



2018

Global Drug Delivery & Formulation

R E P O R T

Two of a Four-Part Series

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Introduction

Companies and patients continue to reap the benefits of the significant investments made in drug delivery and formulation technologies over the past few decades. Despite the absence of recent breakthrough drug delivery technologies, the pharmaceutical industry has harnessed well validated drug delivery and formulation technologies to deliver important product approvals in 2018.

One well validated technology that goes back almost 30 years with the approval of Adagen is PEGylation. Three Notable Approvals of 2018, Asparlas, Jivi, and Palynziq, all use PEGylation technologies, albeit with markedly different strategies. Asparlas, a next-generation Oncaspar, uses the same non-specific multi 5-kDa PEGylation strategy of its predecessor, but with more stable linker chemistry to improve shelf stability. Jivi, sees a 170-kDa recombinant protein conjugated with a single 60-kDa branched PEG molecule to yield the 230-kDa product. Palynziq, a 62-kDa enzyme, uses a strategy similar to that of Asparlas but with an average of nine larger 20-kDa PEG molecules. What is notable about these products is their use of multisource PEG reagents. No longer are we hearing mention of Enzon, Shearwater and their successors as technology or reagent suppliers. A technology that once commanded as much as a 7% royalty has seemingly become just another reagent sold on the basis of purity and price.

Two of the more interesting small molecule drug delivery and formulation approvals in 2018 included Inbrija and Jornay PM. Inbrija, an inhaled formulation of levodopa, represents an interesting formulation/device approach to addressing issues related to off symptoms with Parkinson's patients. Jornay PM, a colonic release formulation of methylphenidate administered in the evening, uses a totally different drug delivery facilitated dosing strategy to address the early day dosing requirements of children with ADHD.

In total, 20 products are highlighted that represent either fresh approaches or a new twist on well-understood drug delivery and formulation strategies.

Notable Drug Delivery and Formulation Approvals of 2018

Product Name	Company	Active(s)	Dosage Form	Status US	Status EU	Status JP
Allesaga Tape	Hisamitsu Pharmaceutical	Emedastine Difumarate	Transdermal Patch	Undisclosed	Undisclosed	Approved
Apadaz	KemPharm	Benzhydrocodone Hydrochloride, Acetaminophen	Oral Tablet	Approved	Undisclosed	Undisclosed
Arikayce	Insmed	Amikacin Sulfate	Inhalation Suspension	Approved	Phase 3	Phase 2
Asparlas	Servier	Calaspargase Pegol	Injection Solution	Approved	Undisclosed	Phase 3
Brilique Orodispersible	AstraZeneca	Ticagrelor	Oral Tablet	Approved	Undisclosed	Undisclosed
Buvidal	Camurus	Buprenorphine HCl	Injection Solution	Tentative Approval	Approved	Undisclosed
Dextenza	Ocular Therapeutix	Dexamethasone	Ophthalmic Insert	Approved	Undisclosed	Undisclosed
DSUVIA	AcelRx Pharmaceuticals	Sufentanil	Sublingual Oral Tablet	Approved	Approved	Undisclosed
Epidiolex	GW Pharmaceutical	Cannabidiol	Oral Solution	Approved	Registration	Undisclosed
Inbrija	Accorda Therapeutics	Levodopa	Inhalation Powder in Capsule	Approved	Registration	Undisclosed
Jivi	Bayer Healthcare	Damoctocog Alfa Pegol	Injection Lyophilized Powder for Solution	Approved	Approved	Approved
Jornay PM	Ironshore Pharmaceutical	Methylphenidate Hydrochloride	Oral Capsule	Approved	Undisclosed	Undisclosed
Licart	Institut Biochimique	Diclofenac Epolamine, Heparin (enhancer)	Topical Patch	Approved	Undisclosed	Undisclosed
Makena (SC Auto-injector)	AMAG Pharmaceuticals	Hydroxyprogesterone Caproate	Injection Solution	Approved	Undisclosed	Undisclosed
ONPATTRO	Alnylam Pharmaceuticals	Patisiran	Injection Solution	Approved	Approved	Registration
Palynziq	BioMarin Pharmaceutical	Pegvaliase	Injection Solution	Approved	Registration	Unknown
Perseris	Indivior	Risperidone	Injection Powder for Suspension	Approved	Undisclosed	Undisclosed
Rapalimus Gel	Nobelpharma	Sirolimus	Topical Gel	Phase 3	Phase 3	Approved
Sympazan	Aquesitive Therapeutics	Clobazam	Oral Film	Approved	Undisclosed	Undisclosed
Yutiq Implant	EyePoint Pharmaceuticals	Fluocinolone Acetonide	Ophthalmic Implant	Approved	Registration	Undisclosed



