Global Formulation Report

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If coders are the anonymous engineers and architects of the software that drives computers, handhelds, and the worldwide web, then formulators and drug delivery professionals are the anonymous engineers and architects who drive the pharmaceuticals that are changing medical treatment paradigms. It’s the formulators and drug delivery professionals who ensure that increasingly complex molecules are delivered to the right organ, in the right dose, and at the right time to optimize efficacy and safety.

The new therapeutic molecules coming out of the chemistry and biotech labs are neither well-behaved from a physiochemical perspective nor easily tamed. Too often, they are highly insoluble or are too quickly excreted to be of any practical therapeutic benefit without the help of formulation and drug delivery. And at the same time, the right drug is only as useful as the patient’s willingness to take it according to the prescribed schedule. Making drugs easy and simple to use helps ensure the patient and the healthcare system receives the optimal benefit from these new breakthrough pharmaceuticals. It’s the job of formulation and drug delivery professionals to ensure products provide optimal efficacy, safety, and convenience.

The importance of formulation, the common denominator in all pharmaceuticals, is too easily ignored by industry pundits and the public in the same way they ignore the coders of the software running our tools and toys. This Global Formulation Report takes a closer look at the business and science of formulation and drug delivery as revealed by the past year. The subjects covered range from new formulation-enhanced drug approvals, to combination products, to the technologies and deals underpinning these products, and much more. A panel of industry experts also offers their thoughts on what is yet to come.

The Report is a collaborative effort between the well-respected team at Drug Development & Delivery, and the information, analysis, and writing team of the delivery and formulation experts at PharmaCircle (Kurt Sedo, Tom DePaul, and Josef Bossart). The format is intended to provide an overview of what happened in 2014 and how these events are likely to shape the coming years. We hope you enjoy this issue. Please drop us a line if you have suggestions for how we can improve future issues.

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Ten Notable Drug Delivery & Formulation Technologies of 2014

The biggest technology accomplishment in 2014 most certainly was the validation of Mannkind’s Technosphere formulation and Dreamboat device with the FDA’s approval of Afrezza. Smaller and more patient-friendly than Nektar’s Exubera, it remains to be seen if strong technical and design performance will translate into physician and patient acceptance as well as payor reimbursement. With Afrezza now approved, the question is whether the Technosphere and Dreamboat platforms can be successfully applied to the systemic delivery of macromolecules. Dreamboat wasn’t the only inhalation device to gain traction in 2014. GlaxoSmithKline’s Ellipta device continued to gain momentum with the approval of two additional products. Ellipta provides a number of important advantages over the tried and true Diskus dry powder inhaler that should translate into improved patient outcomes.

PEGylation was well represented with two major product approvals in 2014. Biogen’s Plegridy, a PEGylated version of their interferon beta-1a was a very obvious line extension. More interesting was the approval of Nektar’s Movantik, a PEGylated small molecule. Using a markedly smaller polyethylene glycol polymer, and ether linkage, Movantik is defining a new set of applications for the use of PEG. Nektar also pushed the frontiers of PEGylation with its prodrug PEG irinotecan tetramer (NKTR-102). The intention is to have the macromolecule preferentially taken up by tumors where the active, irinotecan in the case of NKTR-102, will be released. Recent disappointing Phase III results may, however, give Nektar cause to pause and reconsider this strategy. Enzon tried a similar approach using high molecular weight PEG conjugated anticancer agents more than a decade ago with discouraging results.

Drug delivery and formulation advances in 2014 highlighted the merging of protein technologies with, and into, drug delivery. There has been little argument as to whether PEGylation, the attachment of polyethylene glycol to proteins, is a drug delivery technology. But what about the various protein fusion technologies? These technologies depend on genetic engineering to create a single polypeptide that retains the properties of the therapeutic protein but with the customized benefit of a linked protein. Unlike first- and second-generation PEGylation, the resulting product does not require subsequent chemical conjugation and is a relatively well-characterized molecule. Smells like drug delivery, but with a whole new set of tools. Among the many products approved in 2014 using protein fusion technologies, two employed Biogen’s Synfusion technology that was part of Biogen’s acquisition of Syntonix. GlaxoSmithKline’s fusion protein, Tanzeum, an albumin fusion for the treatment of diabetes that arrived with the acquisition of Human Genome Sciences protein, was also approved last year.

The whole issue of macromolecule delivery continues to be an area of focus for formulation- and device-oriented companies. While the dream of orally active macromolecules remains a significant challenge, many companies recognize that injections are effective and safe, but not patient friendly. To that end, several companies have made progress with devices that simplify and disguise the process of injection. The prospects for microneedle injections were boosted by Lilly signing on to Zosano’s clinical-stage parathyroid hormone product, ZP-PTH. Success in Phase III could be just the validation needed to spur more development in this area. Crossject and Enable Injections advanced their platform injection devices based on traditional injection technologies, needle and needle free, by disguising and simplifying the devices with non-traditional form factors to make them appear less needle-like and less threatening. Both companies have rejected the traditional syringe and pen look for their devices.

Large-volume subcutaneous administrations were further validated by the approval of Roche’s MabThera-PH20 using Halozyme’s Enhance technology, human recombinant hyaluronidase. With several Big Pharma partners, approved products and a remarkably full pipeline, Enhance technology seems to have a bright future. Sometimes the best idea is to work with what works and make it better.

Many more drug delivery and formulation technologies made strong moves in 2014. Ten technologies have been selected that provide a snapshot of the developments in 2014 and perhaps point to where drug delivery and formulation are headed.
**Technology: Accurins**

**Type:** Nanoparticles, Emulsion/Polymerization, Receptor/Carrier

**Company:** BIND Therapeutics

**Applicability:** A wide range of drug classes, including peptides, proteins, small molecules, and siRNA. The system is also applicable to the delivery of diagnostic and prophylactic agents.

**Products/Partners**

**Phase II:** BIND-014/BIND

**Preclinical:** AZD2811/AstraZeneca, BIND-510/BIND, Bind/Pfizer Accurins Program/Pfizer, KSP Inhibitor Program/ Merck, PKI1 Inhibitor Program/Merck, Roche Non-Oncology Nanomedicines/Roche

**Notable:** A novel technology portfolio that extends the applicability of nanoparticles to long circulating polymers that can be further tagged with targeting ligands.

**Technology Overview:** Long circulating, PEGylated, biodegradable polymer (PLGA-PEG, PLA-PEG, etc.)-based targeting nanoparticles that deliver high drug concentrations to target cells and tissues resulting in increased efficacy and reduced toxicity. The platform permits the engineering of libraries of drug-encapsulated targeted nanoparticles that differ systematically in their biophysico-chemical properties and the selection of nanoparticles that provide optimal properties. The targeting groups on the surface of the particles (attached to the biodegradable polymers) can be small molecule, peptide, protein, nucleotide or antibodies.

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**Technology: Ellipta**

**Type:** DPI (Dry Powder Inhaled)

**Company:** GlaxoSmithKline

**Applicability:** Small molecule single agent and drug combinations.

**Products/Partners**

**Marketed:** Anoro Ellipta/Theravance, Arnuity Ellipta/GlaxoSmithKline, Breo Ellipta/Theravance, Incruse Ellipta/GlaxoSmithKline

**Phase III:** GSK2384425/GlaxoSmithKline

**Notable:** With four products now approved, two in 2014, the Ellipta dry powder inhaler has become the device workhorse of the GlaxoSmithKline inhalation portfolio. An update to the well-validated Diskus inhaler, Ellipta offers a number of important benefits for patients and formulation developers.

**Technology Overview:** A dual-strip, multidose, disposable dry powder inhaler device. Each strip can contain a different active or be configured for delivery of a single medication. The device includes a dose counter and is designed to prevent the patient from taking a double dose in one inhalation.

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**Technology: Enhance**

**Type:** Injection Site Absorption Enhancers

**Company:** Halozyme, Inc.

**Applicability:** All biologics and small molecule medications up to 200 nm.

**Products/Partners**

**Marketed:** Hylenex/Halozyme, HyQvia/Baxter, MabThera/Biogen, Herceptin SC/Roche

**Phase II:** PEGPH20 Oncology/Halozyme, Analog Insulin-PH20/Halozyme, HTI-501/Halozyme

**Phase I:** Enhance Artificial Pancreas Program/Yale, Actemra-PH20 SC/Roche

**Preclinical:** rHuA1AT-PH20/Intrexon, RN316 (PCSK9)-PH20/Pfizer, Rivipsenel-PH20/Pfizer, Daratumumab SC Program/Janssen

**Notable:** The list of products and partnerships are testament to the versatility of the Enhance technology. Not included are a number of co-therapy programs being undertaken by Halozyme involving approved insulins and chemotherapeutics. The ability to deliver large-volume macromolecules subcutaneously without the need for prolonged infusion provides benefits for patients and caregivers. Halozyme has a number of active collaborations: Janssen - 5 targets, Pfizer - 6 targets, and Roche - 8 targets.

**Technology Overview:** Recombinant human hyaluronidase enzyme is used as a drug delivery enhancement system. The enzyme digests hyaluronic acid, which facilitates the penetration and dispersion of other drugs by temporarily opening flow channels under the skin or into tumors that accumulate hyaluronic acid. Molecules as large as 200 nm may pass freely through the perforated extracellular matrix. The technology is being applied to local anesthesia, especially ophthalmology, solid tumor malignancies, and to improve the absorption of injectable products. The technology makes large-volume subcutaneous injections practical.

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**Technology: Cosmo Multi-Matrix**

**Type:** Colonic Release, Oral Matrix

**Company:** Cosmo Pharmaceuticals

**Applicability:** Drugs with solubility properties ranging from freely soluble to practically insoluble. Drugs noted in patent applications include budesonide, metformin, gabapentin, levodopa, carbidopa, ibuprofen, diclofenac sodium, and chlorohexidine. The MMX technology may also be used for diagnostics targeting the gastrointestinal tract.

**Products/Partners**

**Marketed:** Lialda/Shire, UCERIS/Salix (Valeant), Zacol NMX/Dr. Falk Pharma

**Phase III:** CB-17-01/Cosmo Pharmaceuticals: Rifamycin SV MMX/Dr. Falk Pharma

**Preclinical:** CB-01-12/Cosmo Pharmaceuticals, CB-01-16/Cosmo Pharmaceuticals, Bioker Diabetes Program/Bioker

**Notable:** The importance and commercial value of drug delivery and formulation technologies specific for gastrointestinal conditions was further validated in 2014 and early 2015 by the increasing sales of products targeted to these conditions and the bidding war for Salix, a specialty pharma company with a gastrointestinal focus.

**Technology Overview:** Multi-Matrix System (MMX) comprises controlled-release and taste-masked tablet compositions containing one or more drugs inglobated in a three-component matrix structure, i.e., a structure formed by successive amphiphilic, lipophilic (or inert) matrices, and finally inglobated or dispersed in a hydrophilic matrix. Compositions are coated with pH-resistant acrylic copolymers that delay the release until the tablet reaches the indicated intestinal location where the programmed dissolution begins.
Technology: Enable Injector

Type: Patch Pumps/Micropumps/Microinfusors, Reconstitution Systems, Large-Volume Injectors, Concentrated Suspension/Viscous Solution
Company: Enable Injections
Applicability: All biologics and small molecule medications.
Products/Partners: Undisclosed

Notable: A novel small body-worn single-use device that permits subcutaneous dosing using a standard container closure system while providing tactile feedback. The Enable Injector is intended to allow for extended injection times and deliver volumes up to 20 mL.

Technology Overview: A circular shaped, mechanical-driven patch pump injection device designed to deliver 2-10 cc or 10-20 cc in volume (two sizes of device). The device accepts standard vials and cartridges and is able to automatically reconstitute lyophilized products. It also automatically warms the drug during the transfer from the vial to in the injector. The injector is ready for use immediately, eliminating the 30-min wait time for refrigerated medications. The device is activated with a push of a button and when injection is complete, the needle retracts. The device can deliver 1-100 cp solutions at 1 mL/min through a 29 G needle. Flow rates and delivery volumes can be modified to meet requirements of products.

Technology: ZP Patch

Type: Poration Microneedles
Company: Zosano Pharma Corp.
Applicability: The ZP Patch technology can deliver peptides, small water-soluble molecules, biopharmaceuticals, and vaccines with good non-refrigerated stability. The technology has been applied to a variety of molecules, including PTH, hGH, PTHrP EPO, GSCF, GLP-1, antibodies, BNP, fentanyl, granisetron, naratriptan, sumatriptan, zolmitriptan, and various vaccines.

