doses
- Implantable pumps is relatively less expensive and results into less wasting of the drug
- Insulin pump makes delivery of bolus insulin easier
- Insulin pump eliminates unpredictable effects of intermediate- or long-acting insulin

Duros Implantable Pump



- The DUROS delivery system is comprised of a small, matchstick-sized osmotic pump that is inserted subcutaneously (just beneath the skin) to deliver a slow and consistent flow of medication
- Each device contains an appropriate volume of drug to treat a patient for a predetermined extended duration of time
- The DUROS device is activated when subcutaneous tissue fluid passes through the device inlet, expanding the osmotic engine
- The osmotic engine drives the piston at a constant rate, delivering consistent drug levels through the device outlet
- The device can be inserted in a subcutaneous space in various locations on the arms and abdomen in as little as five minutes by a physician and ensures 100 percent patient adherence to therapy

Injector

- Injectors are designed to provide an accurate method of injecting a dose of drug/biological product contained in a cartridge, reservoir, or syringe through an automatically or manually inserted hypodermic needle or a high velocity jet injector
- They are intended for use by a healthcare provider or for self-administration by a patient/caregiver
- Example: Byetta pen and BydureonBCise autoinjector used in type 2 diabetes mellitus

Type of Use	Description
Single-dose	Entire injector and primary container closure or drug container is discarded after a single use
Disposable	Injector can be used more than once for a single patient only with the same primary container closure or drug container in place and is discarder after the drug container is empty
Reusable	Injector can be used more than once for a specified single patient only with replaceable primary container closure or drug container
Other	Any other unique type-of-use or intended user conditions

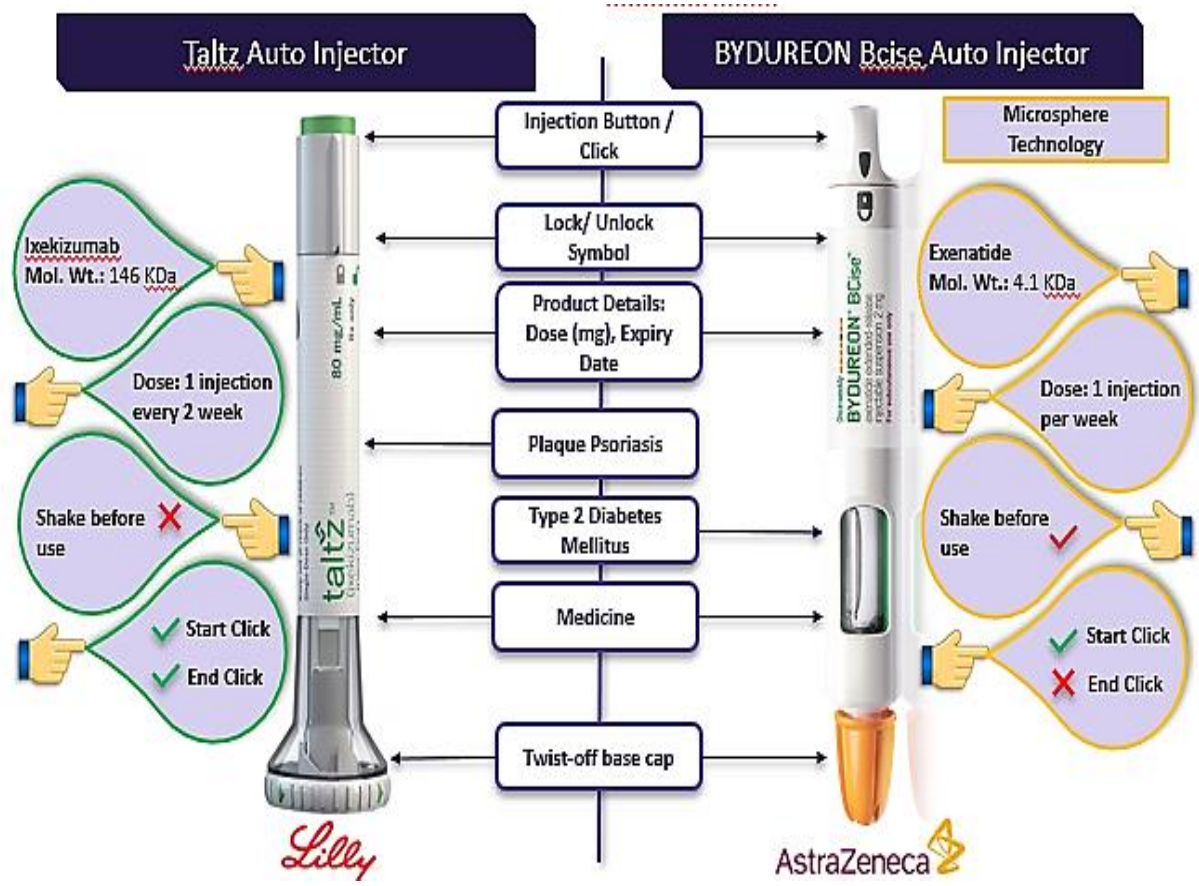


FIGURE 10: ATTRIBUTES OF TALTZ AND BYDUREON INJECTORS

Wearable Injector:

