2021 Global Drug Delivery & Formulation REPORT

Part Two of a Three-Part Series

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Introduction

It appears the industry's attention has moved on from gene therapy and mRNA. Despite remarkable commercial and therapeutic successes, both platforms are searching for their "second acts." In 2021, attention returned to drug delivery- and formulation-based products and technologies applicable to larger patient populations and more diverse indications.

The notable approved drug delivery- and formulation-enabled and approved products of 2021 include Ascendis' weekly human growth hormone product Skytrofa, and Janssen's 6-month formulation of paliperidone aptly named Invega Hafyera, both variations on earlier themes. The list also includes a trio of products targeted to ophthalmic indications, Oyster Point's Tyrvaya, J&J's ACUVUE Theravision, and Genentech's Susvimo, the latter representing first approvals for their novel delivery platforms. ViiV's Cabenuva Kit rounds out the list delivering sustained-release depot therapy to the HIV patient population.

Platform technology best describes the notable technologies of 2021. Included are Genentech's Port Delivery System that underlies its Susvimo product, a notable product of 2021, providing important dosing options for their well-validated AMD treatment ranibizumab. Medicago's Virus Like Particles (VLP), with the approval of their first product, a COVID-19 vaccine, demonstrates the prospects of the platform for additional vaccines and therapeutics. Ionis's LICA technology further refines the potential of oligonucleotides by providing greater selectivity and improved efficiency. The Denali Transport Vehicle (TV) platform, currently at a Phase 2 stage of development, includes four separate technologies intended to provide facilitated crossing of the blood-brain barrier by antibody, enzyme, oligonucleotide, and protein therapeutics. At an earlier stage of development, LaGalli's MedRing platform integrates a pump, liquid drug reservoir, and electronics to permit a connected "intelligent" vaginal ring delivery system for both therapeutic and diagnostic applications.

The stars of the past couple of years, gene and cell therapy technologies, as well as mRNA delivery platforms, are struggling to move beyond a few highly specialized therapeutic uses. Gene therapy is facing safety and durability concerns while mRNA searches for validation outside of the field of vaccines. Both platforms continue to earn significant industry interest as evidenced by transaction activity and litigation related to the underlying intellectual property.

Even in an age of disruption, the pharmaceutical industry continues to demonstrate remarkable resilience and innovation. COVID too will pass.

Notable Drug Delivery and Formulation Products of 2021

Skytrofa (Ascendis Pharma)

Active: lonapegsomatropin-tcgd
Molecule Type: PEG-protein
Indication: Growth Failure - Pediatric
Delivery Route: Injection, Subcutaneous
Dosage Form: Lyophilized Powder, Dual Chamber Cartridge Technology
DD Category: Conjugates, PEG Polymer
Dosing: Weekly
First Approval: 2021-08-25 (USA)
Technology: TransPEG/TransCon
Owner: Ascendis Pharma

Development Summary

Development started in 2009 with the initiation of a pharmacokinetics study. Phase 3 trials were initiated in 2016 followed by filing with the FDA in June of 2020. First-in-human to approval took 10.7 years.

Platform/Technology/Formulation Summary

The TransPEG/TransCon technology application to Skytrofa involves the attachment of a 40kDa mPEG to the human growth hormone (hGH) molecule with a proprietary TransCon linker. This "transient" linker releases the parent hGH molecule and produces a linear IGF-1 response peaking about 2 days post dosing with average IGF-1 levels in the normal range for the week. Skytrofa uses the Vetter Dual Chamber Cartridge system in conjunction with of the Skytrofa Autoinjector developed in partnership with Phillips Medisize. The rechargeable and reusable injection device offers wireless connectivity and mixes the medication, easing the burden of self-injection for patients.

Reflections

In addition to providing improved convenience with weekly injections, Skytrofa provides increased Annualized Height Velocity of about 1 cm/year (0.2-1.5) versus daily injections of hGH. This improved growth comes at the expense of a slight increase in generally mild adverse events. The experience with Skytrofa seems to parallel that of the PEG-interferons used for the treatment of Hepatitis C in which moving from multiple doses per week to a single weekly injection consistently improves therapeutic outcomes. Whether there is a physiological reason for the improvements, or it is the result of better compliance, there is strong evidence to support the therapeutic value of longer-acting pharmaceuticals with extended dosing intervals.