Products/Partners
Phase II: Daily ZP-PTH/Lilly, ZP-Glucagon/Zosano
Preclinical: ZP-Triptan/Zosano GIP-1/Novo Nordisk

Notable: The most advanced generation of microneedle delivery technology, Zosano’s ZP-PTH is partnered with Eli Lilly and is will be entering Phase III testing. This will largely determine the fate of microneedle technologies given that several companies developing similar technologies have failed. With the development of easy-to-use needle and needle-free devices, including inhalation, the market for macromolecule delivery is becoming very congested which should benefit patients.

Technology Overview: A user-friendly transdermal delivery system that incorporates Zosano’s thin titanium Macroflux microneedle array technology into a patch the size of a coin with a reusable, spring-loaded applicator to create holes in the stratum corneum and deliver drugs systemically. The microneedles are dry coated with the active. The patches contain an adhesive backing and are typically worn for up to 30 mins. The Macroflux microarrays can be used in conjunction with iontophoresis.

Technology: Nektar Polymer Drug Conjugates

Type: Prodrugs, PEG Polymer
Company: Nektar Therapeutics
Applicability: Nektar’s very low molecular weight polyethylene glycol (PEG) conjugation technology is most suitable for small molecules. The higher molecular weight releasable PEG technology is applicable to both low and high molecular weight actives.

Products/Partners
Marketed: Movantik/AstraZeneca
Phase II: NKTR-102 (etirinotecan)/Nektar, NKTR-181/Nektar
Phase I: NKTR-171/Nektar

Notable: Movantik (naloxegol), approved in 2014, embodies Nektar’s new approach to the use of polyethylene glycol polymers conjugated to small molecules for the purpose of restricting distribution. NKTR-102, using hydrolyzable PEG linkers, recently hit a bump in the road with Phase III results in advanced breast cancer showing an improvement, albeit not statistically significant, in median overall survival.

Technology Overview: These latest iterations of the use of polyethylene glycol (PEG) involves:

1. The attachment of very low molecular weight PEG polymers to small molecules to restrict distribution of the conjugate to the periphery and prevent CNS uptake.
2. The use of hydrolyzable linkers with higher molecular weight PEG polymers permitting the inactive PEG conjugated chemotherapeutics to be preferentially taken up by tumors followed by release of the active agent.

Technology: Synfusion

Type: Prodrugs, Antibody-ADC
Company: Biogen
Applicability: Proteins, by coupling a therapeutic protein, such as factor VIII and factor IX, to the Fc domain of an immunoglobulin.

Products/Partners
Marketed: Alprolix/Swedish Orphan Biovitrum, Eloctate/Swedish Orphan Biovitrum

Notable: Two Synfusion products, Alprolix and Eloctate, were approved in 2014 for the treatment of Hemophilia-related conditions. The use of fusion proteins is becoming more and more common and achieves drug delivery outcomes using the genetic engineers toolbox.

Technology Overview: Novel Fc-fusion constructs that link a single copy of a therapeutic protein to the Fc region on an antibody so as to optimize the pharmacokinetic and pharmacodynamic properties of the biopharmaceutical. The constructs are optimized to bind to FcRn in the endothelial cells that line the blood vessels, effectively “recycling” the drug to increase its circulating half-life.
**Technology: Technosphere/Dreamboat**

**Type:**
- **Technosphere:** Inhalation Formulations, DPI, Oral Peptide/Protein/Macromolecule, Nasal Formulations
- **Dreamboat:** DPI-Dry Powder Inhalers

**Company:** Mannkind Corp.

**Applicability:** Technosphere is a dry powder formulation for inhalation that can deliver potent peptides, small water-soluble molecules, biopharmaceuticals, and vaccines with good non-refrigerated stability. Technosphere has been applied to a variety of molecules, including PTH, hGH, PTHm EPO, GSCF, GLP-1, antibodies, BNP, fentanyl, granisetron, naratriptan, sumatriptan, zolmitriptan, and various vaccines.

Dreamboat is an easy-to-use, whistle-like, low-cost, multidose DPI device platform that is adaptable to a broad range of products, including proteins and peptides.

**Products/Partners**
- **Marketed:** Afrezza/Sanofi
- **Preclinical:** Mannkind Bone Agent Program/Mannkind, MKC180/Mannkind

**Notable:** Technosphere (Formulation) and Dreamboat (Device) are the technologies behind Mannkind's Afrezza. The performance and portability of this dry powder inhalation treatment addresses physician and patient needs with a good chance of establishing the value of inhalation as an alternative to injections for macromolecules.

**Technology Overview:** Technosphere - A platform technology based on a novel and inert excipient that forms microparticles appropriately sized, between 0.5 and about 5 µm, for inhalation into the deep lung without the traditional requirement for subsequent processing, i.e., milling, sizing etc. The microparticles have a very rapid dissolution profile and can mimic the PK of intra-arterial administration. The Technosphere platform is broadly applicable to other delivery routes, including nasal, oral, as well as SC or IV injection.

Dreamboat - Dreamboat is a smaller, more discrete, easier to use, dry powder inhalation device that requires lower airflow and less powder to deliver clinically meaningful plasma concentration. It shows little change in performance over a wide range of airflow rates.

**Technology: Zeneo**

**Type:** Needle-Free Injector

**Company:** Crossject

**Applicability:** The technology platform has been clinically proven for intradermal, subcutaneous, and intramuscular injection of small molecules, therapeutic proteins, and vaccines, both for human and animal health applications.

**Products/Partners**
- **Phase I:** Fluarix Needle-Free/GlaxoSmithKline, Methotrexate Supergeneric/Crossject, Epinephrine Supergeneric/Crossject
- **Preclinical:** Sumatriptan, Supergeneric/Crossject

**Notable:** An injection device using needle free technology and that doesn't look, or operate, like more traditional needle and needle-free injection systems. The device offers customizable delivery depths from subcutaneous to intramuscular. The winner of several design awards.

**Technology Overview:** A single-use, prefilled, fixed-dose needle-free injector utilizing a novel gas-generating technology adapted from the automobile safety field (similar to airbags), as the power source. Device is proven to be suitable for intradermal, subcutaneous, and intramuscular injections. The injector is customizable for different volumes (0.1-0.6 ml) and viscosities.
Ten Notable Drug Delivery & Formulation-Related Transactions of 2014

The PharmaCircle database lists a total of 1,277 transactions in 2014 involving PharmaBio assets. This total included 325 transactions that directly involved technologies, products, or companies related to drug delivery and formulation. Table 1 provides a breakdown of drug delivery and formulation transactions for the years 2012, 2013, and 2014 as classified by PharmaCircle. There is often overlap in categories; Product Deals might well include technology assets, and Company Acquisitions are likely to include the acquisition of products. These types of transactions are not “double-counted.”

<table>
<thead>
<tr>
<th>Table 1. Drug Delivery &amp; Formulation Transactions (2012-2014)</th>
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<tr>
<td><strong>2014</strong></td>
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<tr>
<td>Amendment Deals</td>
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<tr>
<td>Company Acquisitions</td>
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<tr>
<td>Technology Deals</td>
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<tr>
<td>Joint Venture</td>
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<tr>
<td>Option Agreement</td>
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<td>Pharma Services Deals</td>
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<td>Product Acquisitions</td>
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<td>Product Deals</td>
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<tr>
<td>Termination Deals</td>
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<td>Total</td>
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As is apparent from the table above there is sufficient variability in year-to-year to make firm conclusions regarding trends. What does jump out is the substantial drop in the number of Technology Deals from the years 2012 and 2013 to 2014. Is this an anomaly or does it reflect an actual shift in the need for companies to access proprietary technology and know-how? Do companies already possess the necessary technology and expertise to be able to “do it in house”? Is the cost of sourcing external technology too high in terms of financial resources and partnership management? It’s hard to tell, but there was no uptick in technology transactions in the first quarter of 2015. A total of 64 drug delivery and formulation transactions were reported in the first quarter of 2015, with 17 classified as Technology Deals.

Over the same period, there appears to be an uptick in the number of Product Deals and Product Acquisitions, perhaps reflecting the industry’s increasing focus on applying technologies to products that validate the technology and provide very saleable assets. The first quarter of 2015 had 25 Product Deals and 4 Product Acquisitions. It has become obvious the real value of drug delivery is in the products that can be developed with the technology, not the technology itself. This is more apparent if we look at the number of products at some stage of preapproval development, Research to Phase III. PharmaCircle identified 10,461 active drug delivery or formulation-related products at some stage of premarket development, including 863 in Phase III as of the end of the first quarter of 2015.

Examining individual transactions reveals a common theme – caution; limited upfronts in the product and technology deals, with a much greater portion of the value being back-loaded in regulatory and commercial milestones. In these back-loaded deals with limited upfront payments, the development costs are most often taken on by the licensor, providing for a reasonable sharing of risk. The drug delivery company has taken the risk to develop the technology, while the licensee takes on most of the development risk going forward. Not what drug delivery companies were used to in the 1990s, but a pragmatic approach to the financial realities of the 2010s.

The big drug delivery deal of the year certainly was Mannkind’s Afrezza deal with Sanofi. Even this deal, with $150 million upfront, is relatively small when one considers the preapproval investment that Pfizer had made in Nektar’s Exubera.

A number of transactions have been selected for examination to provide a bit of insight into the mood of licensors and licensees. These are not the megadollar acquisitions seen in the larger BioPharma area, but the types of transactions that help finance the drug delivery and formulation sector, spur additional investment, and lead to breakthrough technologies and products.
### Product Development – Long-Acting Depot

**Type:** Technology Licensing/Product Option  
**Active:** buprenorphine hydrochloride  
**Indication:** Opioid Dependence  
**Delivery Route:** Injectable - Depot  
**Dosing Interval:** 30 days  
**Licensor/Licensee:** Evonik/BioDelivery Sciences  
**Deal Summary:** Evonik will be applying their FormEZE technology to developing a one-monthly injectable formulation of buprenorphine. BioDelivery Sciences has an option to license “Phase I ready formulations” in exchange for milestones and royalties to Evonik.  
**Comment:** BioDelivery Sciences has made the transition from an Emerging Stage Specialty Pharma Company developing products through development to approval to a Commercial Stage Specialty Pharma Company with a USA sales and marketing effort. Their first commercialized product, Bunavail (buprenorphine/naloxone film) targeted to the management of opioid dependence has been launched in the USA. This deal beefs up their development pipeline with a complementary product for their portfolio, albeit at a very early stage. It’s unlikely that any product coming out of this agreement would be marketed before 2020.  
This transaction reinforces the value of companies such as Evonik who have the necessary technology, intellectual property and expertise to develop ‘higher tech’ pharmaceutical formulations. Although not reported it is likely that Evonik is conducting the formulation development at their own expense, or with limited financial support from BioDelivery Sciences. While this represents a risk it allows Evonik to further explore and validate their FormEZE technology with the comfort that a willing and capable licensee is waiting to take it through clinical developments.

### Technology Licensing – Subcutaneous

**Type:** Collaboration/Licensing Agreement (Worldwide)  
**Active:** Five Undisclosed Targets  
**Indications:** Undisclosed Dependence  
**Delivery Route:** Injectable - Subcutaneous  
**Licensor/Licensee:** Halozyme/Janssen Biotech  
**Agreement Announcement:** 2014-12-17  
**Deal Summary:** Janssen will be permitted to apply Halozyme’s subcutaneous enhancing human hyaluronidase enzyme (rHuPH20, Enhanze) to a total of five proprietary targets. The deal terms include $15 million upfront and $566 in development, regulatory and sales related milestones, plus royalties.  
**Comment:** Halozyme appears to be walking a very pragmatic line between developing their own pipeline while providing technology and ‘materials’ to partners and customers. Halozyme has significant partnerships with five Big Pharma companies to apply Halozyme’s Enhance technology to their proprietary products, of which three products are already approved and providing ongoing revenue. Their proprietary pipeline includes three products in clinical development. Halozyme also markets and sells recombinant hyaluronidase, Hylanex, as a prescription product to enhance tissue permeability of co-administered drugs. Sales of Hylanex accounted for about $13 million in 2014. Sales of bulk rHuPH20 to partners accounted for an additional $25 million. The late 2014 deal with Janssen further validates the Enhanze technology and provides the potential for additional revenue without adding additional risk or resource demands on Halozyme. The $15 million upfront is a pragmatic balance of receiving value for a license to the asset and encouraging a deal that can have significant value going forward.  
Despite receiving more than $75 million in revenue in 2014 Halozyme reported an Operating Loss of $63 million, largely based on research and development expenses of almost $80 million, of which more than two-thirds was invested in their propriety product pipeline.