Company	Device	Drug Container	End Dose Indication	Adhesive layer	Usage	Mobile app based
BD	BD Libertas	Primary drug container	Yes	-	Single use	Yes
Subcuject	Subcuject	Prefillable cartridge	No	Manual	Single use	No
SONCEBOZ	Sonceboz drug delivery platform	Single primary container Dual cartridge container Automatic reconstitution injector	No	Manual	Single use	Yes
YPSOMED	YpsoDose	Ready-to-fill cartridge	Yes	Manual	Single use	Yes
enable injections	Enable Smart enFuse	Syringe and vial filing, Reconstitutional filling system	No	Automated	Multiple use	Yes
West	SmartDose Gen III	Prefillable cartridge	Yes	Manual	Single use	Yes

Pulmonary Delivery System

- Targeting drug delivery into the lungs has become one of the most important aspects of systemic or local drug delivery
- The delivery of protein drugs through the pulmonary route has been achieved
- Example: Technosphere technology platform has also been used to deliver salmon calcitonin (sCT) and parathyroid hormone (PTH) by inhalation. Both of these peptide drugs are approved for the treatment of osteoporosis

Nebulizers

Inhalers

Advantages

- Its use to achieve systemic absorption of the administered drug substances
- Particularly for those drug substances that exhibit a poor bioavailability when administered by the oral route, as for example peptides or proteins, the respiratory tract might be a convenient port of entry
- Provides rapid drug action and reduces the dose
- Allows for a reduction in systemic side-effects

Examples: AeroEclipse (Nebulizer); Aerogen()Vibrating Mesh technology Nebulizer); Technosphere (Dry powder inhaler); Aradigm (Nanoparticle Liquid formulation inhaler)

Sublingual Delivery System

- Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth
- **Example:** Exenatide biobetter by Biolingus is under development

Advantages

- A relatively rapid onset of action can be achieved

- Improved patient compliance due to the elimination of associated pain with injections
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption
- Fast dissolution or disintegration in the oral cavity, without the need for water or chewing

