THE PHARMACY

LANDSCAPE

THE PHARMACY LANDSCAPE

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MARKET FORCES

UPDATE ON PATENT EXPIRATIONS

FIRST-TIME GENERICS

The introduction of new generic drugs contributes to lower overall drug costs.

In 2018, the generic versions of 16 brand name drugs were introduced to the Canadian market. These brand name therapies made up 1.62% of 2018 private plan spending, considerably less than the percentage of spending associated with brand name drugs for which generics became available in 2017.

The generics that became available in 2018 were mostly for traditional drugs. As interchangeability is not often a clinical issue within this drug category, potential savings are available to plan sponsors who adopt mandatory substitution plans.

Of note: generic versions became available for Coversyl®, a drug widely used to lower blood pressure, and Pradaxa®, a drug commonly prescribed to treat cardiovascular diseases.

A minimal number of patents for specialty drugs expired in 2018. These drugs do not represent a significant portion of overall spending, as detailed in the table below.

BRAND NAME DRUGS FOR WHICH GENERIC ALTERNATIVES WERE MADE AVAILABLE IN 2018

CATEGORY	BRAND NAME DRUG	CHEMICAL NAME	COMMON INDICATION	% OF TOTAL SPEND IN 2018
TRADITIONAL	Ofirmev®	Acetaminophen injection	Pain/Inflammation	n/a
	Toctino®	Alitretinoin	Skin Conditions	0.06%
	Volibris®	Ambrisetan	Pulmonary Hypertension	0.02%
	Abilify®	Aripiprazole	Mental Disorders	0.40%
	Entocort®	Budesonide	Steroids Anti-Inflammatory	0.04%
	Clobex Spray®	Clobetasol	Skin Conditions	0.04%
	Pradaxa®	Dabigatran	Cardiovascular Disease	0.12%
	Aggrenox®	Dipyridamole/ acetylsalicylic acid	Cardiovascular Disease	0.01%
	Monurol®	Fosfomycin tromethamine	Infections	0.03%
	Vimpat®	Lacosamide	Neurological Disorders	0.08%
	HpPAC®	Lansoprazole/amoxicilline/clarithromycine	Ulcer/Reflux	0.03%
	Bactroban Cream®	Mupirocin	Skin Conditions	0.00%
	Coversyl®	Perindopril	Infections	0.00%
	Coversyl Plus®	Perindopril/indapamide	High Blood Pressure	0.71%
	Twynsta®	Telmisartan/amlodipine beslate	High Blood Pressure	0.06%
	Aristopan®	Triamcinolone hexacetonide injection	Steroids Anti-Inflammatory	0.00%
	Levitra®	Vardenafil	Erectile dysfunction	0.02%
SPECIALTY	3-TC™	Lamivudine oral liquid	HIV/AIDS	0.00%
	Mepron®	Atovaquone	Infections	0.01%
	Vistide®	Cidofovir	Infections	n/a

2018 BIOSIMILARS INTRODUCTION

Health Canada approved a few biosimilars – drugs that are similar to the (often costly) brand reference biologic – in 2018.

As a biologic drug is made within a living cell and not from a chemical substance, the therapy molecule has natural variability and is often complex and larger than chemical drug molecules. It is therefore impossible to produce an identical biologic drug. To be approved, biosimilars are compared thoroughly to their brand name reference and must demonstrate high therapeutic similarity.

Because they are not identical, biosimilars and their reference drugs are not considered interchangeable, unlike non-biologic drugs and their generics. As interchangeability is not a practice that is necessarily endorsed by doctors in Canada, the use of biosimilars as a substitute for the reference drug is limited. For the most part, only newly diagnosed patients can start treatment with biosimilars. Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar should be made by the physician, in consultation with the patient, taking available clinical evidence and any policies of the relevant jurisdiction into account.

Despite not being interchangeable with brand reference drugs, the use of biosimilars is growing. First, as clinical experience with these products increases, physicians are more inclined to prescribe them. Additionally, many provinces have adopted policies that encourage mandatory use of biosimilars for newly diagnosed patients. For example, in Ontario, all newly diagnosed patients prescribed the drug Filgrastim must use the biosimilar Grastofil, funded under the Ontario Benefit Drug Program. Neupogen, Grastofil's reference biologic, is funded only under specific circumstances as a controlled benefit through the Exceptional Access Program. Private sponsors who decide to adopt similar policies will see increasing use of biosimilars and, consequently, lower spending.