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1 Development times are estimated by Pharamnumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.
## Product Licensing - Inhalation

**Type:** Product Licensing Agreement (Worldwide)  
**Product:** Afrezza  
**Indication:** Diabetes, Type 1 and Type 2  
**Delivery Route:** Inhalation – Dry Powder  
**Licensor/Licensee:** Mannkind/Sanofi  

**Deal Summary:** Sanofi gains worldwide commercialization rights for Afrezza, Mannkind retains certain manufacturing rights. In addition to an upfront payment of $150 million, and $775 million in milestones to Mannkind, the parties will split profits 35%/65%, Mannkind/Sanofi.  

**Comment:** This was doubtless the biggest drug delivery related deal of 2014 with Mannkind’s Afrezza finding a substantial partner in Sanofi. It appears to be a win-win for both parties. Mannkind is able to bring Afrezza to the market with the resources of a diabetes market leader that will be essential if Afrezza is to be a success. Sanofi at the same time picks up a new product option that has considerable market appeal and can elevate awareness of their whole diabetes portfolio.  

With an accumulated net loss of almost $2.5 billion, largely related to Afrezza development, Mannkind depends on a strong market acceptance of Afrezza to recoup their investment and turn any type of profit. Even with the $150 million upfront payment the larger cost to Sanofi will be related to the product launch expenses and the lost opportunity it might entail if Afrezza is not a blockbuster. Early market returns indicate that Afrezza is not being taken up as quickly as some analysts had forecast causing peak sales forecasts to be lowered to $1 billion annually.  

The approval of Afrezza in its current presentation is a big step forward for the delivery of inhaled macromolecules. Assuming there are no untoward safety issues, and the product is not completely rejected by the market, there is an opportunity for Mannkind to leverage their inhalation platform with other partners’ actives and finances.

## Product Acquisition - Buccal Spray

**Type:** Product Acquisition Agreement (Worldwide)  
**Product:** ZolpiMist  
**Indication:** Insomnia  
**Delivery Route:** Buccal - Spray  
**Licensor/Licensee:** NovaDel/Amherst  

**Deal Summary:** NovaDel Pharma transfers all assets related to ZolpiMist to Amherst Pharmaceuticals in exchange for Amherst assuming $2.2 million in fees owed to the FDA and a 10% royalty on sales aggregated to a total of $500,000.  

**Comment:** This is the type of deal that gets done as the lights are being turned off. NovaDel in its various incarnations has been around for more than two decades managing to get two products through to FDA approval, NitroMist (nitroglycerin) and ZolpiMist (zolpidem). Neither product though was able to find a strong partner able to capture market share from competing simple oral and sublingual dosage forms.  

The deal basically hands off ZolpiMist to Amherst in exchange for assuming the costs of the product’s FDA approval fees, and penalties for late payment. The product was approved in 2008 and never managed to gain significant market acceptance.  

NovaDel is representative of many other smaller drug delivery technology companies who developed products that offer a new dosage form, with no therapeutic benefits and limited convenience improvements. It’s a cautionary tale for other companies. While a major pharmaceutical company may be able to succeed with this as part of a lifecycle management strategy, that opportunity is not available to smaller emerging companies.

1 Development times are estimated by Pharmannumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.
### Product Licensing – Needle Free, Nasal

**Type:** Product Licensing Agreement (Worldwide)  
**Product:** Sumavel DosePro  
**Delivery Route:** Injection – Needleless Device  
**Licensor/Licensee:** Zogenix/Endo  
**Agreement Announcement:** 2014-04-24  
**Technology:** Needle Free Injection (DosePro)  
**Current Status:** Marketed (EU, USA)  
**Deal Value:** $85 million plus $20 million in commercial milestones  

**Comment:** These two product deals by Endo in 2014 highlight the continuing need of non-research based specialty pharma companies to feed their commercial infrastructure. These two deals provide limited upside but fit well with Endo’s CNS and male health portfolios. Endo acquired the rights to Sumavel DosePro for about three-times 2013 sales, a little lower than the five-times norm, perhaps reflecting future prospects for the product. Zogenix seems to have made a major shift in clearing out their commercial stage assets, most recently their marketed opioid Zohydro ER. The $25 million upfront paid for Natesto probably covers Trimel’s development and licensing costs with perhaps a little left over to reinvest in their pipeline. The rewards for Trimel will depend on commercial success in the USA and selling overseas marketing rights. They seem committed to building their own Canadian sales and marketing infrastructure, a strategy that was developed by Biovail with mixed success. These two deals reflect the pragmatic behavior of licensors and licensees. The parties to these two transactions did as well as they could given the opportunities presented. Companies with sales and marketing resources will continue to in license even small products so long as they generate sufficient sales to offset a portion of the salesforce costs. At the same time smaller companies without the resources to establish or support commercial operations will wisely depend on a partner to generate the necessary sales to support their development of additional products. The challenge for these small companies is to develop a future product with sufficient potential to allow them to make leap to the commercialization stage. It seems Zogenix took this step and has decided to step back. It’s a big step, and it’s not easy.

### Product Licensing – Transdermal

**Type:** Product Licensing Agreement (Worldwide)  
**Product:** ZP-PTH  
**Indication:** Osteoporosis  
**Delivery Route:** Transdermal  
**Licensor/Licensee:** Zosano/Eli Lilly  
**Agreement Announcement:** 2014-12-02  

**Deal Summary:** Eli Lilly invests $15 million coincident with Zosano’s initial public offering. Additional payments will be made for the achievement of regulatory and sales milestones, up to $300 million and $25 million respectively, plus double digit royalties on sales.  

**Comment:** In many ways this seems to have the feel more of an option rather than license agreement. The upfront amount is small for a pre-Phase 3 stage product and made as an investment in Zosano. Should ZP-PTH make it through to the market and enjoy market success both companies will be well rewarded. If the product fails in development there will be little loss for Lilly. An upfront investment of $15 million represents a relatively inexpensive option for a valuable product. The benefit for Zosano was the validation of a large and successful partner like Eli Lilly that allowed them to successfully secure their initial public offering that netted them $45 million. Zosano will be responsible for all expenses through to approval but have the benefit of Lilly’s expertise in the area of endocrinology and osteoporosis.
Deal Summary: Following a research collaboration signed in 2011 Biogen has exercised its option to license the XTEN technology for novel, fully-recombinant Factor VIII products. The agreement includes $1 million upfront, $38 million in development and commercial milestones, and royalties on commercial sales.

Comment: This seems to be a ‘throwback’ Big Pharma – Drug Delivery company deal with a limited upfront payment with rewards for Amunix mostly back loaded as milestones and royalties that are unlikely to exceed mid-single digits. The technology offers a number of benefits over PEGylation for extending in vivo half-life of macromolecules. But at this point there is limited data and no approved products to validate the safety and scalability of the technology. The technology does offer partners a degree of intellectual property protection that is no longer possible with PEG technology.

With a couple of Big Pharma product development deals in hand Amunix has the basis to validate its technology and secure more attractive future deals. PEGylation will continue to be a lower cost competitor.

Deal Termination – Roche / Chiasma

Type: Product Deal Termination
Product: Octreolin (octreotide)
Indication: Acromegaly
Delivery Route: Oral
Licensor/Licensee: Chiasma/Roche AG

Deal Summary: The original deal, signed in 2013, granted Roche a worldwide license to Chiasma’s Octreolin in exchange for $65 million upfront, $530 million in milestones and double digit royalties. The parties announced a year later that the deal had been cancelled.

Comment: The sun rises and the sun sets on deals as well as the day. Despite the significant upfront investment by Roche a year and a half earlier, they chose to terminate the agreement. The reasons are not obvious. Chiasma claimed “the drug had favorable results in Phase 3 clinical trials” and suggested that the decision was in part related to Roche’s waning interest in the endocrinology sector. Chiasma stated their intention to move forward with the product.

The deal termination highlights a couple of important considerations. Deals like all relationships are not predictable and companies need to protect themselves from the fallout of a termination. Following termination of the deal with Roche, Chiasma has gone back to existing and new investors to raise an additional $70 million, and more recently brought in a new CEO. Significant upfront payments, such as the $65 million received by Chiasma, are needed to ensure continuity in the event a deal is terminated for reasons unrelated to product performance.

What is the future of technologies for the oral delivery of macromolecules? With injection formulations and devices becoming increasingly convenient and painless is there really a need for oral delivery if there is any question on the part of the clinician regarding efficacy? The recent clinical results for Octreolin support its ability to treat acromegaly, but perhaps not as reliably as the injectable comparator. In the end it seems that the market is most interested in delivery systems that are effective, safe and convenient, probably in that order. New delivery systems need to ensure they can match on efficacy and safety, and exceed in the area of convenience if they are to succeed.

1 Development times are estimated by Pharmanumbers based on an audit of development times and success rates for drug delivery and formulation enhanced pharmaceuticals in the USA between 1996 and 2010.
### Company Acquisition – Archimedes Pharma

**Type:** Company Acquisition  
**Company:** Archimedes Pharma Ltd.  
**Business Sector:** Specialty Pharma  
**Therapeutic Area:** Central Nervous System  
**Acquirer:** ProStrakan Group [Kyowa Hakko Kirin]  
**Agreement Announcement:** 2014-08-06  
**Deal Value:** $361.9 million

**Deal Summary:** ProStrakan purchased the share capital of Archimedes for £230 million. The deal values Archimedes at about 5.5 times 2013 sales.

**Comment:** Archimedes, founded in 2004, managed to assemble a commercial portfolio of a dozen marketed products through in licensing, acquisition and internal development. Focused primarily on CNS products the company in licensed complementary products. Its first pipeline product, a nasal fentanyl for the treatment of breakthrough cancer pain was approved in Europe in 2010 (PecFent) and in the USA in 2011 (Lazanda). To date it has achieved limited sales.

ProStrakan, a commercial stage specialty stage pharma company, was itself acquired by Kyowa Hakko Kirin in 2011. It continues to be active acquiring and in licensing commercial stage products for promotion by European sales and marketing teams.

### Company Acquisition – Activaero

**Type:** Company Acquisition  
**Company:** Activaero GmbH  
**Business Sector:** Drug Delivery Technology  
**Technology Area:** Inhalation - Nebulization  
**Acquirer:** Vectura Group Plc  
**Agreement Announcement:** 2014-03-13  
**Deal Value:** $33.6 million

**Deal Summary:** Vectura, best known for their dry powder respiratory technologies, products and pipeline, with the acquisition of Activaero gained access to Activaero’s unique proprietary nebulized device technology and a late stage corticosteroid for asthma.

**Comment:** Critical mass continues to be a requirement for technology focused drug delivery and formulation companies. In this case Vectura gains access to a complementary inhalation platform, collaboration partners, and a late stage development candidate that will complement Vectura’s pipeline and technology activities. Activaero in turn receives access to the resources necessary to further develop and successfully commercialize its AKITA and FOX liquid aerosol delivery systems.

It’s not clear that investors in Activaero were rewarded with the acquisition of the company. But at the same time there was a meaningful transaction that provides a benchmark value for similar companies. The AKITA technology has been in development for more than a decade and a half and clearly needed to be pushed forward.
Ten Notable Drug Delivery & Formulation Approvals of 2014

Drug Delivery in 2014 continued to deliver on the promise of enhanced efficacy, safety, and convenience in an ever-increasing breadth of products that spanned the range from cancer to neurological disease to ophthalmic indications. Drug Delivery has left behind the novelty and excitement it enjoyed in the 1980s and 1990s, where a few select companies seemed to be practicing alchemy, turning well-worn actives into pipeline gold. The 2010s has seen Drug Delivery demystified and become a discipline that has many experienced professionals practicing with an art and science that was not anticipated even a decade ago, bending the performance of a molecule to the needs of the patient.

Among the many drug delivery and formulation-enhanced approvals of 2014, we have selected 10 that effectively summarize the current focus of drug delivery and formulation in terms of therapeutic products. All of these products have a little something extra in terms of technology, or have managed to fill an important gap in the therapeutic armamentarium of clinicians. Products that benefit from both formulation and device enhancements can be found in the Ten Notable Drug-Device Approvals of 2014 section of this report. In some cases the differences were not so obvious, and certain products might well have been placed in either category, or both.

PEGylation, a technology conceived in the 1970s with its first approvals in the 1980s and followed by massive commercial success in the early 2000s, features prominently in the list of Top Ten Drug Delivery & Formulation Approvals of 2014. Plegridy, a PEGylated version of Biogen’s Interferon beta-1a, follows closely the trail blazed by the Peginterferon alphas (PegIntron and Pegasis), offering extended dosing intervals and patient-friendly injection formats. It’s interesting to speculate as to why the Plegridy approval lagged behind the Interferon alphas by more than a decade. Was it a technical challenge or a commercial decision? Interestingly, Plegridy does not seem to use technology from the two leading companies in the field of PEGylation, Enzon and Nektar.