Invega Hafyera (Janssen Pharmaceuticals)

Active: paliperidone palmitate
Molecule Type: Small Molecule
Indication: Adult Schizophrenia
Delivery Route: Injection, Intramuscular
Dosage Form: Injection Suspension, Prefilled Syringe
DD Category: Biodegradable Gel/Suspension
Dosing: Every 6 Months
First Approval: 2021-08-30 (USA)
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

Hafyera was submitted to the FDA in October 2020 as a supplement to the Invega Trinza (3-month paliperidone palmitate) and approved 10 months later. The earliest human trial found for Invega Hafyera is a November 2017 efficacy trial comparing it with the approved 1-month and 3-month formulations of paliperidone, suggesting a 3.7-year interval between first human trial and approval.

Platform/Technology/Formulation Summary

A look at the available information for Invega Hafyera suggests it is a larger volume version of Invega Trinza. Both formulations report 312-mg/ml concentrations of paliperidone and similar mg per ml excipient amounts with varying dosage volumes. Invega Sustenna, the 1-month formulation, has a 156-mg/ml concentration. The excipients include Polyethylene Glycol 4000 and Polysorbate 20.

Reflections

The technology associated with Invega Hafyera is at this point unremarkable. What is remarkable is the Janssen lifecycle management for their Invega franchise, which for almost 2 decades has captured significant revenue with its Invega portfolio, over $4 billion in 2021 despite loss of exclusivity for the parent molecule. Invega Hafyera represents a development bargain essentially requiring little more than a pair of efficacy-confirming clinical trials and investments in fill and finish upgrades and validation.

Tyrvaya (Oyster Point Pharma)

Active: varenicline
Molecule Type: Small Molecule
Indication: Dry Eye
Delivery Route: Nasal
Dosage Form: Nose Spray
DD Category: Nasal Spray Pumps/Devices
Dosing: Twice Daily
First Approval: 2021-08-30 (USA)
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

US development started in June 2018 with an announcement the FDA had cleared the company's IND for Tyrvaya. This was followed by Phase 2 and Phase 3 trials, an FDA submission in December 2020, and approval in October 2021. The rather compact clinical development and approval time of 3.3 years is notable for an active previously approved in an oral formulation to assist smoking cessation.

Platform/Technology/Formulation Summary

Tyrvaya represents the first approval for Aptar's CPS Spray Pump, a preservative-free nasal delivery platform for the treatment of Dry Eye. The formulation itself is simple, consisting of water, sodium phosphate, and buffer solution

Reflections

The challenge of administering drops to the eye cannot be overestimated, particularly in the target population of individuals who tend to be older and/or experiencing compromising medical conditions. Tyrvaya represents a practical and elegant drug delivery-based solution for a too common therapeutic challenge. Notable as well is the efficient use of drug delivery to repurpose an active for a whole new therapeutic indication.

ACUVUE Theravision (Johnson & Johnson Vision Care)

Active: ketotifen
Molecule Type: Small Molecule
Indication: Ocular Itch (allergic conjunctivitis)
Delivery Route: Contact Lens
Dosage Form: Ophthalmic Insert
DD Category: Ocular Lenses/Inserts
Dosing: Daily
Fast Approval: 2021-03-24 (Japan)
Delivery Route: Contact Lens
Technology: J&J Drug Eluting Contact Lens
Technology Owner: J&J Vision Care

Development Summary

The earliest reported clinical trial of ACUVUE Theravision is a Phase 3 trial initiated December 2017. It is likely that pharmacokinetic and safety studies were conducted earlier. Underlying patents to the technology have priority dates of 2012. The product was approved February 2022 in the US.

Platform/Technology/Formulation Summary

The antihistamine (ketotifen)-releasing contact lenses are corrected disposable lenses worn daily. The lens material, etafilcon A, is a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid cross-linked with 1, 1, 1-trimethylol propane trimethacrylate and ethylene glycol dimethacrylate. The lenses are tinted blue using blue 2-hydroxyethyl methacrylate to make the lenses more visible for handling.

Reflections

The concept of using contact lenses, corrected or not, provides a compelling platform for the continuous delivery of any number of drugs that require the application of drops and possibly injection. While ACUVUE Theravision is limited to the treatment of ocular itch associated with allergic conjunctivitis, and daily replacement of the contact lenses, the application of the technology to other indications and actives is obvious. The limitation of the technology is that it requires the patient to apply the contact lens daily, something not necessarily appealing to patients not currently using contact lenses. A major technical accomplishment is the stabilizing of the drug in the contact lens to prevent leaching.

