2020 Global Drug Delivery & Formulation REPORT

Part Two of a Four-Part Series

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Introduction

Drug Delivery and Formulation is increasingly becoming as much an opportunity to creatively apply available technology to existing therapeutic challenges as it is to develop novel technology. This past year presented examples of both.

The most notable new products of 2020 were the first two COVID-19 vaccines to be introduced for clinical use, Pfizer/BioNTech's Comirnaty and the Moderna COVID-19 Vaccine. These products depended on a novel mechanistic approach, the use of mRNA to express antigen proteins, and novel technologies to deliver these therapeutics in sufficient quantities to the nucleus of cells.

Also notable was the approval of two antibody-based products, Janssen Biotech's Darzalex FasPro and Roche's Phesgo. Both products used Halozyme's well-validated Enhanze formulation technology to turn hours-long infusions into much more patient-friendly subcutaneous injections. The applications may have been obvious to some, but the development work was done remarkably quickly, with both products taking about 4.5 years from first clinicals to approval.

Mycapssa from Chiasma joined a very short list of approved oral peptides. A combination of oral absorption enhancer and enteric liquid-filled capsule technologies were necessary to provide the quantities of octreotide required to provide a therapeutic benefit for the treatment of acromegaly. Following on last year's approval of Rybelsus, Mycapssa provides additional validation for the oral administration of peptides.

The notability of Jazz's Xywav, an oral liquid formulation of calcium, magnesium, potassium, and sodium oxybates, revolves more around concept than formulation. By eliminating a problematic sodium issue with their blockbuster Xyrem product but retaining the same dosage form and instructions, Jazz Pharmaceuticals has provided an important patient benefit and given the company an extended commercial runway. It doesn't necessarily take sophisticated technology breakthroughs to meaningfully address real-world patient needs.

A shout out goes to two products that used relatively pedestrian technologies to address real-world patient needs. The first, Hanmi Pharmaceuticals' Amosartan XQ Oral Tablets, combines four multisource cardiovascular agents into a single oral tablet for the treatment of hypertension and hyperlipidemia, making it much easier for patients to be compliant. Mallinckrodt's Gimoti Nasal Spray for diabetic gastroparesis provides metoclopramide in a delivery form that doesn't depend on reliable enteral absorption without the need for an injection.

A common theme over the past few years has been the realization that innovation in the drug delivery and formulation space is as dependent on creative ideas using existing technology than it is waiting for the next big technology breakthrough. In next month's report, we will take a look at exactly what is new and exciting in the area of drug delivery technologies.

Comirnaty & Moderna COVID-19 Vaccines

Comirnaty (Pfizer Inc, BioNTech, Inc.)

Active: BNT162b2
Molecule Type: mRNA
Indication: Active Immunization to Prevent COVID-19
Delivery Route: Injection - Intramuscular
Dosage Form: Injection Suspension, Multidose Vial
DD Category: NP Solid Lipid, NP Lipid Cationic
Dosing: Two doses, 21 Days Apart
First Approval: Temporary Authorisation 2020-12-02 (UK)
Delivery Technology: Acuitas LNP Technology
Delivery Technology Owner: Acuitas Therapeutics

Moderna COVID-19 Vaccine (Moderna, Inc.)

Active: mRNA-1273
Molecule Type: mRNA
Indication: Active Immunization to Prevent COVID-19
Delivery Route: Injection - Intramuscular
Dosage Form: Injection Suspension, Multidose Vial
DD Category: NP Solid Lipid, NP Lipid Cationic
Dosing: Two doses, 28 Days Apart
First Approval: Emergency Use Approval 2020-12-19 (US)
Delivery Technology: Moderna LNP Technology
Delivery Technology Owner: Moderna, Inc.

Development Summary

Both products began development in the first quarter of 2020 following the disclosure of the COVID-19 virus structure.

Comirnaty's first in human trials began in April followed by Phase 2/3 trials in July. The first approval, a Temporary Authorisation in the UK, was granted in December, followed later in the month by similar approvals in the US, EU, and other countries.

Trials for the Moderna COVID-19 Vaccine were initiated in February 2020, followed by Phase 2 in May, Phase 3 in July, and a rolling submission in Canada in October. First approval, Emergency Use Authorization, was received in the US in December. This was followed by an approval in the EU and other countries in early January 2021.

Although labelled as Temporary and Conditional, these are for all practical purposes full approvals with potentially hundreds of millions of doses being administered by the end of 2021.

Platform/Technology Summary

Both products rely on the use of mRNA for the expression of the COVID-19 spike antigens. The mRNA is delivered to the nucleus of cells with the use of lipid nanoparticles. In the case of Comirnaty, the delivery technology, Acuitas LNP Technology, is provided by Acuitas Therapeutics, a small Vancouver Canada-based company. A related Acuitas delivery technology has been previously used for the delivery of RNAi therapeutics, notably Alnylam's Onpattro.

The Moderna COVID-19 Vaccine uses a similar delivery approach albeit with its own proprietary nanoparticle lipid technology, Moderna LNP Technology.