The more remarkable PEGylated product approval in 2014 was Nektar’s Movantik. As the first-approved PEGylated small molecule product, Movantik has defined a new whole class of applications for polyethylene glycol conjugates. Enzon took a run at small molecule PEGylation in the early 2000s with its PEGylated anticancer agents hoping to preferentially accumulate PEG-linked antineoplastic agents at the site of the tumor based on preferential uptake and retention of macromolecules. The strategy with Movantik is simpler and arguably more elegant; restrict the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion. Being limited to the distribution of the agent, a PEGylated narcotic antagonist, to the gastrointestinal tract following oral ingestion.

The second opioid approval of note in 2014 was Mallinckrodt’s Xartemis XR. A sustained-release formulation of oxycodone and acetaminophen using DepoMed’s AcuForm Diffusional technology, Xartemis XR really doesn’t break much new ground from the therapeutic or technology perspective, but it seems to have met a regulatory and patient need, with the FDA having granted it priority review status. The combination of acetaminophen or acetylsalicylic acid with an opioid has been de facto abuse-deterrent strategy used for several decades. Including either of these non-opioid analgesics generally permits an opioid to be classified by the DEA at a lower Controlled Substance Schedule, with looser prescribing restrictions, but in this case, Xartemis XR still carries a Schedule II classification perhaps because it incorporates oxycodone.

MabThera-PH20, Alprolix, and Eloctate offer their own unique take on what formulation and drug delivery mean in the second decade of the 21st century. The well-equipped Drug Delivery and Formulation toolbox now includes technologies normally associated with protein chemists and gene jockeys. MabThera-PH20, Alprolix, and Eloctate all provide the types of benefits associated with drug delivery, more convenient dosing, and extended circulating life, respectively, but through the use of gene engineering.

Each of these ten products offers insight into the opportunity offered by the creative use of drug delivery and formulation technologies to new and previously approved actives. The products highlighted provide additional detail on each of the products with information gleaned from the PharmaCircle database. Four of the Notable Products of 2014 are presented with additional information because, in our opinion, they point to where drug delivery and formulation is likely to head in the years to come.
Movantik

**Active:** naloxegol oxalate  
**Molecular Weight**: 652 Da  
**Indication:** Opioid-induced constipation  
**Delivery Route:** Oral – Tablet  
**Dosing Interval:** 24 hours  
**Company/Partner:** Nektar Therapeutics/AstraZeneca  
**First Approval:** 2014-09-16 (USA)  
**Formulation Type:** Oral, PEG-Conjugate

**Comment:** As an oral PEG small molecule conjugate Movantik’s distribution is intended to be limited to the gastrointestinal tract. By acting to block opioid binding at mu-opioid receptors Movantik is able to antagonize the constipating effects of opioids, particularly oral opioids, most importantly in the post surgical setting. Chemically Movantik is a reduced ketone naloxone derivative conjugated to a 7-unit polyethylene glycol linear chain through a 14-position alcohol. This is a rather simple but previously untried drug delivery strategy that does not depend on any particular uptake preference for the PEG-conjugated narcotic antagonist to be effective. Nektar’s late stage PEG-small molecule targeted to cancer, NKTR-102 a novel topoisomerase I inhibitor, depends on preferential uptake and retention in tumors to provide for a greater therapeutic index. Recent results in the clinical setting have been disappointing. Opioid-induced constipation is a significant issue for hospitalized patients and a major cause of discharge delay. Nektar has publicly stated that their commercial partner, AstraZeneca who has partnered with Daiichi Sankyo for the USA market, is expecting sales to top $1 billion annually.

Hysingla

**Active:** hydrocodone bitartrate  
**Molecular Weight**: 299 Da  
**Indication:** Chronic Pain  
**Delivery Route:** Oral, Tablet  
**Dosing Interval:** 24 hours  
**Company:** Purdue Pharma  
**First Approval:** 2014-11-20 (USA)  
**Formulation Type:** Oral, Abuse Deterrent, Modified Release

**Comment:** Purdue Pharma is the clear industry leader in developing abuse deterrent opioid formulations to approval and securing abuse resistant labeling from the FDA at launch. The Hysingla approval follows by four years the approval of OxyContin OTR an abuse resistant formulation of oxycodone, and severely diminishes the commercial value of Perrin’s Zohydro ER once it receives similar abuse deterrent claims. Another Purdue abuse deterrent formulation approved by the FDA in 2014, Targiniq, a combination of naloxone and oxycodone addresses the abuse deterrence market with an agonist/antagonist strategy. This is similar to the strategy used with Pfizer’s Embeda, a morphine and naloxone combination, which has been on and off the market since its approval in 2009.

There are no reported forecasts for Hysingla ER but it is reasonable to expect that it will capture a significant share of the extended release opioid market, presumably at a premium price. Peak annual sales in excess of $500 million annually seem reasonable considering that sales of Purdue Pharma’s abuse deterrent OxyContin top $2 billion annually.

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1. Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
**Plegridy**

- **Active:** peginterferon beta-1a
- **Molecular Weight:** ~44,000 Da
- **Indication:** Multiple Sclerosis (Relapsing)
- **Delivery Route:** Injectable – subcutaneous
- **Dosing Interval:** 14 days
- **Company/Partner:** Biogen
- **First Approval:** 2014-07-18 (EU)
- **Formulation Type:** Injection, PEG-Conjugate

**Comment:** With the increasing availability of oral treatments for multiple sclerosis the multi-injection per week requirements of the interferon betas are facing a serious competitive challenge. And at the same time there are three unPEGylated interferon beta agents on the market all jockeying for market share with a very similar set of features and benefits. Plegridy moves the 'needle' on convenience, requiring dosing every two weeks rather than two or three times per week. This is a multibillion-dollar market where even a couple of points shift in market share can mean an increase of tens of millions of dollars. It's not clear why it took so long for Biogen to file for approval. The therapeutic benefits and commercial value of a PEGylated interferon had been well demonstrated with Schering-Plough's PegIntron and Roche’s Pegasys. Both products also demonstrated the comparative benefits of differing PEGylation strategies. The development time of almost 7 years suggests the product was only introduced into the clinic in 2008, some eight years after the first PEGylated interferon alpha had been approved. Plegridy could also have been included in the list of Ten Notable Drug-Device approvals of 2014. At this point the industry has come to recognize that prefilled syringes, and especially pens, are a requirement for the successful uptake of any injectable in the outpatient setting.

**Xartemis XR**

- **Active:** oxycodone hydrochloride, acetaminophen
- **Molecular Weight:** 299 Da
- **Indication:** Acute Severe Pain
- **Delivery Route:** Oral, Tablet
- **Dosing Interval:** 12 hours
- **Company:** Mallinckrodt Pharmaceuticals
- **First Approval:** 2014-03-11 (USA)
- **Formulation Type:** Oral, Modified Release (AcuForm)

**Comment:** Good ideas don’t always stay hidden. That seems to be the case with Mallinckrodt’s Xartemis XR offering twice-daily dosing convenience. While immediate release oxycodone-acetaminophen, and hydrocodone-acetaminophen products have been an approved mainstay of pain management for decades, Xartemis XR represents the first approved sustained release formulation. A product idea worthy of FDA Priority Review designation. Product development seems to have been well managed taking a very short 3.8 years between IND submission and FDA approval. This was no simple bioequivalence type program. There were a total of fourteen studies involving 705 patients, including two Phase 3 efficacy studies and a relative abuse potential study in normal volunteers. Xartemis XR received no abuse deterrent claims in their labeling. Sales forecasts are unavailable for Xartemis XR. Given the significant competition it faces and the lack of any explicit abuse deterrent claims in the product label, hitting $100 million in annual sales seems to be a stretch objective.

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1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
Active: eftrenonacog alfa
**Molecular Weight:** ~98,000 Da
**Indication:** Hemophilia B
**Delivery Route:** Injection – intravenous
**Dosing Interval:** 7-10 days (prophylaxis)
**Company/Partner:** Biogen
**First Approval:** 2014-03-21 (Canada)
**Formulation Type:** Injectable, Fc Fusion (Synfusion)
**Technology Provider:** Biogen
**Device:** Syringe/Vial
**Notable:** Protein-immunoglobulin fusions represent a next generation prodrug approach that blur the line between protein engineering and traditional formulation.

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Active: rituximab
**Molecular Weight:** ~144,000 Da
**Indication:** Cancers (Multiple)
**Delivery Route:** Injection – subcutaneous
**Dosing Interval:** 24 hours
**Company/Partner:** Biogen/Roche
**First Approval:** 2014-03-21 (EU)
**Formulation Type:** Injectable, Absorption Enhancer (Enhanze)
**Technology Provider:** Halozyme Therapeutics
**Device:** None
**Notable:** A novel formulation approach incorporating a proprietary enzyme to digest hyaluronic acid and permit a product normally administered by slow infusion to be delivered intravenously.

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**Alpronix**

**Actives:** buprenorphine hydrochloride / naloxone hydrochloride
**Molecular Weight:** 468 / 327 Da
**Indication:** Opioid Dependence
**Delivery Route:** Oral, Buccal
**Dosing Interval:** 24 hours
**Company/Partner:** BioDelivery Sciences Intl.
**First Approval:** 2014-06-06 (USA)
**Formulation Type:** Transmucosal (BEMA)
**Technology Provider:** BioDelivery Sciences Intl.
**Device:** None
**Notable:** A next generation formulation approach providing greater convenience and requiring half the dose of the two actives to achieve similar plasma levels as Suboxone.

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**Bunavail**

**Actives:** flucinolone acetonide
**Molecular Weight:** 452 Da
**Indication:** Diabetic Macular Edema
**Delivery Route:** Injection - Ocular implant
**Dosing Interval:** Up to 36 months
**Company/Partner:** Alimera Sciences
**First Approval:** 2012-05-07 (EU)
**Formulation Type:** Implant, Non-erodible Intravitreal (Durasert)
**Technology Provider:** pSivida
**Device:** Preloaded 25-gauge needle
**Notable:** Only approved in the USA in 2014 this 36 month implant provides enhanced convenience and outcomes for ophthalmic conditions that require constant intraocular glucocorticoid levels.

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**Copaxone (Concentrated)**

**Active:** glatiramer
**Molecular Weight:** 624n Da
**Indication:** Multiple Sclerosis, Relapsing, Remitting
**Delivery Route:** Injection – subcutaneous
**Dosing Interval:** ~ 48 hours
**Originator/Partner:** Teva
**First Approval:** 2014-01-28 (USA)
**Formulation Type:** Injectable, Mannitol Solution
**Technology Provider:** Not Applicable
**Device:** Prefilled Syringe
**Notable:** A simple lifecycle management high-dose formulation that enhances convenience and promises to extend the commercial prospects of the Copaxone franchise.

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**Eloctate**

**Active:** Efmoroctocog alfa
**Molecular Weight:** ~26,000 Da
**Indication:** Hemophilia A
**Delivery Route:** Injection – intravenous
**Dosing Interval:** 4 days
**Company/Partner:** Swedish Orphan Biovitrum/Biogen
**First Approval:** 2014-06-06 (USA)
**Formulation Type:** Injectable, Fc Fusion (Synfusion)
**Technology Provider:** Biogen
**Device:** Kit (solvent in prefilled syringe)
**Notable:** An Fc fusion protein for the treatment of hemophilia permitting an extended dosing interval of every four days for prophylaxis.

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1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
The Drug Delivery & Formulation Pipeline

So what does the Drug Delivery & Formulation Pipeline look like? How does it compare with the non-drug delivery enhanced/enabled pharmaceutical product pipeline? It’s easier to understand if we define and explain the terminology we will be using:

**Product** - a Product is a pharmaceutical entity that is defined by its brand name and dosage form, but is independent of stage of development or geography. For example Celebrex Capsules is a product.

**Program** - a Program is a Product approved or being studied for a defined indication, independent of geography. For example, the Product Celebrex Capsules is approved or being studied for a total of 11 different indications, all Programs, that range from inflammation to cancer to women’s health.

**Drug Delivery & Formulation** - Products and Programs that depend on some element of formulation technology to provide for tailored administration, distribution, metabolism, and/or excretion of a pharmaceutical active.

**DDEP** - Drug Delivery Enabled/Enhanced Product or Program, refers to any agent that requires the use of an integral device and/or drug delivery or formulation technology.