Health Canada approved three biosimilars in 2018, but none of them were yet commercially available when this report was published.

The Humira® biosimilar, Hadlima™, is especially interesting. Humira® is a biologic drug widely used for various autoimmune diseases, including plaque psoriasis, Crohn's disease and rheumatoid arthritis. Biosimilars are often approved for fewer indications than their brand reference drug; Hadlima was approved for all but one of Humira's indications. Once Hadlima enters the market, we predict that its utilization will grow accordingly, leading to significant savings. Humira represented 3.76% of overall private plan spending in 2018.

Health Canada also approved the first biosimilar for the treatment of cancer in 2018. In the next few years, we expect to see many other biosimilars for oncology introduced to the Canadian market.

In addition, multiple competitors will launch their biosimilars for the same reference brand drugs, with different indications approved, leading to a more competitive pricing environment and further savings.

CHEMICAL NAME	BIOSIMILAR NAME	REFERENCE BRAND NAME BIOLOGIC	COMMON INDICATION	% OF TOTAL SPEND IN 2018
Adalimumab	Hadlima™	Humira®	Inflammatory Conditions	3.76%
Bevacizumab	Mvasi®	Avastin®	Cancer	0.05%
Pegfilgrastim	Lapelga® Fulphila®	Neulasta®	Blood Disorders	0.37%

A LOOK FORWARD

KEY PATENT EXPIRATIONS

In the next three to five years, patents will expire for multiple brands of both traditional and specialty drugs. This will lead to competition from generic drugs that is likely to translate into significant savings for private payers, especially those with mandatory substitution plans. (In many cases, generic prices are 10% to 25% of the equivalent brand name drug.)

Many highly utilized therapies for diabetes, multiple sclerosis, inflammatory conditions and cancer, among others, will have one or more generic versions entering the market by 2023.

The patents for Januvia®, Forxiga® and Onglyza®, three traditional antidiabetics, will expire between 2020 and 2022. Altogether, these brands made up 0.35% of total spending in 2018.

Highly utilized specialty drugs will also be subject to upcoming patent expirations, including Aubagio®, an oral drug used for multiple sclerosis. A generic could become available in 2022 when Aubagio's patent expires. Currently, Aubagio represents approximatively 0.48% of overall spending.

Patents will expire for multiple cancer drugs as well. There may be a generic version of Revlimid® on the market in the next five years. Revlimid is an oral cancer drug used to treat multiple myeloma, a rare type of cancer affecting about four in 100,000 people in Western industrialized countries. Even though utilization is low, Revlimid's cost is very high, estimated at $150,000 per year.

While this scenario is promising, it is important to note that litigation around patent expirations may delay the availability of some generics, also delaying potential savings.

Multiple biologic drug patents will expire in the next five years; consequently, more biosimilars will enter the market. Approval of a rituximab biosimilar is expected sometime between 2019 and 2021. Rituximab is prescribed for the treatment of certain types of blood cancer and autoimmune diseases such as rheumatoid arthritis. If the biosimilar gains approval for many of the indications approved for rituximab, its market penetration will increase, leading to meaningful savings for private plans.

The uptake of biosimilars will depend on many factors:

- The acceptance of interchangeability;
- The number of indications approved for the biosimilar as compared to the brand reference drug;
- The adoption of policies that favour the reimbursement of biosimilars;
- The number of competitors introducing biosimilars for each reference drug.

Again, issues around patent expirations might delay market entry of generics and biosimilars by a few years. Furthermore, in the new trade agreement between the United States, Canada and Mexico (USMCA), protection on biologic drugs has been extended from 8 to 10 years, shielding manufacturers from biosimilar competition for an additional two years. Altogether, these factors could increase upward pressure on costs.