Types of Sublingual Drug delivery System

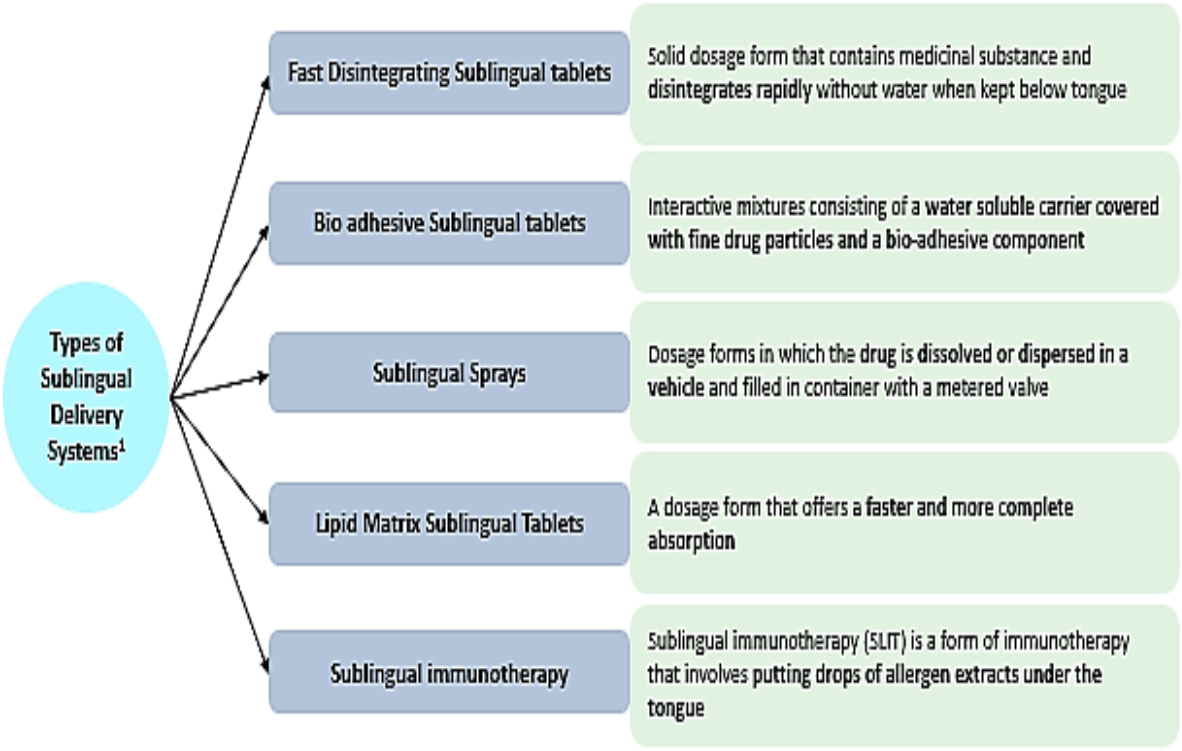
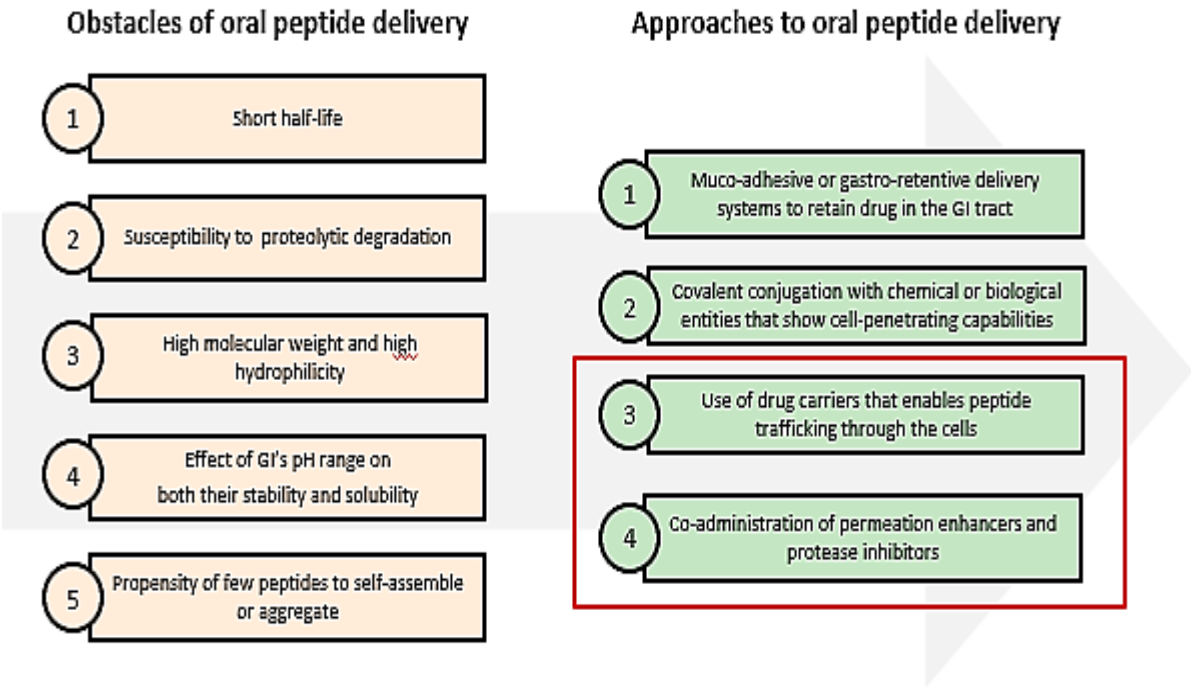


FIGURE 11: TYPES OF SUBLINGUAL DELIVERY SYSTEMS

Oral Delivery System

- Peptides make attractive drug candidates due to their specificity, potency and low toxicity, but present particular challenges for their delivery to the site of action