**PharmaBio** - Products and Programs that do not incorporate tailored formulation technologies. The opposite of a DDEP.

The figures presented are qualified with respect to whether they refer to Products or Programs. Numerically, it can make a very big difference. Why not just stick to Products and ignore Programs? In many cases, Programs can provide a better sense of what’s actually in the pipeline. For example, a product that may have been approved, and is now marketed for depression, might be in Phase III for dementia. It’s the same dosage form, perhaps a sustained-release tablet. The Phase III activity may incorporate the same Product, but it represents a different Program. We’ll clarify as appropriate in the accompanying text.

Comparing Products to Programs is like comparing apples to oranges; they are both fruits in the larger sense, but they are quite different if you look more closely.

It’s worth noting that it is only possible to count Products and Programs that are publicly disclosed. Most emerging and smaller biopharmaceutical companies are quite happy to disclose their pipelines. In many cases, they are obligated to disclose this information because it is material to their operations. This is not the case with the larger biopharmaceutical companies who prefer to limit early Product disclosure and have no obligations to do so at an early stage of Product development. With the more recent requirement for all companies to list clinical trials online with regulatory authorities, it has become easier to identify earlier stage Products and Programs, particularly those that are post-Phase I.

This pipeline analysis for the most part does not make reference to marketed Products and Programs. This is because there are a large number of generic products that unreasonably dilute and skew the relative figures. For every approved innovator product, there may be a half dozen approved generics. Pipeline generic products are also not included because they are, for the most part, only disclosed when filed for approval or approved.

It’s also important to understand what constitutes a Drug Delivery and Formulation Enhanced/Enabled Product (DDEP) for the purpose of this pipeline analysis. In practice, all pharmaceutical products are formulated to some extent, if only with lactose. This review considers any oral product that does not incorporate a specific drug delivery or formulation technology, ie, extended release, nanoparticles, specialized coatings, to be a PharmaBio product or Program. In a similar fashion, any injectable that does not require specialized excipients or processing, and is not a modified active, ie, PEGylated, is considered to be a PharmaBio Product or Program.

A final note, the data provided in this section refers to the pipelines as they existed as of the end of the first quarter of 2015.

### Products and Programs by Phase

It’s interesting to compare the Drug Delivery & Formulation (DDEP) and PharmaBio Product and Program pipelines. What might seem to be a rather simple analysis is actually complicated by a number of issues that cloud the results and their interpretation.

Figure 1 summarizes the pipeline for DDEP versus PharmaBio Products. Figure 2 presents the same for Programs. The first
thing one notes is the larger number of products at all stages of development that do not depend on drug delivery or formulation technology, the PharmaBio Products. This is most notable at the Research Stage (3,129 versus 772), a difference that becomes much smaller by the time we look at Phase III Products (609 versus 456). This might suggest there is a trend toward less Drug Delivery & Formulation technology being incorporated in the developing pipeline portfolios of companies. This is probably not the case. In general, there is little formulation-related information available for early stage products. A company might well announce they have an oral product in development for Alzheimer’s disease. While it might require nanoparticle or enteric coating technology, that information is unlikely to be shared publicly until a later stage of development, perhaps only Phase II. In the absence of hard information to support incorporation of a drug delivery or formulation technology, a Product or Program will by default be assigned to PharmaBio. At the same time, an earlier stage Product/Program designed for the treatment of asthma by inhalation will be designated as a DDEP even if the general inhalation technology is not defined. This helps explain why the number of PharmaBio and Drug Delivery & Formulation Programs converge as we move from Research to Phase III Products. More advanced products provide more detailed information about dose and dosage form.

Another apparent oddity is the relatively equal number of Phase I and Phase II Products and Programs. This may again be an issue of disclosure with larger companies choosing not to report their Phase I products.

Despite these limitations, there are still conclusions that can be made regarding the current state of DDEPs.

1. Drug Delivery & Formulation Products and Programs realistically represent a little less than half of all Products and Programs in Phase III development.

2. Each Product is, on average, associated with about 1.5 to 2 Programs. This is not a surprise as additional Programs represent a limited incremental expense for a more advanced Product. All follow-on products with a different dosage form, for example, extended release, are considered a separate Product not a Program.

It would be nice to look at these figures and estimate the success rate of products transitioning from one phase to another, but given the lack of consistent early stage product information, this type of analysis is unreliable. More reliable is the relative Phase II and Phase III data. The Phase II and Phase III information sources include government clinical trials registries, which are, for the most part, complete and consistent.

What does make more sense is comparing information within a well-defined population rather than comparing disparate, potentially incomplete, datasets.

**Top Ten Therapeutic Classes**

It’s interesting to compare DDEPs, Figures 3 and 4, as a function of their therapeutic focus. Because Phase I and Phase II information is often limited and incomplete, emphasis is on the Top Ten Therapeutic Classes for Phase III Products and Programs. Cancer ranks number one for Products and Programs in Phase III development, with many more Programs than Products. This is not surprising and reflects the industry’s interest in exploring the full range of opportunities for their anti-cancer products. Many of these Phase III Programs may well be associated with products that have been approved for one cancer-related condition, for example breast cancer, with additional clinical-stage Programs in ovarian and lung cancer.

The willingness to try an agent for a variety of related conditions may also explain the relatively large jump in the number of Phase III Infections Programs versus Phase III Infections Products. An anti-infective agent may be useful for a variety of different indications, which would represent different Programs.

A similar distribution of Phase III Therapeutic Classes is seen with PharmaBio Products. Cancer sits at number one, followed by infections and inflammation/immune, Figure 5.

**Top Ten Drug Delivery Category**

There is generally more information provided for the general delivery category of a product in development, even in the earlier stages of development, whether it is a DDEP or PharmaBio product. That information might be as simple as defining it as an oral or inhalation agent. This allows us to look a little further upstream in the pipeline to understand what trends there might be in terms of delivery categories.

Figure 6 summarizes Phase II and Phase III DDEP Products by drug delivery category. It is obvious and perhaps surprising to see the large number of Products in development that are based on the injection route. Looking back at the therapeutic class data (Figures 3 and 4), it begins to make sense given the large number of Products in Phase II and Phase III development requiring an injection delivery route, notably anti-cancer and anti-infective agents. Looking at the distribution of DDEP Programs in Phase II and Phase III (Figure 7), one sees a similar emphasis on injection-based Programs with skin and oral swapping positions for second place. Most Products and Programs defined as employing the skin delivery route are DDEPs rather than PharmaBios.

Following the injection, oral, and skin delivery categories are transmucosal (nasal, buccal, sublingual, rectal, and vaginal), ophthalmic, and inhalation, all at about the same level for Products and Programs in Phase II and Phase III. Looking at the corresponding Phase I information (not shown), the distribution is the same, with perhaps an uptick in the relative number of injection products, which shouldn’t be a surprise considering the number of biologics now entering the clinic.

**Injectable Delivery**

The increasing emphasis on injection for the delivery of DDEP warrants taking a look at the intended routes of injectable administration. A cursory look at Figure 8 reveals that the greatest attention, even in Phase III, is on the infusion and subcutaneous routes of injectable administration. These are followed by intramuscular and intravenous, neither of which are well suited to patient self-administration. The growing focus on the use of biologicals for maintenance outpatient treatments suggests those injection routes that can be made patient friendly are most likely to grow in importance.

The increased attention to more patient friendly injection systems has meant more and more injectable Products are launching with prefilled syringe or pen dosage forms. Identifying these Products in the pipeline is a challenge as this information is not public. But with more than 7,100 ongoing Phase III clinical
trials involving injectables, it’s likely that many involve some sort of autoinjector, prefilled syringe, pen, or needle-free injection device.

**Delivering Antibodies**

Antibodies constitute an increasingly important segment of the pharmaceutical market. The PharmaCircle database identified a total of 169 antibody Products in Phase III development, corresponding to 356 Programs. This includes DDEP and PharmaBio Products and Programs. Of the 169 Products, 34 were identified as incorporating an integral device; 28 used prefilled syringes, and 6 used autoinjectors.

Monoclonal antibodies are now in development for almost all therapeutic categories, with inflammation/immune and cancer being the most important for Phase II and III Products and Programs, Figure 9.

More interesting for Drug Delivery and Formulation professionals is understanding the delivery routes and formulation types being used for the antibodies in the development pipeline. In terms of delivery route (Figure 10), infusion IV is the preferred route for both Phase II and Phase III Programs, followed by injectable subcutaneous and injectable IV. The other delivery routes are negligible in comparison with this big three.

In terms of antibody dosage forms (Figure 11), injection solution, lyophilized powder for injection, and injection powder for solution represent more than 98% of the total.

Surprisingly, even in early 2015, it seems there is relatively limited sophistication in terms of the Drug Delivery and Formulation technologies being applied to antibodies. This seems an area of significant opportunity given the industry’s increasing investment in the use of antibodies in the outpatient setting, where success will depend on patient ease of use.
Figure 3. DDEP Phase 3 Products by Therapeutic Class

DDEP Phase 3 Products by Therapeutic Class

- Cancer: 64
- Infectious Diseases: 60
- Inflammation/Immunology: 55
- Neurology: 50
- OBGYN: 49
- Ophthalmology: 44
- Osteoarticular Disease: 42
- Pain Management: 39
- Respiratory: 34
- Women's Health: 24

Data: PharmaCircle LLC

Figure 4. DDEP Phase 3 Programs by Therapeutic Class

DDEP Phase 3 Programs by Therapeutic Class

- Cancer: 262
- Infectious Diseases: 156
- Inflammation/Immunology: 142
- Neurology: 116
- OBGYN: 110
- Osteoarticular Disease: 84
- Ophthalmology: 72
- Osteoporosis: 56
- Pain Management: 48
- Respiratory: 47
- Women's Health: -

Data: PharmaCircle LLC

Figure 5. PharmaBio Phase 3 Products by Therapeutic Class

PharmaBio Phase 3 Products by Therapeutic Class

- Cancer: 169
- Infectious Diseases: 95
- Inflammation/Immunology: 93
- Neurology: 86
- OBGYN: 73
- Osteoarticular Disease: 73
- Osteoporosis: 47
- Pain Management: 45
- Respiratory: 40
- Women's Health: 32

Data: PharmaCircle LLC
10 Notable Fixed-Dose Combination Drug Approvals of 2014

There were two common themes for fixed-dose combination products approved in 2014: additive efficacy and enhanced convenience, with the expectation that both approaches would lead to better therapeutic outcomes. It’s too easy to dismiss the benefits of enhanced compliance on improving therapeutic outcomes and reducing overall healthcare costs. Fewer daily doses to remember, or few “pills” to confuse patients, can reinforce taking medications as prescribed.

It’s worth mentioning that there is no bright line defining what is the difference between a fixed-dose combination, drug-device, or formulation enhanced pharmaceutical product. Combining actives in a fixed-dose manner that is layered upon formulation enhancements, for example, sustained release, and then administered with a device is becoming increasingly common. Several of the products in this list could have just as easily been included in the Drug Delivery and Formulation or Drug-Device lists.

A very successful therapeutic approach for the past two decades has been the use of multiple antiviral agents to avoid the possibility of viral resistance. This multi-agent approach has proven its value in the treatment of HIV/AIDS, leading to sustained reductions in viral loads that in turn have allowed patients to live longer and healthier. 2014 saw the approval of another multidrug combination product for HIV/AIDS, Trumeq, a triple play of sorts, in this case, substituting a newer integrase inhibitor, dolutegravir, with a pair of well-validated nucleoside reverse transcriptase inhibitors. Protocols that once required taking several separate medications to treat HIV/AIDS, often on different dosing schedules, have been replaced with more convenient and better tolerated fixed-dose combination products, often a single oral dosage format.

The benefits of combination therapy for the treatment of Hepatitis C has been well understood with the clinical successes achieved by combining ribavirin and interferon alpha. With the development of oral antivirals for the treatment of Hepatitis C that are effective and well tolerated, attention has turned to combination oral agents with complementary antiviral activities. Gilead’s Harvoni combines two agents in a single tablet and is dosed once daily with excellent outcomes in treating Hepatitis C. Abbvie’s Viekira Pak, a four-agent fixed-dose combination product, takes the much less elegant approach of packaging four separate tablets, one for each antiviral. Three of the tablets are taken once daily, and the other twice daily. In theory, more effective with four separate agents addressing three separate antiviral mechanisms, the question is whether the formulation design and dosing schedule will compromise compliance and clinical outcomes. Expect a more elegant formulation in the near future. It shouldn’t be that difficult to combine at least a couple of the agents into a single presentation and align dosing to a common once per day.