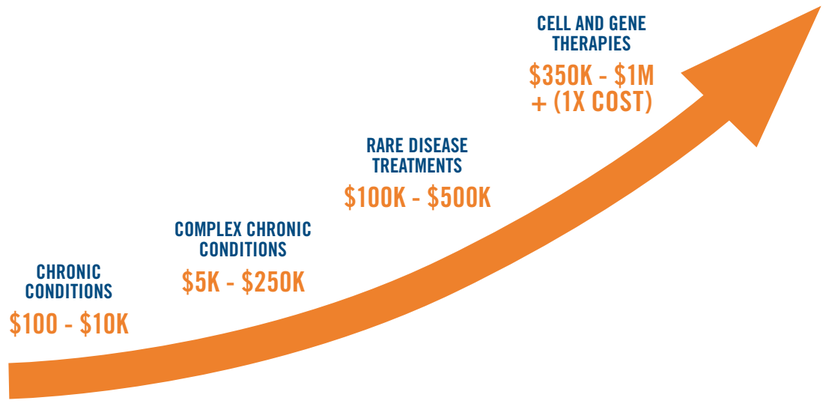
BIOSIMILARS UNDER DEVELOPMENT

CHEMICAL NAME	BRAND NAME REFERENCE DRUG	COMMON INDICATION	% OF OVERALL SPEND IN 2018	EXPECTED LAUNCH
Trastuzumab	Herceptin®	Cancer	0.00%	2019-2021
Rituximab	Rituxan®	Cancer	0.21%	2019-2021
Omalizumab	Xolair®	Asthma / COPD	0.84%	2019-2021
Ranibizumab	Lucentis®	Eye Diseases – Macular Degeneration	0.30%	2019-2021
Natalizumab	Tysabri®	Multiple Sclerosis	0.21%	2020-2022
Insulin aspart	NovoRapid®	Diabetes	0.30%	2022

UPDATE ON INNOVATIONS IN DRUG DEVELOPMENT IN 2018

PRESSURE ON SUSTAINABILITY OF THE DRUG BENEFIT

EVOLUTION OF DRUG DEVELOPMENT IN 2018



In the past year, pharmaceutical research and development has resulted in the introduction of breakthrough drugs that provide welcome hope to patients and their families. However, the high costs of these drugs also put considerable pressure on drug benefits sustainability. In general, pharmaceutical companies are now focused on specialty and niche drugs for which the price tag is very high, with more drugs in the development pipeline that, despite low utilization, mean enormous financial burdens for patients and payers. Drugs that treat rare diseases, for example, are often priced at hundreds of thousands of dollars per year. Those conditions are chronic and often require treatment for a lifetime. Cell and gene therapies are also contributing to the pressure on private plans.

NOTABLE DRUG INNOVATIONS IN 2018

We discussed, in last year's report, a potential new use for the drug Ilaris® (canakinumab). Originally, this high-cost drug was approved for the treatment of a family of rare inflammatory diseases. Ilaris® was also the object of a clinical trial for a new indication to reduce the risk of major cardiovascular events in patients with prior heart attack and atherosclerosis (CANTOS trial). Although promising in the beginning, results showed no statistical difference in mortality in patients using Ilaris® or a placebo. Consequently, the Food and Drug Administration has rejected the submission for cardiovascular diseases. However, benefits for patients with non-small cell lung cancer

were discovered during the trial and it prompted the start of clinical trials for Ilaris® as an oncology drug. Results should be available in 2022.

Gene therapies, including CAR-T cell therapies, remain a promising area of development in the pipeline. Although they generally target cancer, a potential new use for an inflammatory autoimmune condition called lupus is currently under investigation. Lupus is a chronic inflammatory disease that can virtually affect every organ. Symptoms can include pain, skin lesions, inflammation and failure of multiple organs like kidney and heart; the disease is characterized by periods of relapse and remission. While the cause of this disease is unknown, there is evidence that B cells play a central role in the course of the disease by producing autoantibodies in excess and activating other pathways of the immune system, which results in an intense inflammatory immune response. CAR-T cell therapy would allow to introduce modified T cell therapies in a patient that would target a specific protein that is found on B cells that produce autoantibodies. In mice, these modified T cells improved disease symptoms and progression. Although clinical trials are needed to ensure safety and efficacy of CAR-T cell therapies in humans, these preliminary results are promising and might widen the spectrum of diseases for which gene therapies can be effective. Approved CAR-T cell therapies are currently administered in a hospital setting; therefore, cost of these very expensive breakthrough drugs might not impact private payers.