Formulation Summaries

Comirnaty is provided as a 0.45-ml frozen multidose vial suspension requiring thawing and dilution. It is formulated with proprietary lipid nanoparticles.

Moderna COVID-19 Vaccine is provided as 5-ml frozen multidose vial suspensions requiring thawing. It is formulated with proprietary lipid nanoparticles.

Reflections

The development of these two products from "scratch" in less than a year is remarkable. It was built on years of work and investment in understanding the potential of mRNA, the development of the supporting delivery technology to direct and express the antigens, and experienced clinical trial design and execution.

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The Moderna COVID-19 Vaccine may be the more impressive of the two products from a corporate perspective. This was the first Moderna product to be taken through development to approval. The company currently has 20 products in clinical development, 3 in Phase 2, and 17 in Phase 1 for a variety of indications, including COVID-19, CMV, RSV, Influenza, and a variety of cancers.

In the case of Comirnaty, it was fortuitous that BioNTech, who provided the mRNA technology and know-how, had previously established a partnership with Pfizer for the development of mRNA influenza vaccines. BioNTech also had a previous relationship with Acuitas, the delivery technology provider. Only with the contribution of Pfizer's expertise in all aspects of drug development, GMP processes, and distribution was it possible to bring Comirnaty to patients so quickly.

Make no mistake, mRNA technology and the supporting delivery technologies will provide important future therapeutics. A quick look at PharmaCircle's Pipeline & Products Intelligence module finds 52 mRNA products are currently in clinical development with another 163 at the preclinical or research stage.

Darzalex FasPro (Janssen Biotech)

Active: daratumumab
Molecule Type: Antibody
Indication: Cancer, Multiple Myeloma
Delivery Route: Injection - Subcutaneous
Dosage Form: Solution, Single-Dose Vial
DD Category: Injection Site Absorption Enhancers
Dosing: Injection, 3-5 Minutes, Every 1 to 8 Weeks
First Approval: 2020-05-01 (US)
Delivery Technology: Enhanze
Delivery Technology Owner: Halozyme Therapeutics, Inc.

Phesgo (Genentech, Inc.)

Actives: trastuzumab, pertuzumab
Molecule Type: Antibody (both)
Indication: Cancer, Breast
Delivery Route: Injection - Subcutaneous
Dosage Form: Solution, Single-Dose Vial
DD Category: Injection Site Absorption Enhancers
Dosing: Injection, 5-8 Minutes, Every 3 Weeks
First Approval: 2020-06-29 (US)
Delivery Technology: Enhanze
Delivery Technology Owner: Halozyme Therapeutics, Inc.

Development Summary

Both of these products from Janssen and Roche followed very similar timelines, taking about 54 months from first patient dosing to FDA approval. Both products are new formulations of products previously approved for administration by infusion. In the case of Darzalex FasPro, the first approved formulation of daratumumab, Darzalex, was approved in 2015 with a complex administration plan requiring up to a 7-hour infusion.

Phesgo is a subcutaneous combination formulation of Perjeta and Herceptin, which were approved in 2012 and 1998, respectively. The administration of these products involved sequential infusions that took 60 minutes for Perjeta and 90 minutes for Herceptin.

The development of both Darzalex FasPro and Phesgo as follow-on formulations followed what has become a well-understood playbook for the application of Halozyme's Enhanze to antibody therapeutics wishing to transition from infusion to subcutaneous administration.

Platform/Technology Summary

ENHANZE is based on the high-dose recombinant human hyaluronidase PH20 enzyme (rHuPH20). The enzyme depolymerizes hyaluronic acid (HA) and transiently modifies the local injection area, which increases dispersion and absorption of co-administered therapeutics by temporarily opening flow channels under the skin/or into tumors that accumulate HA, making large-volume subcutaneous injections practical.

Formulation Summaries

Darzalex FasPro is provided as a 15-ml refrigerated injection solution in vials. There is very little to the formulation beyond the inclusion of Halozyme's proprietary hyaluronidase. The additional excipients include three amino acids, Polysorbate 20, sorbitol, and water for injection. Phesgo is provided as a 10-ml and 15-ml refrigerated injection solution in vials. The formulation is remarkably similar to Darzalex FasPro but with the substitution of trehalose and sucrose for sorbitol. Both products incorporate 2,000 units per ml of hyaluronidase.

Reflections

Halozyme's Enhanze has become the industry standard technology to improve patient convenience when larger volume injectables, often biologics, require extended intravenous injection times. Both Darzalex FasPro and Phesgo embody the industry's focus on creating competitive advantage with an improved patient experience and reduced administration complexity. In the case of Darzalex FasPro, a 6-hour or longer administration period is reduced to 5 minutes. For Phesgo, administration is reduced to 5 minutes instead of sequential administrations requiring 2.5 hours. Both products will certainly benefit from extended market exclusivity. Any biogeneric product will need to not only address the issues related to the intellectual property (IP) protecting the individual molecules, but also the IP associated with the Enhanze technology and any new IP associated with the reformulated products.

Mycapssa (Chiasma Inc.)