Contrave provides the unexpected, two agents in combination being effective for an indication not treated by either. A novel combination product, Contrave is approved for the management of obesity and combines bupropion, approved for the treatment of depression, and naltrexone, approved for the treatment of narcotic overdoses. Contrave fills a therapeutic void with an agent that does not seem to carry the cardiovascular risks associated with amphetamine-based anti-obesity products.

A more traditional approach is taken with Namzaric, a sustained-release single fixed-dose capsule that combines two agents approved for the treatment of Alzheimer’s disease, donepezil and memantine. In practice, these two agents are commonly prescribed together, albeit as separate tablets and separate prescriptions. Namzaric promises to make compliance a little bit easier. Approval is a win for Adamas and a nice lifestyle play for their licensee Forest Labs (Actavis/Allergan), who are facing threats to their Namenda (memantine) franchise with the imminent approval of memantine immediate-release generic products.

Combination products seem to be the new norm for products directed to Type 2 Diabetes. The common denominator in many of these products is metformin, a biguanide gluconeogenesis inhibitor. Metformin has seemingly become the “hydrochlorothiazide” of diabetes treatment, incorporated into fixed-dose combination products with a wide variety of non-metformin actives. 2014 saw two fixed-dose combination metformin products approved, BMS’ Xigduo XR and Mitsubishi Tanabe’s Invokamet. Xigduo XR incorporates modified-release technology to permit once-daily dosing.

Purdue Pharma’s Targiniq ER, an oxycodone/naloxone combination for the treatment of chronic pain, could just as easily been included in the list of Ten Notable Drug Delivery/ Formulation-Enhanced products. In addition to being a simple agonist/antagonist combination product intended to deter opioid repurposing, Targiniq ER incorporates sustained-release technology to permit twice-daily dosing. Unlike Pfizer’s Embeda morphine/naltrexone combination, Targiniq ER does not depend on the sequestering of an opioid antagonist. This may well help Targiniq ER avoid the stability problems that have seemed to plague Embeda. While Targiniq ER was approved in the US in 2014, it was first approved in 2009 in Europe.

Combination products combine the best thinking of clinical, regulatory, and formulation professionals. Take two or more actives, identify a pressuring therapeutic need, add in drug delivery technologies to enhance convenience, and as appropriate a device, and you have a product that can help patients by providing better efficacy, safety, and/or convenience. The 10 products selected for this section provide a slice of what was accomplished in 2014 with hints of strategies we may see in future years. We’ve taken four of these products and provided a little more information and commentary to help describe the types of opportunities that are available when one does a little “formulation engineering.”
### Contrave

**Active:** bupropion hydrochloride, naltrexone hydrochloride  
**Molecular Weight:** 240 Da, 341 Da  
**Indication:** Obesity  
**Delivery Route:** Oral  
**Dosing Interval:** 12 hours  
**Company/Partner:** Orexigen/Takeda  
**First Approval:** 2014-09-10 (USA)

**Comment:** The development and clinical use of anti-obesity agents, typically amphetamine related, have been plagued with issues of abuse and more concerningly cardiovascular complications. The combination of bupropion and naltrexone, both considered to carry relatively little cardiovascular risk, offers a creative solution to a pressing health issue. The efficacy of bupropion as an anti-obesity agent is perhaps not that surprising when one considers its structure. Bupropion is a cathinone derivative that differs from amphetamines by virtue of a ketone functionality at the benzyl carbon (beta carbon of the side chain). Cathinone, a Schedule I compound in the USA, is the active ingredient in the stimulant khat. Naltrexone also has some anti-obesity activity by virtue of its suppression of pro-opiomelanocortin inhibition, potentiating the actions of bupropion. The anti-obesity market has seen new recent entrants in the past three years, all offering novel actives or combinations. To date none have been particularly successful and it remains to be seen how Contrave will do. At best Contrave might be looking at an upper limit of $500 million in annual sales.

**Formulation Type:** Tablet, Modified Release  
**Review Status:** Standard (FDA)  
**USA Development/Approval Time:** ~7.3 years  
**Sales Potential:** Undisclosed, < $500 million  
**Claim to Fame:** An unusual combination pairing, an antidepressant and narcotic antagonist, for the treatment of obesity.

### Namzaric

**Active:** donepezil hydrochloride, memantine hydrochloride  
**Molecular Weight:** 379 Da, 179 Da  
**Indication:** Dementia  
**Delivery Route:** Oral  
**Dosing Interval:** 24 hours  
**Company/Partner:** Adamas/Forest (Actavis)  
**First Approval:** 2014-12-23 (USA)

**Comment:** With acetylcholinesterase inhibitors such as donepezil coprescribed with Forest’s Namenda (memantine) in the majority of Alzheimer’s patients it made obvious sense to combine the two agents in a single dosage form. This is a patient group for who increased convenience and simpler dosing has particular benefits. For Forest (Actavis/Allergan) the product that was developed by Adamas Pharmaceuticals is an obvious lifecycle product. With their immediate release Namenda facing generics in 2015, and their Namenda XR formulation being taken up slowly, this extended release combination product may be just the answer.

There are no publicly available forecasts for annual sales but we expect annual sales to easily exceed $500 million, if conversion to Namenda XR and Namzaric can be successfully accomplished. Namenda IR sales alone top $1.5 billion.

**Formulation Type:** Capsule, Extended Release Beads (memantine)  
**Review Status:** Standard (FDA)  
**USA Development/Approval Time:** ~4.2 years  
**Sales Potential:** Undisclosed, potentially >$500 million  
**Claim to Fame:** A simple convenience targeted combination product, Namzaric is a lifecycle extension product for the Forest (Actavis) Alzheimer’s portfolio.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
**Omidria**

**Active:** phenylephrine hydrochloride, ketorolac tromethamine  
**Molecular Weight:** 167 Da, 255 Da  
**Indication:** Cataract Surgery, Intraocular Lens Replacement  
**Delivery Route:** Irrigation – intraoperative  
**Dosing Interval:** Single dose, irrigation  
**Company:** Omeros  
**First Approval:** 2014-05-30 (USA)

**Comment:** A good example of a simple convenience enhanced combination product that arises from understanding the needs of clinicians. Both actives, phenylephrine and ketorolac, are approved for intraoperative use but not for intracameral (within the eye) use. Omidria was studied for use as a component in the irrigation solution during cataract surgery and lens replacement. The approval package included nonclinical information on the intracameral use of the agents separately and in the approved Omidria combination. Ophthalmology has become a therapeutic area of interest to many companies given the needs of patients and clinicians and the relative absence of competition. Forecasts for Omidria are not available but peak sales are likely to well short of $50 million annually.

**Formulation Type:** Solution for Reconstitution  
**Review Status:** Standard (FDA)  
**USA Development/Approval Time:** ~6.4 years  
**Sales Potential:** Not Disclosed, < $50 million  
**Claim to Fame:** A practical intraoperative irrigation solution to prevent intraoperative miosis and reduce postoperative pain.

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**Harvoni**

**Active:** sofosbuvir, ledipasvir  
**Molecular Weight:** 529 Da, 889 Da  
**Indication:** Hepatitis C  
**Delivery Route:** Oral  
**Dosing Interval:** 24 hours  
**Company:** Gilead  
**First Approval:** 2014-10-10 (USA)  
**Formulation Type:** Tablet

**Comment:** A follow on to Gilead’s 2013 blockbuster Sovaldi, Harvoni adds in ledipasvir to Sovaldi’s sofosbuvir to create a one-two antiviral “punch”. The development and approval time for Harvoni was remarkably short, apparently benefiting from the previous development and approval of Sovaldi. A logical follow on to Sovaldi, Harvoni will face some competition from AbbVie’s multi-dose Hepatitis C medication Viekira Pak. But with once-a-day dosing versus Viekira Pak’s once and twice-a-day dosing protocols, and both products showing excellent clinical outcomes, market share will likely come down to pricing and perceived value to the patient and the healthcare system.

**Review Status:** Priority (FDA)  
**USA Development/Approval Time:** 2.4 years  
**Sales Potential:** Billions and billions  
**Claim to Fame:** The latest antiviral from Gilead, a combination product, is expected to advance the treatment of Hepatitis C and break all records for fastest product to reach each and every sales record.

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1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
Triumeq

Actives: abacavir sulfate/dolutegravir sodium/lamivudine

Molecular Weight: 286/419/229 Da

Indication: HIV/AIDS

Delivery Route: Oral

Company/Partner: Viiv (GlaxoSmithKline)/Shionogi

First Approval: 2014-08-22 (USA)

Formulation Type: Oral, Tablet-Combination

Notable: Another fixed-dose antiviral combination product for the treatment of HIV/AIDS featuring three previously approved actives each available in single active dosage forms.

Actives: metformin hydrochloride/dapagliflozin propanediol

Molecular Weight: 129/409 Da

Indication: Diabetes, Type 2

Delivery Route: Oral

Company/Partner: Bristol-Myers Squibb/AstraZeneca

First Approval: 2014-07-11 (Australia)

Formulation Type: Oral, Tablet-Combination, Modified Release

Notable: A member of the metformin combination club. Approved in a twice-daily formulation in the EU earlier in 2014 it was developed and approved first in Australia and then the USA as a once-a-day tablet.

Actives: metformin hydrochloride/canagliflozin

Molecular Weight: 129/445 Da

Indication: Diabetes, Type 2

Delivery Route: Oral

Company/Partner: Mitsubishi Tanabe/Johnson & Johnson

First Approval: 2014-08-20 (USA)

Formulation Type: Oral, Tablet-Combination

Notable: Another member of the metformin fixed-dose combination club, but with Mitsubishi Tanabe’s proprietary Sodium-Dependent Glucose Co-Transporter 2 Inhibitor, canagliflozin. It matches Xigduo XR as a once-daily formulation.

Actives: netupitant/palonosetron hydrochloride

Molecular Weight: 579/296 Da

Indication: Nausea & Vomiting, Post Chemotherapy

Delivery Route: Oral

Company/Partner: Helsinn/Roche

First Approval: 2014-10-10 (USA)

Formulation Type: Oral, Capsule-Combination

Notable: Designed to provide immediate and extended anti-nausea benefits in a single fixed-dose oral combination product. Palonosetron provides immediate activity while netupitant, with a longer elimination half-life, provides extended activity.

Actives: dasabuvir/ombitasvir/paritaprevir/ritonavir

Molecular Weight: 494/894/766/721 Da

Indication: Hepatitis C

Delivery Route: Oral

Company/Partner: AbbVie

First Approval: 2014-12-19 (USA)

Formulation Type: Oral, Tablet-Combination Pack

Technology Provider: Internal

Notable: In the age of multi-agent viral therapies, Viekira represents the first 4 active combination product. While not elegant in terms of formulation design, four separate tablets, and differing dosing regimens, it has proven efficacy and offsets convenience issues with an aggressive pricing strategy.

Actives: oxycodone hydrochloride/naloxone hydrochloride

Molecular Weight: 315/327 Da

Indication: Chronic Pain

Delivery Route: Oral

Company/Partner: Purdue Pharma

First Approval: 2009-01-23 (EU)

Formulation Type: Oral, Tablet-Combination, Abuse Resistant, Modified Release

Notable: Approved in the US only in 2014 this product uses an agonist/antagonist strategy for abuse deterrence and extends Purdue’s significant abuse resistant opioid portfolio.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
Ten Notable Drug-Device Approvals of 2014

The common theme for drug-device products in 2014 was improved patient convenience. This seems a very appropriate strategic response in a marketplace where multiple products treating the same condition are common, be they proprietary or generic. Distinguishing a product on the basis of the convenience and ease of use of the device is often a critical differentiator in a crowded market.

Improved convenience also leads to better therapeutic outcomes, in theory at least, reducing overall healthcare costs. Patients who take their medications on schedule and properly, be it injected or inhaled, are less likely to experience relapses or other complications. Simple devices that are easy to understand support proper use and regular dosing. This principle seemingly underlies the development of an increasing number of formulations offering reduced dosing frequencies, easy-to-use drug-device pairings, and even drug-drug combinations.

The biggest drug-device approval in 2014 surely was the FDA’s approval of Mannkind’s inhaled insulin, Afrezza. Intended to meet a major market need, a non-injectable option for insulin, while addressing the shortcomings of Nektar’s Exubera, Afrezza seems well positioned to capture what opportunity there might be for managing type 2 diabetes via pulmonary administration. Partnered with Sanofi, the therapeutic and commercial success of Afrezza will be a strong indicator of the future for not only inhaled insulin but also other chronically dosed inhaled macromolecules.