	Lead Peptide (Formulation)	Molecular Weight	Amino acids	Technology	Technology composition
enteris TARSA BIOPHARMA	TBRIA (Tablet)	3.45 Kda	32	Peptelligence	Absorption enhancer (acyl carnitine) and enzyme inhibitor (organic acid: citric acid)
oramed	ORMD-0801 type 2	5.81 KDa	51	POD	Peptide with absorption enhancer (e.g. EDTA) and protease inhibitors (e.g. soya bean trypsin inhibitor, EDTA) enteric coated tablet/capsule
	ORMD-0801 type 1	5.81 KDa	51		
	ORMD-0901 (Exenatide)	4.1 KDa	39		
Biocon	Insulin	5.81 Kda	51	HIM2	Amphiphilic oligomers conjugate with proteins
MERRION novo nordisk	Insulin and GLP-1 analogues (Tablet)	5.81 Kda	51	GIPET	Absorption enhancer : medium chain fatty acids (sodium caprate)
Emisphere novo nordisk	Salmon calcitonin, GLP-1, heparin, hGH and PTH (Tablet)	4.11 KDa	31	Eligen	Absorption enhancers SNAC, SNAD, 5-CNAC. Nanoparticles are used as carriers
NOD	Insulin (Capsule)	-	-	NOD	Bio adhesive calcium phosphate nanoparticles (no updates since 2016)
Rani THERAPEUTICS	Insulin and GLP 1 analogues (Capsule)	1.0 Kda – 74 KDa	>692	Robotic pill	Balloon-like structure outfitted with hollow micro needles made of sugar and preloaded with peptides

FIGURE 12: ATTRIBUTE ANALYSIS OF ORAL DELIVERY TECHNOLOGIES OF PROTEINS AND PEPTIDES

Drug Carriers

Microparticles

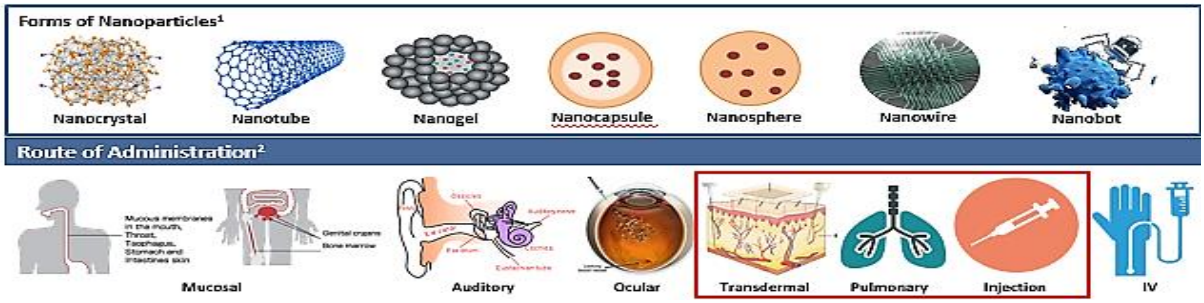
- Microparticles are in the size of 1-1000 µm and have emerged as a candidate for the sustained release vehicles for the drugs
- Microparticles are used for the long-term delivery (1 week or longer) of proteins, peptides and some small molecules and are generally injected either intraperitoneally, intramuscularly, subcutaneously or directly to the target organ
- Example: Glucagon-like peptides for treating Type 2 Diabetes like Victoza

Advantages

- Applications in the therapies where the requirement of site-specific activities is of profound importance
- Reduce concentration of drugs at the non-targeted sites
- Serves as effective delivery systems for insoluble or sparingly water soluble active agents
- Provide accurate and sustained release of potent drugs
- Increases the relative bioavailability of drugs and shows taste masking property
- The microparticles have great potential in providing maximum efficacy with reduced dosage frequency and adverse effects

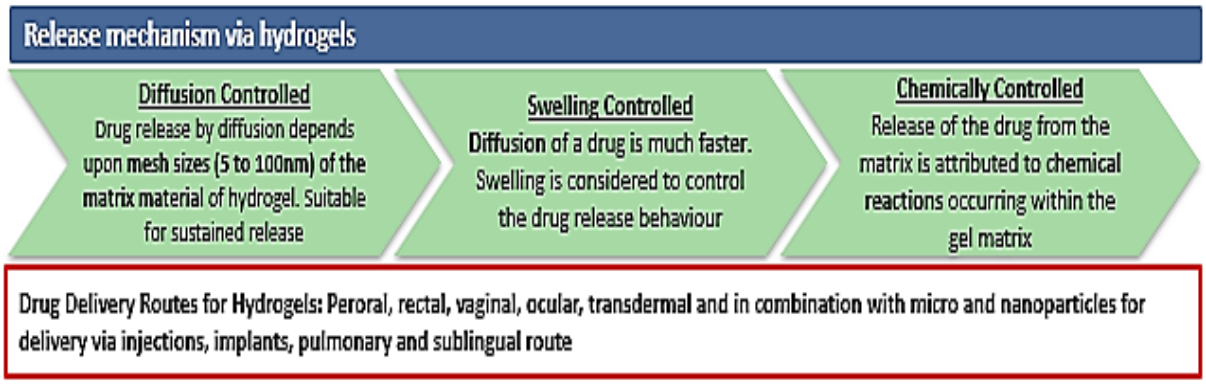
Nanoparticle

- Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix
- Example: Cimzia for autoimmune diseases and Neulasta for cancers; Nanocin PRO by Tecrea used to deliver proteins and peptides