Active: octreotide (1019 Da)
Molecule Type: Peptide
Indication: Acromegaly
Delivery Route: Oral
Dosage Form: Capsule
Dosing (Duration): Single Infusion (One Hour)

DD Category: Oral Peptide / Macromolecule, Tight Junction Modifiers, Oral Enteric/ Delayed Release
First Approval: 2020-06-26 (US)
Technology: Transient Permeability Enhancement (TPE) Technology
Technology Owner: Chiasma Inc.

Development Summary

The development of Mycapssa from first clinical trials to approval has taken about 10 years with Phase 1 safety and pharmacokinetic results announced in June 2010. Phase 3 trials were initiated in 2012, and a New Drug Application was filed in 2015. This was followed by a 2016 Complete Response Letter from the FDA that required the company to conduct an additional double-blind efficacy trial. Positive results were announced in 2019, followed by a resubmission the same year and FDA approval a year later.

Platform/Technology Summary

The Transient Permeability Enhancement Technology as applied to Mycapssa consists of an enteric-coated liquid-filled capsule containing an oily suspension of the drug and sodium caprylate in hydrophilic microparticles that are mixed with castor oil or a medium-chain glyceride and/or caprylic acid. Sodium caprylate is claimed to provide a transient opening of the tight junctions, providing enhanced paracellular peptide absorption.

Formulation Summary

Mycapssa is provided as 20-mg liquid-filled capsules requiring refrigeration. The formulation has a dozen and a half listed excipients, including sodium caprylate, glyceryl monocaprylocaprate, and tricaprylin.

Reflections

Mycapssa provides octreotide, a well-validated treatment for acromegaly, as an oral formulation that previously required injection either two to three times daily (Sandostatin and generics) or monthly (Sandostatin LAR). Octreotide is a smaller peptide with a molecular weight of 1,109 Daltons. The Mycapssa formulation has a bioavailability of about 0.5%. This compares with Novo Nordisk's Rybelsus, which has a bioavailability of about 0.4%-1%, although Rybelsus is a much larger peptide with a molecular weight of 4,114 Daltons.
The Chiasma TPE Technology, like Novo Nordisk's Eligen Technology, is based on the use of sodium salts of caprylic acid. While the Eligen technology uses a variety of proprietary caprylic acid analogs, including sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNC), the TPE technology uses sodium caprylate in combination with other glycerides. Importantly, Mycapssa is delivered in a liquid-filled enteric capsule, Capsugel's Liquid-Filled Hard Capsule.

Mycapssa, following on the approval of Rybelsus the previous year, validates the opportunity for the oral delivery of smaller relatively sensitive biologicals. It will take a big step to deliver even larger peptides, such as insulin, 5,808 Daltons, and a veritable leap to address the challenge of cytokines where molecular weights approach 20,000 Daltons. In the meantime, outpatient administration of these larger molecules is being made much easier with the continuing development of new injection technologies and devices.

Jazz Pharmaceuticals®

Xywav (Jazz Pharmaceuticals)

Actives: sodium oxybate, calcium oxybate magnesium oxybate, potassium oxybate (126 to 246 Da as salts)

Molecule Type: Small Molecule

Indication: Cataplexy, Excessive Daytime Sleepiness

Delivery Route: Oral

Dosage Form: Solution

DD Category: Oral

Dosing: Twice Daily

First Approval: 2020-07-21 (U.S.)

Delivery Technology: Not Applicable

Delivery Technology Owner: Not Applicable

Development Summary

The first evidence of clinical development for Xywav, also known as JZP-258, was the initiation of a multicenter Phase 3 trial in March 2017 for the treatment of cataplexy or excessive daytime sleepiness, an Orphan indication that became the approved indication. A subsequent trial in idiopathic insomnia was initiated in November 2018. A New Drug Application was filed in March 2020, and approval received in July 2020, in total a little more than 3 years after first clinical trials. Xywav's remarkably short regulatory approval time of 4 months was due in part to its receiving Priority Review Status.

Platform/Technology Summary

There is nothing notable regarding the formulation technology, a simple aqueous- based solution with sweetener.

Formulation Summary

Xywav is provided as an aqueous solution with sucralose, an artificial sweetener in room-temperature stable bottles of 180 ml. Dosing is similar to previously approved Xyrem.

Reflections

Sometimes important new products don't require breakthrough technology, just breakthrough thinking. Improved formulations of approved pharmaceuticals have a checkered reputation, often perceived as developed solely for the purpose of extending market exclusivity. While this may be a major reason for the development of Xywav, the formulation provides an important benefit for patients that is easy to overlook.

Xywav, a mixture of calcium, magnesium, potassium, and sodium oxybate salts, reduces the sodium daily dose by more than 90% compared to Xyrem. The recommended doses of Xywav deliver only 4%-6% of the RDA of sodium. This means one less thing for patients and physicians to worry about and that can only improve compliance, which leads to more sales. The formulation was carefully designed to keep the dosing instructions for Xywav exactly the same as for Xyrem. A dosage of 3 g of Xyrem, 6 ml, is exactly the same for Xywav, 3 g and 6 ml, making the transition seamless. Combination of oxybate salts were balanced to keep exactly the same recommended doses. There is a slight difference in formulations with a sweetener added to the Zywav formulation.