Amgen’s Neulasta Delivery System approval represents an interesting shift in the setting for the infusion of medications, at least on a single-dose basis. The Neulasta “kit” includes a small plastic infusion pump the size of a muffin-top that is applied to the patient’s skin prior to discharge following a course of chemotherapy. The device is programmed to infuse Neulasta subcutaneously some 27 hours later. Rather than requiring the patient to return to the clinic or a doctor’s office for the infusion, or requiring a home visit by a nurse, the patient walks out with the device already attached and simply removes it once the dose has been completed. And Amgen provides it at no additional cost. For the patient and healthcare system, this not-so-simple device represents a huge potential savings in cost.

2014 saw continuing efforts by companies to refresh and update their delivery devices, particularly injection and inhalation devices. GlaxoSmithKline continued to refresh its respiratory product portfolio in 2014, with the launch of Arnuity and Incruse Ellipta, using its Ellipta dry powder device. The Ellipta device offers a number of patient benefits over GlaxoSmithKline’s tried and true Diskus dry powder device. The real question is whether the device will offer sufficient benefits to shore up the company’s respiratory franchise from the influx of branded and generic dry powder inhalation products.

The inclusion of pens or prefilled syringes for the delivery of injectable medications has become an essential requirement for injectable products entering any chronic market, especially diabetes. 2014 saw incremental, rather than revolutionary, improvements in device design and patient-friendly features. Injection devices will need even more substantial improvements if Mannkind’s Afrezza manages to gain significant patient and market acceptance.

There were two drug-device products approved in 2014 that are likely to find limited commercial success despite their rather novel approach to device integration. Trimel’s Natesto intranasal gel device, designed to eliminate issues of inter-patient transfer of topically administered testosterone, faces market acceptance challenges with a 3x daily dosing schedule and a softening testosterone replacement market. It’s questionable that it will succeed even with the support of Endo’s increasingly substantial male health investments. Kaléo’s Evzio seems that it will be a therapeutic if not commercial winner. The ability for law enforcement, EMS personnel, and family members to quickly and easily reverse narcotic overdoses in the field promises to save lives. Managed properly, and in conjunction with their Auvi-Q epinephrine delivery device and additional pipeline products, the company is likely to prosper.

Combining drugs with devices is all about improving patient convenience in hopes that it will improve compliance and patient acceptance. Limited advances in the development of oral formulations for the delivery of macromolecules will ensure there is continued investment in more effective and patient-friendlier drug-device combinations. If Afrezza can validate the efficacy, safety, convenience, and commercial viability of inhaled insulin, it is likely we will see many more inhaled proteins reach approval and the market.

The following Ten Notable Drug-Device Products of 2014 (four of them are highlighted in detail) provide a snapshot of what was approved last year and suggest future directions in drug-device development.
Afrezza

**Active:** insulin, human recombinant  
**Molecular Weight:** 5,808 Da  
**Indication:** Diabetes, hyperglycemia  
**Delivery Route:** Inhalation, Dry Powder  
**Company/Partner:** Mannkind/Sanofi  
**First Approval:** 2014-06-27 (USA)  
**Formulation Type:** Dry Powder (Technosphere)  
**Technology Provider:** Mannkind

**Comment:** Both Mannkind and Sanofi have much riding on the success of Afrezza. Mannkind seeks vindication for their investment in Afrezza and Sanofi needs a driver for their diabetes portfolio. Afrezza is a remarkable combination of formulation and device design. The ‘bong-like’ device that was used with Exubera has been shrunk to the size of an asthma inhaler with Afrezza. The Afrezza Dreamboat device requires no cleaning and is simply replaced every couple of weeks. Launched in February 2015 industry experts are uncertain about how it will be accepted by patients and its eventual commercial success. Prescription figures suggest uptake will be slower than initially forecast which has caused analysts to drop their peak sales estimate from $2 billion to $1 billion. While only a 6 kilodalton molecule the effective pulmonary delivery of insulin represents a huge step forward for the future of macromolecule delivery. It will be interesting to see what additional molecules Mannkind intends to incorporate into their Technosphere and Dreamboat technologies. Mannkind has shown it can be done, now the question is whether are patients and physicians are sufficiently interested in pulmonary rather than parenteral administration to accept the associated higher costs and additional safety monitoring requirements.

Natesto

**Active:** testosterone  
**Molecular Weight:** 288 Da  
**Indication:** Hypoandrogenism  
**Delivery Route:** Nasal  
**Company/Partner:** Trimel/Endo  
**First Approval:** 2014-05-28 (USA)  
**Formulation Type:** Intranasal Gel  
**Technology Provider:** Met P Pharma, Trimel

**Comment:** A product that took almost ten years to develop from IND to approval, Natesto may have reached the market too late to realize it’s full potential. Recent medical opinion and FDA restrictions on the prescribing of testosterone will negatively impact the market for testosterone replacement therapies much as women’s hormone replacement therapy prescriptions and sales were impacted by negative clinical opinion more than a decade ago. The novel gel and nasal device combination do point to additional opportunities for nasal delivered products. Seemingly intended to provide a delivery system that was effective and discreet while avoiding issues related to interpersonal transference of testosterone, the three-time daily dosing schedule does not compare well with topical gels that are administered daily or implants that last up to six months. Sales estimates for Natesto are unavailable but it is unlikely the product will capture annual sales in excess of $50 million. Even with a twice-daily dosing regimen that is in development Natesto is unlikely to receive significant uptake, especially in a market with generic topical agents.

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1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
Comment: Evzio represents an important step forward in the management of opioid overdosing in the outpatient setting. Effectively a multimedia delivery device, Evzio provides printed and audio dosing instructions to allow untrained individuals to quickly and effectively administer the dose.

This simple device incorporates a prefilled syringe along with a gas cylinder that injects the naloxone over a five second period when pressed against the body, typically the thigh. More interesting is the “Intelligent Prompt System (IPS)” that provides audio step-by-step instructions in real time once the case wrapper is removed.

Evzio promises to offer families, as well as EMS and law enforcement officials, a user-friendly resource for rapidly treating individuals suspected of opioid overdosing. This follows the introduction of Auvi-Q/Allerject, an epinephrine autoinjector device by Kaléo (formerly Intelliject) in 2012 using the same device design. Even the premium price of the product represents a bargain if it can save a life.

Comment: The Neulasta Delivery Kit with the On-body Injector represents a reasonably high-tech approach to providing a prolonged single subcutaneous injection, mimicking an infusion pump, following chemotherapy. The difference is that the device is disposable and it is designed to deliver the dose a full 27 hours after the device is applied. The benefits appear to be twofold, the dose is administered over an extended period for improved tolerability, and compliance and convenience is improved. Rather than returning to the clinic for a post chemotherapy session infusion the patient can remain at home. The Neulasta system is applied by a healthcare professional following chemotherapy treatment and requires no further attention from the patient. The kit is provided at no extra cost.

The value of disposable on-demand or programmed delivery devices for acute conditions has not been validated. Alza and J&J’s Ionsys on-demand fentanyl active delivery system for post-surgical inpatient use was a huge disappointment, essentially being withdrawn soon after approval and launch. The Neulasta Delivery Kit may well point to additional opportunities for higher tech single-use disposable injection devices.

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1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate. 2 Development times are calculated from the submission of an IND through to first approval in the USA and represent both clinical development and regulatory review times.
Active: insulin degludec, liraglutide
Molecular Weight: ~6,104 / 3,751 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: Novo Nordisk
First Approval: 2014-09-18 (EU)
Formulation Type: Aqueous
Technology Provider: Novo Nordisk
Integral Device: Prefilled Syringe (FlexTouch)
Notable: Xultophy incorporates the latest generation Novo Nordisk dose-adjustable prefilled insulin syringe system providing easier use and greater accuracy.

Active: exenatide
Molecular Weight: 4,187 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: AstraZeneca/Amylin
First Approval: 2014-03-03 (USA)
Formulation Type: Biodegradable PLGA (Medisorb)
Technology Providers: Ypsomed, Alkermes
Integral Device: Dual-chamber Monodose (LyoTwist Trio)
Notable: Bydureon Dual provides incremental injectable delivery format/device convenience improvements that should translate into better compliance and therapeutic outcomes.

Active: albiglutide
Molecular Weight: 72,971 Da
Indication: Diabetes, Type 2
Delivery Route: Injection - subcutaneous
Company/Partner: GlaxoSmithKline
First Approval: 2014-03-21 (EU)
Formulation Type: Fusion protein (Albufuse)
Technology Providers: Ypsomed, Novozymes
Integral Device: Dual-chamber Monodose (LyoTwist)
Notable: The first of Human Genome Science’s albumin fusion proteins to reach approval, Tanzeum offers once-weekly dosing in conjunction with Ypsomed’s patient friendly injection device.

Active: fluticasone furoate
Molecular Weight: 445 Da
Indication: Asthma
Delivery Route: Inhalation - dry powder
Company/Partner: GlaxoSmithKline
First Approval: 2014-08-20 (USA)
Formulation Type: Dry Powder
Technology Provider: GlaxoSmithKline
Integral Device: Dry Powder Inhaler (Ellipta)
Notable: Arnuity Ellipta is the latest in a series of new and ‘refreshed’ dry powder inhalation products using GSK’s next-generation Ellipta dry powder device that offers improved ease of use and dual active delivery without the need for co-formulation.

Active: dulaglutide
Molecular Weight: 59,670 Da
Indication: Pain, chronic
Delivery Route: Injection - subcutaneous
Company/Partner: Eli Lilly
First Approval: 2014-09-18 (USA)
Formulation Type: Fusion Protein
Technology Provider: Eli Lilly
Integral Device: Prefilled Syringe, Pen
Notable: Trulicity is another example of what has been an increasingly common strategy, Fc fused proteins in a patient friendly injection system intended to provide an extended duration of action while encouraging patient compliance.

1 Molecular weights are reported as Daltons (Da) and are the weight of the active without the corresponding salt, i.e., hydrochloride, bitartrate.
Any product that requires a separate, non-integral device, for example, an infusion pump, is not considered a DDEP. A product that includes an integral device, a multidose pen, for example, would be considered a DDEP. A topical agent that is administered by means of a transdermal patch is a DDEP, while a simple topical steroid is not, unless it incorporates some specific technology to modify or enhance absorption.

Sales in this section refer to manufacturer reported sales, and generally represent the ex-factory shipments and sales net of all discounts offered to purchasers and government agencies. These can vary from the figures reported from audits of prescriptions at the pharmacy and hospital levels that are extrapolated to full market sales estimates. Using manufacturer-reported figures also means that the products of certain private companies that do not publish their sales figures are excluded. The most notable with regard to DDEPs is the Purdue Pharma/Mundipharma/Napp Pharmaceuticals group and their sustained-release opioids.

Top 20 Pharmaceutical Products

The products in Table 1 are listed in order of published global sales. Most product categories will be obvious, but the DDEP category is worth explaining. In the case of DDEPs, there are three possible designations: Yes, No, and Partial. Partial refers to pharmaceutical products with one or more, but not all, marketed dosage forms incorporating a delivery technology or integrated device. Common examples of Partial DDEPs are products that are marketed in vials and prefilled syringes or pen-type devices. In the case of oral agents, the product line may include immediate-release and sustained-release dosage forms.