Cabenuva Kit (ViiV Healthcare)

Active: cabotegravir, rilpivirine
Molecule Type: Small Molecule (both)
Indication: HIV-1 Infection
Delivery Route: Injection, Intramuscular
Dosage Form: Injection Suspension

DD Category: NP Milling, Biodegradable Gel/Suspension
Dosing: Monthly
First Approval: 2020-03-18 (Canada)
Delivery Route: Contact Lens
Technology: NanoCrystal
Technology Owner: Alkermes

Development Summary

This product represents a new combination incorporating a new active, cabotegravir. The earliest human trials for cabotegravir date back to 2008. First human trials of a combination of the two actives date to 2011. The first trial of the long-acting injectables dates to May 2012. The application for FDA approval was filed April 2019.

Platform/Technology/Formulation Summary

The "kit" incorporates separate vials of cabotegravir and rilpivirine. Both suspensions use NanoCrystal nanoparticle milling technology. The cabotegravir formulation uses Polysorbate 20 and Polyethylene Glycol 3350, while the rilpivirine formulation uses a Poloxamer base.

Reflections

Cabenuva Kit is similar to other long-acting agents in which there are therapeutic benefits to maintaining consistent and adequate therapeutic serum levels. Patients prescribed the Cabenuva Kit are dosed orally for about a month before the monthly injections are initiated. Clinicians are increasingly appreciating the benefits of longer-acting injectables for conditions in which compliance can be a concern and patient initiated "drug holidays" can have serious consequences. (In March 2022 the FDA approved the use of Cabenuva Kit without the need for an oral dosing lead-in and extended dosing to two months.

Susvimo (Genentech)

Active: anibizumab
Molecule Type: anibizumab
Indication: Wet Acute Macular Degeneration
Delivery Route: Injection, Intravitreal
Dosage Form: Implant

DD Category: Ocular Implants / Rods / Microcapsules
Dosing: Every 6 Months
First Approval: 2021-10-22 (USA)
Technology: Port Delivery System
Technology Owner: ForSight Vision4 (Roche)

Development Summary

The earliest clinical trials for the ranibizumab using the Port Delivery System (PDS) date to 2010. Roche acquired ForSight Vision4 in 2017 and filed for approval of Susvimo with the FDA in April 2021, receiving Priority Review. The overall clinical and approval time for Susvimo totaled a little more than 11 years.

Platform/Technology/Formulation Summary

The Port Delivery System (PDS) is a novel refillable eye implant, approximately the size of a grain of rice, providing controlled delivery to the vitreous humor over months or years. Following initial implantation, refills can be performed in the office as needed, as used for standard-of-care intravitreal injections. The PDS implant is made of non-biodegradable materials. The aqueous drug formulation uses Polysorbate 20 and histidine.

Reflections

With an aging population and high patient expectations for continued functional performance, companies are finding therapeutic and commercial opportunity with novel of ophthalmic drugs and delivery methods. Even presbyopia has received attention with a recent pharmaceutical approval. Susvimo validates the possibilities for the treatment of other eye diseases with the PDS and similar implantable systems to provide for better compliance and outcomes.

Notable Drug Delivery and Formulation Technologies of 2021

Technology: Port Delivery System
Most Advanced Stage: Marketed
Technology Category: Ocular Implant
Company: ForSight VISION4 Roche/Genentech
Notable Pipeline: Marketed - Susvimo (ranibizumab)
Notable: Refillable ocular implant that extends dosing intervals of macromolecules for up to six months

Technology Summary: The Port Delivery System (PDS) is a novel refillable eye implant, approximately the size of a grain of rice, which continuously delivers drugs over months or years into the vitreous humor in a controlled manner. Following initial implantation, refills can be performed in the office similar to that used for standard-of-care intravitreal injections. Susvimo uses a customized Polysorbate 20 and histidine formulation of ranibizumab distinct from the intravitreal injection marketed as Lucentis. The PDS system includes implant, injector and implant inserter.

Technology: Medicago Virus Like Particles (VLP) Technology
Most Advanced Stage: Approved
Technology Category: Virus Like Particles
Company: Medicago/Mitsubishi Tanabe Pharma
Notable Pipeline: Approved - Covifenz (COVID-19 Vaccine)
Notable: First approved plant based Virus Like Particle technology product

Technology Summary: Medicago's plant-derived vaccine development technology platform uses tobacco-related plants indigenous to Australia (Nicotiana benthamiana) as bioreactors to produce non-infectious Virus Like Particles (VLP) that mimic the target virus. The plants are not genetically modified. Plant-specific bacterial vectors containing antigenic viral gene sequences transfect the plants, which produces VLPs for 4-6 days. The Covifenz injectable emulsion vaccine formulation uses a wide variety of excipients, including 1018 ISS, AS03, Polysorbate 80, Squalene, and Alpha tocopherol as adjuvants.