Allesaga Tape

Company: Hisamitsu Pharmaceutical

Active(s): Emedastine Difumarate

Molecule Type: Small Molecule

Indication: Allergic Rhinitis

Delivery Route: Transdermal

Dosage Form: Transdermal Patch

DD Category: Patches, Drug-in-Adhesive

Dosing (Duration): Once Daily

First Approval (Country): 2018-01-19 (JP)

Technology/Provider: TransDermaSal/
Hisamitsu Pharmaceutical

Notable: A different approach to the management of allergic rhinitis by means of a transdermal patch formulation.



Apadaz

Company: KemPharm

Active(s): Benzhydrocodone Hydrochloride,
Acetaminophen

Molecule Type: Small Molecule

Indication: Acute Pain

Delivery Route: Oral

Dosage Form: Oral Tablet

DD Category: Conjugates, Small Molecule

Dosing (Duration): 4 to 6 Times Daily

First Approval (Country): 2018-02-03 (US)

Technology/Provider: Ligand Activated Therapy/
KemPharm

Notable: Apadaz builds on the success of other prodrug CNS products attempting to discourage abuse by injection and insufflation using a prodrug approach rather than physical abuse-deterrent technologies. The FDA, while approving the product, did not judge the product to deter abuse by the oral or nasal routes of administration.



Asparlas

Company: Servier

Active(s): Calaspargase Pegol-mknl

Molecule Type: Protein Polymer Conjugate

Indication: Acute Lymphoblastic Leukemia

Delivery Route: Injection (Infusion IV)

Dosage Form: Injection Solution (Refrigerated)

DD Category: Conjugates, PEG Polymer

Dosing (Duration): No More Frequently than 21 Days

First Approval (Country): 2018-12-20 (US)

Technology/Provider: Enzon PEGylation Linker
Technology/Belrose Pharma

Notable: A next-generation Oncaspar that with improved stability. The L-asparaginase molecule (tetramer) is PEGylated with 5-kDa monomethoxypolyethylene glycol (mPEG) units using a succinimidyl carbonate (SC) linker.



Brilique Orodispersible Tablets

Company: AstraZeneca

Active(s): Ticagrelor

Molecule Type: Small Molecule

Indication: Acute Coronary Syndrome

Delivery Route: Oral

Dosage Form: Oral Tablet

DD Category: Oral Dispersible

Dosing (Duration): Twice Daily

First Approval (Country): 2018-05-18 (EU)

Technology/Provider: Undisclosed

Notable: A simple formulation enhancement to improve acceptance and compliance in a more elderly patient group.



Buvidal

Company: Camurus

Active(s): Buprenorphine HCl

Molecule Type: Small Molecule

Indication: Opioid Dependence

Delivery Route: Injection (IM)

Dosage Form: Injection Solution

DD Category: Biodeg Gel/Suspension, Prefilled Syringes

Dosing (Duration): Weekly, Monthly

First Approval (Country): 2018-11-21 (EU)

Technology/Provider: FluidCrystal Depot/Camurus

Notable: Available in once-weekly and once-monthly dosage forms Buvidal represents the first approval of a long-acting treatment for opioid dependence in the EU.



Dextenza

Company: Ocular Therapeutix

Active(s): Dexamethasone

Molecule Type: Small Molecule

Indication: Post-Operative Pain

Delivery Route: Ophthalmic

Dosage Form: Ophthalmic Insert (Refrigerated)

DD Category: Ocular Implants/Rods/Microcapsules

Dosing (Duration): Single Insertion

First Approval (Country): 2018-12-03 (US)

Technology/Provider: Ocular Therapeutix Punctal Plug/Ocular Therapeutix

Notable: Dextenza is the first FDA-approved intracanalicular insert delivering dexamethasone to treat post-surgical ocular pain for up to 30 days.



Epidiolex

Company: GW Pharmaceutical

Active(s): Cannabidiol

Molecule Type: Small Molecule

Indication: Lennox-Gastaut Syndrome

Delivery Route: Oral

Dosage Form: Oral Solution

DD Category: Oral

Dosing (Duration): Twice Daily

First Approval (Country): 2018-06-25 (US)

Technology/Provider: None

Notable: Developed as a simple sesame formulation, Epidiolex provides a benchmark for companies developing cannabis-based products in terms of regulatory authority (FDA & DEA) accommodations.