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>2014</th>
<th>Rank</th>
<th>Molecule Type</th>
<th>Route</th>
<th>DDEP</th>
<th>Dosage Forms</th>
<th>First Approval</th>
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</thead>
<tbody>
<tr>
<td>Humira</td>
<td>AbbVie</td>
<td>$12,543</td>
<td>1</td>
<td>Antibody</td>
<td>Injection</td>
<td>Partial</td>
<td>Syringe, Vial</td>
<td>2002/USA</td>
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<td>Savoldi</td>
<td>Gilead</td>
<td>$10,283</td>
<td>2</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Tablet</td>
<td>2013/USA</td>
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<td>Remicade</td>
<td>Janssen/J&amp;J</td>
<td>$9,916</td>
<td>3</td>
<td>Antibody</td>
<td>Injection</td>
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<td>Vial</td>
<td>1998/USA</td>
</tr>
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<td>Enbrel</td>
<td>Amgen</td>
<td>$8,949</td>
<td>4</td>
<td>Protein</td>
<td>Injection</td>
<td>Partial</td>
<td>Syringe, Vial</td>
<td>1998/USA</td>
</tr>
<tr>
<td>Lantus</td>
<td>Sanofi</td>
<td>$8,435</td>
<td>5</td>
<td>Protein</td>
<td>Injection</td>
<td>Partial</td>
<td>Syringe, Vial</td>
<td>2000/USA</td>
</tr>
<tr>
<td>Abilify</td>
<td>Otsuka/ Bristol-Myers Squibb</td>
<td>$8,404</td>
<td>6</td>
<td>Small Molecule</td>
<td>Oral/ Injection</td>
<td>Partial</td>
<td>Tablet, ODT, Depot</td>
<td>2002/USA</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Biogen/Roche</td>
<td>$7,553</td>
<td>7</td>
<td>Antibody</td>
<td>Injection</td>
<td>Partial</td>
<td>Vial</td>
<td>1997/USA</td>
</tr>
<tr>
<td>Advair (Diskus/HFA)</td>
<td>GlaxoSmithKline</td>
<td>$7,035</td>
<td>8</td>
<td>Small Molecule</td>
<td>Inhalation</td>
<td>Yes</td>
<td>DPI, MDI</td>
<td>1999/EU</td>
</tr>
<tr>
<td>Avastin</td>
<td>Genentech/Roche</td>
<td>$7,024</td>
<td>9</td>
<td>Antibody</td>
<td>Injection</td>
<td>No</td>
<td>Vial</td>
<td>2004/USA</td>
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<tr>
<td>Hercaptopin</td>
<td>Genentech/Roche</td>
<td>$6,868</td>
<td>10</td>
<td>Antibody</td>
<td>Injection</td>
<td>No</td>
<td>Vial</td>
<td>1998/USA</td>
</tr>
<tr>
<td>Crestor</td>
<td>ActaZenea</td>
<td>$5,512</td>
<td>11</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Tablet</td>
<td>2002/EU</td>
</tr>
<tr>
<td>Lyrica</td>
<td>Pfizer</td>
<td>$5,167</td>
<td>12</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Capsule</td>
<td>2004/EU</td>
</tr>
<tr>
<td>Revlimid</td>
<td>Celgene</td>
<td>$4,980</td>
<td>13</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Capsule</td>
<td>2005/USA</td>
</tr>
<tr>
<td>Gleevec</td>
<td>Novartis</td>
<td>$4,746</td>
<td>14</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Tablet</td>
<td>2001/EU</td>
</tr>
<tr>
<td>Neulasta</td>
<td>Amgen</td>
<td>$4,599</td>
<td>15</td>
<td>Protein</td>
<td>Injection</td>
<td>Yes</td>
<td>Syringe, On-body Injector</td>
<td>2002/USA</td>
</tr>
<tr>
<td>Prexevar (7 &amp; 13)</td>
<td>Pfizer (Wyeth)</td>
<td>$4,463</td>
<td>16</td>
<td>Vaccine</td>
<td>Injection</td>
<td>Yes</td>
<td>Syringe</td>
<td>2000/USA</td>
</tr>
<tr>
<td>Spiriva</td>
<td>Boehringer Ingelheim</td>
<td>$4,304</td>
<td>17</td>
<td>Small Molecule</td>
<td>Inhalation</td>
<td>Yes</td>
<td>DPI, MDI</td>
<td>2001/EU</td>
</tr>
<tr>
<td>Lucentis</td>
<td>Genentech/Roche</td>
<td>$4,303</td>
<td>18</td>
<td>Antibody</td>
<td>Injection</td>
<td>No</td>
<td>Vial</td>
<td>2006/USA</td>
</tr>
<tr>
<td>Copaxone</td>
<td>Teva</td>
<td>$4,237</td>
<td>19</td>
<td>Protein</td>
<td>Injection</td>
<td>Yes</td>
<td>Syringe</td>
<td>1996/USA</td>
</tr>
<tr>
<td>Januvia</td>
<td>Merck &amp; Co.</td>
<td>$3,993</td>
<td>20</td>
<td>Small Molecule</td>
<td>Oral</td>
<td>No</td>
<td>Tablet</td>
<td>2006/Mexico</td>
</tr>
</tbody>
</table>
It’s interesting to note how many biologics, antibodies, and proteins are in this Top 20 Sales list (11/20). This reflects in part their significant acceptance in clinical practice for conditions that had been poorly managed with small molecule therapeutics, but perhaps even more importantly, it reflects their premium pricing and extended market exclusivity. Any number of small molecule products approved in the same period also managed to reach the Top 20 list only to shed market share and sales once they lost market exclusivity. Among the nine small molecule products on the list, almost half will drop off this list in the next couple of years as their exclusivity expires and generic competitors enter the market.

In terms of delivery route, 12 of the 20 products are injectables, with 6 others primarily featuring oral presentations, and the remaining 2 administered by inhalation. This is a remarkable reversal of what was seen 1 and 2 decades ago when oral products targeted to chronic outpatient indications represented the majority of products on this list. Among the Top 20 products, 10 do and 10 don’t incorporate formulation or device technologies. Of the 10 that do, and are considered DDEPs, fully half depend on formulation or integral device technologies, while the other half, designated as Partial, incorporate formulation technology or integral devices in a subset of their approved presentations.

Total sales for the Top 20 in 2014 amounted to USD $133.3 billion. Breaking out this total, DDEP-related products accounted for 53% of the total Top 20 sales; split 19% for full DDEP and 34% for Partial DDEP. If we look further to the full set of product sales actively monitored by PharmaCircle, which include only originator products in the major markets, the ratio shifts to a total 36% of sales accounted for by DDEPs.

### Top Drug Delivery Enhanced/Enabled Pharmaceuticals (DDEPs)

#### Humira

**Sales (Launch through 2014):** $65 billion  
**Formulation(s):** Injection Solution  
**Approved Indication(s):** Rheumatoid Arthritis, Crohn’s Disease, Psoriasis, Ulcerative Colitis  
**Delivery Route:** Injection - Subcutaneous  
**Company:** AbbVie  
**First Approval:** 2002 (USA)  
**Presentation(s):** Prefilled Syringe, Single-Dose Pen  

Formulation Development: While the formulation for Humira has remained largely constant since launch, there have been changes in the drug/device configuration to better match outpatient needs. Launched in early 2003 with a vial presentation, a switch was made in mid-year 2004 to prefilled syringes, with a discontinuation of the vial presentation. This was followed in 2006 with a single-use disposable pen presentation. With twice-monthly maintenance dosing, the requirement for patient self-injection has not limited the uptake of Humira and its climb to the number one sales position.

#### Lantus

**Sales (Launch through 2014):** $48 billion  
**Formulation(s):** Injection Solution  
**Approved Indication(s):** Diabetes - Type 1 & Type 2  
**Delivery Route:** Injection - Subcutaneous  
**Company:** Sanofi (USA)  
**First Approval:** 2000  
**Presentation(s):** Multidose Vial, Injection Pen (Disposable), Injection Pen (Reusable)  

Formulation Development: With a requirement of daily dosing, attention with Lantus has been placed on making the injection process as convenient and as painless as possible. This has led to the introduction of room-temperature-stable (28 days) multidose disposable and reusable pen devices with increasingly fine needle gauges.

#### Enbrel

**Sales (Launch through 2014):** $75 billion  
**Formulation(s):** Injection Solution  
**Approved Indication(s):** Rheumatoid Arthritis, Psoriasis, Ankylosing Spondylitis  
**Delivery Route:** Injection - Subcutaneous  
**Company:** Amgen  
**First Approval:** 1998 (USA)  
**Presentation(s):** Multidose Vials, Prefilled Syringe, Prefilled Autoinjector  

Formulation Development: Launched by Immunex/Wyeth-Ayerst as a lyophilized powder for reconstitution, Enbrel has progressively added in multidose vials, prefilled syringes, and pen presentations. At the same time, dosing has been extended from twice weekly to once weekly at higher doses.

#### Abilify

**Sales (Launch through 2014):** $54 billion  
**Formulation(s):** Oral Tablet, Oral Solution, Lyophilized Melt Tablet, Injection Solution, Lyophilized Powder for Suspension  
**Approved Indication(s):** Schizophrenia, Bipolar Disease, Depression, Autistic Disorder  
**Delivery Route:** Oral, Injection - Intramuscular  
**Company:** Otsuka  
**First Approval:** 2002 (USA)  
**Presentation(s):** Tablet, Oral Solution, Injection Solution, Injection for Reconstitution (Depot)  

Formulation Development: The formulation development of Abilify has paralleled the expansion of its label indications. Current formulations are intended to provide oral maintenance dosing with simple tablet formulations. Swallowing issues are addressed with melt tablet and oral solution presentations. Cyclodextrins are used as solubility enhancers with the injection solution presentation, while the product defaults to a lyophilized formulation requiring reconstitution for the depot presentation.
Prevnar (7 & 13)

Sales (Launch through 2014): $35 billion
Formulation(s): Injection Suspension with Adjuvant
Approved Indication(s): Pneumonia, Otitis Media
Delivery Route: Injection – Intramuscular
Company: Pfizer (Wyeth)
First Approval: 2000 (USA)
Presentation(s): Prefilled Syringe
Formulation Development: Introduced as a heptavalent vaccine in 2000, the vaccine was replaced with a broader coverage 13-valent presentation in Europe in 2009 and the USA in 2010. Intended as a prophylactic treatment, often in a public health setting, the use of prefilled syringes simplifies administration, although it is recommended to vigorously shake the syringe to re-suspend the adjuvant.

Rituxan/MabThera-PH20

Sales (Launch through 2014): $66 billion
Formulation(s): Injection Solution, Injection Site Absorption Enhancer
Approved Indication(s): Non-Hodgkin’s lymphoma, Chronic lymphocytic Leukemia, Rheumatoid Arthritis, Granulomatosis
Delivery Route: Injection – Infusion, Injection – Subcutaneous (MabThera-PH20)
Company: Biogen, Roche
First Approval: 1997 (USA)
Presentation(s): Vial
Formulation Development: 2014 saw the approval and introduction of a subcutaneous formulation of rituximab (MabThera-PH20) in the EU by Roche using Halozyme’s Enhanze technology. This simplifies the usual dosing protocol that involves intravenous infusion over one to two hours.

Advair/Seretide

Sales (Launch through 2014): $84 billion
Formulation(s): Inhalation Powder, Pressurized Inhalation Solution
Approved Indication(s): Asthma, COPD
Delivery Route: Inhalation
Company: GlaxoSmithKline
First Approval: 1999 (EU)
Presentation(s): Dry Powder Inhaler, Metered Dose Inhaler
Formulation Development: First approved in 1999 as a dry powder device combination product (salmeterol/fluticasone), it was followed a year later with a metered dose formulation. Advair quickly gained market acceptance and has been a multibillion-dollar product for more than a decade. With generics imminent, GSK seems intent on moving prescribers and patients to their new Ellipta drug/device products.

Spiriva

Sales (Launch through 2014): $34 billion
Formulation(s): Inhalation Powder in Capsule, Inhalation Solution Pressurized
Approved Indication(s): Asthma, COPD
Delivery Route: Inhalation
Company: Boehringer Ingelheim
First Approval: 2001 (EU)
Presentation(s): Dry Powder Inhaler, Liquid Inhaler/Nebulizer
Formulation Development: First approvals were for the dry powder inhaler configuration that required a patient to insert a capsule into the device, administer the dose, then remove the spent capsule and occasionally clean the device. The Respimat presentation, first introduced in the EU in 2007, simplifies dosing and only requires weekly cleaning of the mouthpiece.

Neulasta

Sales (Launch through 2014): $38 billion
Formulation(s): PEGylated Protein, Injection Solution
Approved Indication(s): Neutropenia
Delivery Route: Injection – Subcutaneous
Company: Amgen
First Approval: 2002 (USA)
Presentation(s): Prefilled Syringe, On-Body Injector
Formulation Development: Neulasta is a PEG conjugated G-CSF first approved in 2002 as a prefilled syringe. A disposable autoinjector presentation approved in 2005 (USA) was subject to recalls in 2006 because of incomplete dose delivery and was withdrawn from the market. An "apply-now-deliver-later" device, the Neulasta On-Body Injector, was approved in 2014 and permits the healthcare professional to attach the device to the patient in a clinical setting and have a standard single dose of Neulasta administered subcutaneously by infusion about 24 hours later with no further patient or clinician involvement.

Copaxone

Sales (Launch through 2014): $31 billion
Formulation(s): Injection Solution
Approved Indication(s): Multiple Sclerosis, Relapsing, Remitting
Delivery Route: Injection – subcutaneous
Company: Teva
First Approval: 1996 (USA)
Presentation(s): Prefilled Syringe, Autoinjector
Formulation Development: Initially introduced as a lyophilized powder for injection, this injectable intended for outpatient use has evolved to include prefilled syringes and a higher dose formulation that permits extended dosing intervals (3 per week). A reusable autoinjector, the autoinject 2 (Owen Mumford), that fits the standard prefilled syringe is provided at no additional cost.