Technology: LICA Technology
Most Advanced Stage: Phase 3
Technology Category: Conjugates, Carbohydrate; Receptor/Carrier, Liver Targeting
Company: Ionis Pharmaceuticals
Notable Pipeline: Phase 3 - Pelacarsen (Apo(a)), Eplontersen (ATTR), Olezarsen (ApoC-III), Donidalorsen (Hereditary Angioedema)
Notable: Increased cell and tissue selectivity with increased potency

Technology Summary: LICA, or Ligand Conjugated Antisense, involves the attachment of ligands that bind with targeted receptors on the surfaces of cells. LICA permits effective delivery of antisense drugs with specificity to cell types expressing these receptors. The specificity provides for a 20- to over 30-fold increase in potency compared to non-conjugated antisense drugs. Triantennary N-acetyl galactosamine (GalNAc, GN3), a subset of LICA technology, is designed to enhance the delivery of antisense oligonucleotides (ASOs) to hepatocytes. LICA technology can target additional cell types by means of different ligands.

Technology: Denali Transport Vehicle (TV) Platform
Most Advanced Stage: Phase 2
Technology Category: Brain Targeting; Receptor Carrier
Company: Denali Therapeutics/F-Star Biotechnology
Notable Pipeline: Phase 2 - DNL310 (Hunter Syndrome), DNL343 (ALS)
Notable: The TV platform encompasses four related platforms directed to the delivery of antibodies (ATV), enzymes (ETV), oligonucleotides (OTV), and proteins (PTV) to the brain.
Technology Summary: This technology is based on (TfR)-specific Fcab (antibodies), Fc-enzyme fusion (enyzmes), Fc-oligonucleotide fusion (oligonucleotides), or Fc-protein fusion (proteins) constructs, which engage transferrin receptor (TfR) on the blood vessel wall in the brain. The engineered TfR bound molecule is delivered into the brain via receptor-mediated endocytosis. Antibodies engineered with the ATV technology have demonstrated a 20-fold greater brain penetration than control antibodies. ATV platform technology also utilizes the blood brain barrier receptor binding Fc domain to engineer bispecific and bivalent antibodies.

Technology: MedRing
Most Advanced Stage: Phase 2
Technology Category: Vaginal Inserts/Devices; Drug Delivery Compliances
Company: LiGalli
Notable Pipeline: Phase 2 - LIG MR1 (Therapeutic, Overactive Bladder), LIG MR16 (Diagnostic, Compliance)
Notable: Unique 'intelligent' vaginal ring delivery system with pump, liquid drug reservoir, and supporting electronics to permit connected therapeutic and diagnostic applications
Technology Summary: MedRing comprises a flexible ring-shaped device that can be manually collapsed and which assumes an extended shape when little to no external force is being applied. It can be inserted and removed by the patient, assuming a position in the posterior fornix of the vagina. MedRing contains a miniaturized liquid formulation drug container with pump, battery, antenna, electronics, and sensors. Current prototypes include sensors to monitor temperature and confirm drug delivery. It can also be equipped with sensors that monitor other kinds of biometric data, such as glucose levels and ovulation status. MedRing can be controlled for adjustment of dose, schedule, and timing with a smart phone. Drug compounds with a low bioavailability or high first-pass effect are well suited.

Technology: Q-Sphera
Most Advanced Stage: Phase 1
Technology Category: Biodegradable PLGA Microspheres; 3D Printing
Company: Midatech Pharma
Notable Pipeline: Preclinical - MTD-211 (CNS), MTD219 (anti-rejection), MTX-214/MTX216 (undisclosed)
Notable: The use of 3D printing technology to encapsulate biological drugs into PLGA based microspheres providing sustained release injectable depot formulations for up to 6 months
Technology Summary: The bioencapsulation process involves two or more fluid phases containing a polymer and the biological material. These are pumped continuously into a microfluidic device in which they are segmented into discrete droplets with an immiscible liquid phase. Droplets are cured into solid beads using benign chemical, UV, or phase change methods. Monodisperse particles can be manufactured in the size range of 25-2000 microns. Working with model antibodies, Midatech has demonstrated encapsulation and preservation of functional integrity and antigen binding in vitro. The Q-Sphera platform does not use surfactants, toxic solvents, biphasic mixtures, shear, or heat forces and permit use with a wide range of solvents, bioresorbable polymers, and stabilizing excipients to finely tune product characteristics. product characteristics.