DEVELOPMENT IN MIGRAINE THERAPY

Migraine is an often debilitating disease that is a major cause of disability and affects approximately 8.3% of Canadians.

Treatment often includes the long-term use of preventative drugs to reduce the number of episodes experienced.

In 2018, the first calcitonin gene-related peptide (CGRP) inhibitor was launched on the Canadian market. Aimovig™ constitutes a breakthrough, the first drug that directly targets a molecule implicated in the cascade of reactions that lead to a migraine attack. Aimovig is a biologic drug, administered subcutaneously, once a month, by the patient.

Although treatment is approved only for patients who experience at least four migraine days monthly, the prevalence of migraines makes the number of potential users very high. The annual cost for Aimovig ranges from $6,000 to $12,000, depending on the dosage. As more patients gain access to this specialty drug used for the treatment of a common condition, costs will increase substantially for private payers.

This field is expected to expand as other molecules targeting CGRP are in the pipeline, with one, galcanezumab, currently under review by Health Canada.

NEW ORPHAN DRUGS IN 2018

A rare disease is one that affects fewer than five in 10,000 persons in Canada. While the prevalence of these conditions is extremely low, there are currently over 7,000 rare diseases listed, cumulatively impacting about one in 12 Canadians.

Only a small number of treatments for these conditions are available, and none are curative. Rare diseases are complex conditions, often life-threatening, that have huge consequences on patients' health.

About 80% of rare diseases have a genetic component and are therefore more difficult to study. Low prevalence also limits research by restricting the number of eligible patients available for clinical trials. Consequently, prices for these therapies are ultra-high, putting significant pressure on private plans.

Two new drugs for rare diseases were commercialized in Canada in 2018, Radicava™ (edaravone) and Kanuma® (sebelipase alfa).

Radicava is indicated for amyotrophic lateral sclerosis or Lou Gehrig's disease (or ALS). ALS is a life-threatening, progressive disease that leads to general muscle weakness and, eventually, respiratory failure. There are currently 3,000 Canadians diagnosed with this disease. Radicava slows the progression of ALS in patients in the early disease stage, but this breakthrough comes at a high price – the annual cost is about $190,000 per year. Recently, the Institut national d'excellence en santé et services sociaux (INESS) in Quebec recommended that the RAMQ formulary include Radicava under the condition that

it be listed as a Médicament d'exception and that the manufacturer reduces the price. This inclusion would mean that private plans in Quebec would also have to provide coverage for this costly drug.

Kanuma® is used for the treatment of children and adults diagnosed with lysosomal acid lipase (LAL) deficiency. This genetic condition is characterized by an abnormal accumulation of fat in cells throughout the body, especially in the liver, within the first weeks of life. This accumulation of lipids leads to several health problems, including enlarged liver and spleen, vomiting, diarrhea, and poor absorption of nutrients. The result is tissue scarring, leading to cirrhosis and multi-organ failure. Infants generally do not survive past their first birthday. The annual cost of Kanuma is estimated to be $445,000 for infants and $666,588 for children and adults.

Some types of cancers are also considered rare diseases. Cancer can affect multiple organs and have many subtypes, depending on which genes mutate. For the same type of cancer, it is possible that one mutation is widespread and others rare. As treatments become more and more specialized, new drugs tend to target extremely specific forms of cancers, attacking cells with a particular mutation.