Bayer HealthCare

Jivi

Company: Bayer Healthcare

Active(s): Damoctocog Alfa Pegol

Molecule Type: Protein Polymer Conjugate

Indication: Hemophilia A

Delivery Route: Injection (IV Infusion)

Dosage Form: Injection Lyophilized Powder for Solution (Refrigerated)

DD Category: Conjugates, PEG Polymer

Dosing (Duration): Once/ Twice Weekly (Prophylaxis)

First Approval (Country): 2018-08-29 (US)

Technology/Provider: Not Disclosed

Notable: A PEG conjugate of Factor VIII, Jivi was approved all 3 markets in 2018. Jivi is the first B Domain Deleted PEGylated product; 60-kDa branched PEG.



Jornay PM

Company: Ironshore Pharmaceutical

Active(s): Methylphenidate Hydrochloride

Molecule Type: Small Molecule

Indication: ADHD

Delivery Route: Oral

Dosage Form: Oral Capsule

DD Category: Oral Enteric/Delayed Release, Oral Barrier Film & Microparticles, Colonic Release

Dosing (Duration): Once Daily

First Approval (Country): 2018-08-08 (US)

Technology/Provider: DELEXIS/Ironshore, Highland Therapeutics

Notable: Jornay PM provides a markedly different approach to dosing for ADHD with a colonic delayed-release formulation taken in the evening. Tmax was reached about 14 hours after dosing with only 5% of the drug available in the first 10 hours.



Caring Innovation

Licart

Company: Institut Biochimique

Active(s): Diclofenac Epolamine, Heparin (enhancer)

Molecule Type: Small Molecule

Indication: Acute Pain

Delivery Route: Topical

Dosage Form: Topical Patch

DD Category: Topical, General, Patches, Drug-in-Adhesive

Dosing (Duration): Once Daily

First Approval (Country): 2018-12-19 (US)

Technology/Provider: Hydroadhesive/Teikoku Seiyaku

Notable: A second-generation nonsteroidal anti-inflammatory in patch presentation formulated with heparin to improve local absorption.



ONPATTRO

Company: Alnylam Pharmaceuticals

Active(s): Patisiran

Molecule Type: siRNA

Indication: Amyloidosis

Delivery Route: Injection (IV Infusion)

Dosage Form: Injection Solution (Refrigerated)

DD Category: NP lipid cationic, NP solid lipid

Dosing (Duration): Every 3 Weeks

First Approval (Country): 2018-08-10 (US)

Technology/Provider: Arbutus LNP Technology/Arbutus Biopharma, Acuitas Therapeutics

Notable: Onpattro is the first approved siRNA product and employs a lipid nanoparticle technology that largely targets hepatocytes.



Palynziq

Company: BioMarin Pharmaceutical

Active(s): Pegvaliase-pqpz

Molecule Type: Protein Polymer Conjugate

Indication: Phenylketonuria

Delivery Route: Injection

Dosage Form: Injection Solution

DD Category: Conjugates, PEG Polymer, Prefilled Syringes

Dosing (Duration): Daily to Weekly

First Approval (Country): 2018-05-24 (US)

Technology / Provider: PEGylation / Biomarin Pharmaceuticals

Notable: A PEGylated version of an enzyme that involves nine separate 20-kDa PEG molecules [N-hydroxysuccinimide (NHS)-methoxypolyethylene glycol (PEG)]. PEGylation continues to be the preferred polymer for half-life extension and immunogenic reduction with protein-based molecules.



Perseris

Company: Indivior

Active(s): Risperidone

Molecule Type: Small Molecule

Indication: Schizophrenia

Delivery Route: Injection (SC)

Dosage Form: Injection Powder for Suspension (Refrigerated)

DD Category: Biodeg Gel/Suspension

Dosing (Duration): Once Monthly

First Approval (Country): 2018-07-27 (US)

Technology/Provider: ATRIGEL/Tolmar

Notable: The first subcutaneous, long-acting, formulation of a second-generation antipsychotic using the well-validated Atrigel technology.



NOBEL

Rapalimus Gel

Company: Nobelpharma

Active(s): Sirolimus

Molecule Type: Small Molecule

Indication: Tuberous Sclerosis Complex

Delivery Route: Topical

Dosage Form: Topical Gel (Refrigerated)

DD Category: Topical Gel

Dosing (Duration): Every 12 Hours

First Approval (Country): 2018-03-23 (JP)

Technology/Provider: Not Disclosed

Notable: Using relatively unremarkable topical formulation technology and a well-validated multisource active (sirolimus), Rapalimus addresses a rare genetic disease with few therapeutic options.