Hydrogels

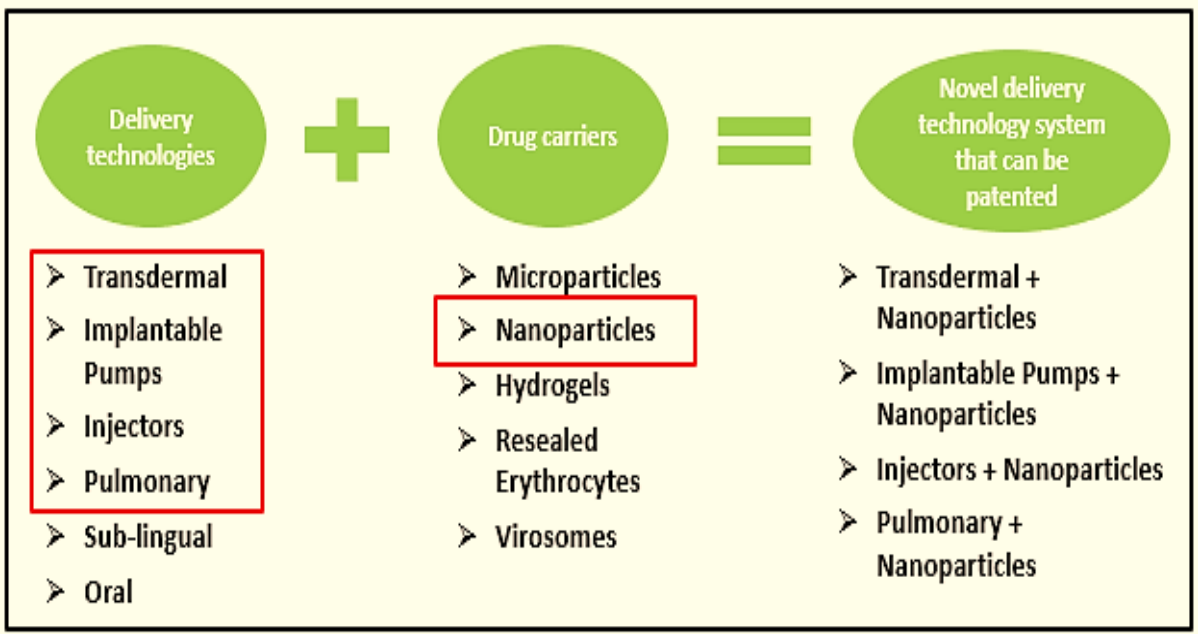
- Hydrogels evolved as an outstanding carrier material for local and controlled delivery of small drugs (NSAIDS) and large peptides and proteins
- The application of hydrogel can also be problematic sometimes; though some hydrogels are ultra-deformable to be injected, many are not, thus need surgical insertion
- **Smart Hydrogels:**New hydrogels that are composed of materials able to undergo transitional changes in response to environmental stimuli. These transitional changes include swelling, shrinkage, degradation, or a sol to gel phase transition when exposed to external physical or chemical stimuli, such as changes in pH, glucose, temperature, solvent, pressure, ionic strength, light, and concentration of specific biomolecules



Attribute Analysis of Delivery technologies that can be explored for Proteins & Peptides

	Implantable Pump	Injectors	Transdermal	Pulmonary	Sublingual	Oral
Suitable Drug Carriers	Microparticles, Nanoparticles, Hydrogels		Nanoparticles, Hydrogels			
Delivery route	Implants or patch	SC, IM, ID	Transdermal patches	Inhalation	Buccal (sublingual)	Oral
Controlled/ sustained release	Yes			No		Yes
Developmental Cost	High	High	Low	High	Low	Low
Patient Compliance	High	Medium	High	High	High	High
Examples	DUROS device	BydureonBCise	Viador	Technosphere technology	Exenatide	Robotic pill of insulin

Recommendation and Conclusion



- **Consideration:** Use of new delivery route alone may not give it a required edge, but combining it with the novel drug carriers might help in obtaining a long-term patent protection (due to increase in complexity of the technology)

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