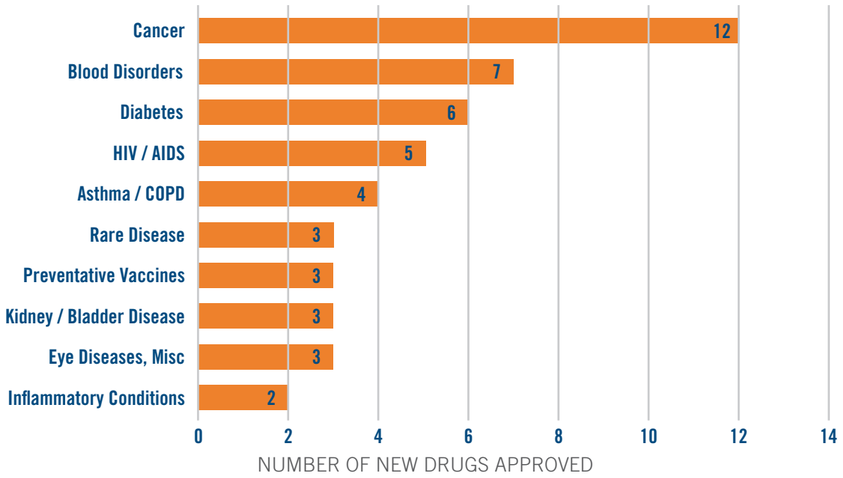
For example, in 2018, Rydapt™ (midostaurin) gained approval to treat mast cell leukemia, aggressive systemic mastocytosis and systemic mastocytosis with associated hematological neoplasm, three very rare forms of blood cancer. The annual cost of Rydapt for these indications is estimated at $483,000. Bavencio™ (avelumab), another drug approved in 2018, is approved for a rare type of skin cancer called Merkel cell carcinoma, which has a prevalence of 0.7 cases per 100,000 persons in the United States. The annual cost for Bavencio is estimated to be $137,000.

Although utilization may remain low for these indications individually, the collective cost of these and similar therapies will unquestionably put additional cost pressure on payers.

Continued medical innovation means that more rare cancers are diagnosed, and that novel treatments are developed with ever-increasing regularity. It is also predicted that the prevalence of these cancers may increase with the aging of the population.

NEW BRAND DRUG APPROVALS IN 2018

TOP 10 COMMON INDICATIONS FOR WHICH NEW DRUGS WERE APPROVED IN 2018



Newly approved drugs increased pressure on spending again in 2018, partly because a substantial portion was in the specialty category.

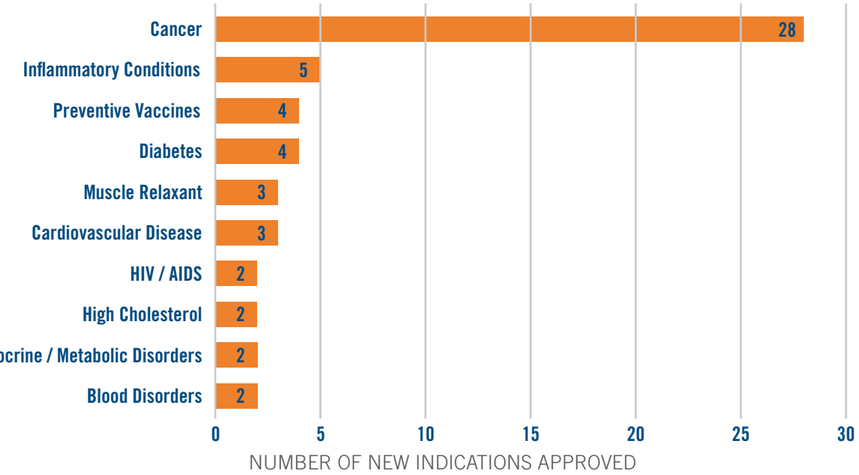
Cancer treatment once again leads in number of newly approved drugs, perpetuating a three-year trend. As most of these therapies are self-administered orally by the patient, private payers are more exposed to the enormous costs relative to these drugs. (Older oncology drugs were mainly administered in hospital and were therefore covered by public medical plans.)

See table *2018 New Brand Approvals* in Appendix.

NEW INDICATION APPROVALS IN 2018

See table *2018 New Indication Approvals* in Appendix

TOP 10 COMMON INDICATIONS FOR WHICH NEW INDICATIONS WERE APPROVED IN 2018



Approval of new indications for existing drugs continued to drive costs up, especially as more specialty drugs gained expanded use. For example, Repatha®, a drug that lowers cholesterol and costs about $7,000 per year of treatment, was approved for two additional indications in 2018: prevention of cardiovascular events and primary hyperlipidemia. As a consequence, the portion of overall spending for Repatha went from 0.01% in 2016 (a year after its initial approval) to 0.15% in 2018. Hypercholesterolemia is a widespread condition, so it is safe to assume that Repatha's impact on overall spending will continue to grow.