Sympazan

Company: Aquestive Therapeutics

Active(s): Clobazam

Molecule Type: Small Molecule

Indication: Lennox-Gastaut Syndrome

Delivery Route: Oral

Dosage Form: Oral Film

DD Category: Rapidly Disintegrating Films

Dosing (Duration): Once/Twice Daily

First Approval (Country): 2018-11-01 (US)

Technology/Provider: PharmFilm/Aquestive, MidaSol Therapeutics

Notable: One of the very few rapidly disintegrating films approved in 2018, Sympazan is well suited for the approved pediatric population of 2 years and above.



Yutiq Implant

Company: EyePoint Pharmaceuticals

Active(s): Fluocinolone Acetonide

Molecule Type: Small Molecule

Indication: Uveitis

Delivery Route: Implant (Intravitreal)

Dosage Form: Ophthalmic Implant

DD Category: Ocular Implants/Rods/Microcapsules, Injectable Non-biodeg. Polymeric Implants

Dosing (Duration): 3 Years

First Approval (Country): 2018-10-12 (US)

Technology/Provider: Durasert/MEDIDUR, Psivida Ocular Implant Inserter/EyePoint

Notable: Another lower volume specialty type indication benefiting from drug delivery, a non-bioerodible intravitreal micro-insert in a drug delivery system containing 0.18-mg fluocinolone acetonide, designed to release consistently over 36 months.

Notable Drug-Device Approvals of 2018



Arikayce

Company: Insmmed

Active(s): Amikacin Sulfate

Molecule Type: Carbohydrate

Indication: Infections, Respiratory Tract

Delivery Route: Inhalation

Dosage Form: Inhalation Suspension (Refrigerated)

DD Category: NP liposome, Liquid Inhalers/
Nebulizers, Inhalation Formulations, Nebulizer

Dosing (Duration): Once Daily

First Approval (Country): 2018-09-28 (US)

Technology/Provider: PULMOVANCE Liposomal
Technology/Insmmed, eFlow Rapid Nebulizer (Lamira)/
Pari Pharma

Notable: An orphan product approved under the FDA's Accelerated Approval pathway, Arikayce reinforces the benefits of nebulized formulations that address locoregional indications. The combination of a vibrating mesh nebulizer with a liposomal formulation provides for effective therapy in a convenient delivery format.



DSUVIA

Company: AcelRx Pharmaceuticals

Active(s): Sufentanil

Molecule Type: Small Molecule

Indication: Acute Pain

Delivery Route: Sublingual

Dosage Form: Sublingual Oral Tablet

DD Category: Sublingual Formulations, Sublingual
Delivery Devices

Dosing (Duration): As Required

First Approval (Country): 2018-06-25 (EU)

Technology/Provider: NanoTab SDA/AcelRx

Notable: DSUVIA was approved in part at the request of the US Military to address battlefield needs for a rapid acting non-injectable analgesic. The product contains a notably potent opioid with standard sublingual formulation technology packaged in a single-dose dispenser.



Inbrija

Company: Accord Therapeutics

Active(s): Levodopa

Molecule Type: Small Molecule

Indication: Parkinson's

Delivery Route: Inhalation

Dosage Form: Inhalation Powder in Capsule

DD Category: Inhalation Formulations,
DPI Dry Powder Inhalers

Dosing (Duration): Once to five times daily

First Approval (Country): 2018-12-21 (US)

Technology/Provider: ARCUS Dry Powder
Formulations, ARCUS Inhaler/Accorda, Civitas,
Alkermes

Notable: A novel approach to the delivery of levodopa using the lung to shorten onset of action (Tmax - 0.5 hours) and overcome issues related to variable oral absorption and first-pass metabolism.



Makena (SC Auto-Injector)

Company: AMAG Pharmaceuticals

Active(s): Hydroxyprogesterone Caproate

Molecule Type: Small Molecule

Indication: Preterm Birth

Delivery Route: Injection (SC)

Dosage Form: Injection Solution

DD Category: Autoinjectors, Disposable,
Concentrated Suspension/Viscous Solution,
Oil Formulations

Dosing (Duration): Weekly

First Approval (Country): 2018-02-04 (US)

Technology/Provider: VIBEX, QuickShot/
Antares Pharma

Notable: Approved as a supplement, the auto-injector provides the improved convenience of subcutaneous dosing with the simplicity of an auto-injector. This simple improvement should provide a competitive advantage following the 2018 approval of generics to the original IM vial presentation of Makena.