Cancer drugs have also gained their share of new indications this year, with 28 approvals. This is a slight increase over 2017 when 24 new indications were approved.

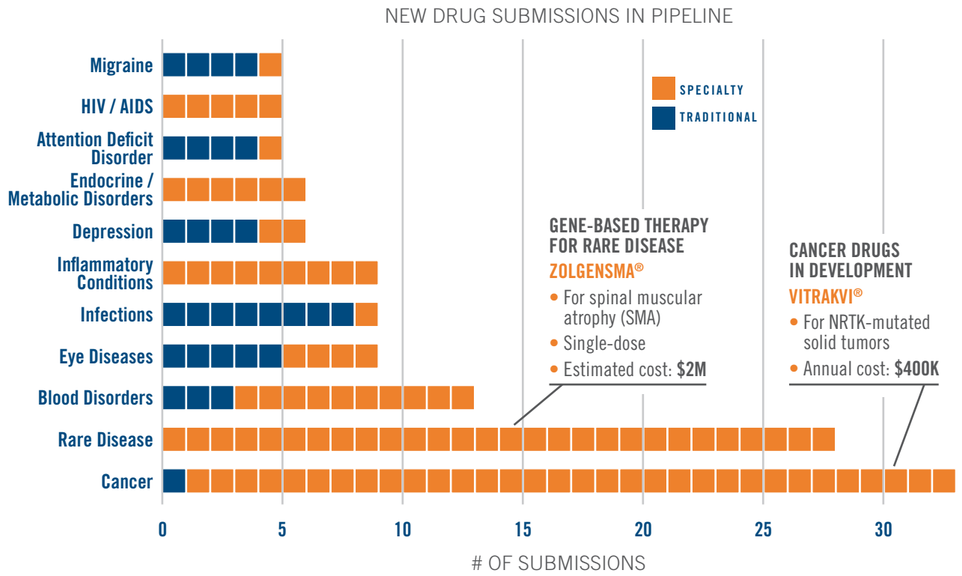
With more drugs designed for outpatient therapy (to be taken outside of the hospital setting), this trend is expected to continue for the foreseeable future.

PIPELINE

NEW MEDICATIONS IN THE DEVELOPMENT PIPELINE

DRUG DEVELOPMENT PIPELINE

NEW MEDICATIONS UNDER DEVELOPMENT



Unsurprisingly, based on recent trends, cancer therapies lead the drug development pipeline, with more than 30 drugs currently in Phase III clinical trials or under review by the FDA and/or Health Canada.

As mentioned, pharmaceutical companies are investing substantial resources in developing gene-based therapies and CAR-T cell therapies. Gene therapy is a technique that uses genes to treat or prevent diseases. Instead of using surgery or drugs, a gene is inserted into a patient's cells to:

- Replace a disease-causing mutated gene with a healthy gene;
- Inactivate a mutated gene that does not function properly;
- Introduce a new gene that will help fight a disease.

This technique is very promising for a number of diseases: genetic disorders currently without cures, some types of cancers and certain viral infections. In CAR-T cell therapy (chimeric antigen receptor T cells), the patient's T cells (a type of immune system cell) are modified in a laboratory to attack the patient's cancer cells. These 'upgraded' cells are then infused in large numbers into the patient's bloodstream. Currently, this technique is only used to treat some types of blood cancer.

The first gene-based therapy to be approved in Canada was Kymriah™ (tisagenlecleucel), in 2018. It is used to treat children and adolescents with resistant or recurring forms of acute lymphoblastic leukemia. As this drug requires administration in a hospital setting due to its complex monitoring requirements, it does not directly impact private plans. In early 2019, Yescarta® became the second

CAR-T cell therapy to be approved in the country. It is used to treat certain forms of blood cancers, non-Hodgkin and other large B-cell lymphomas.

Targeted oral therapies for cancer are also populating the pipeline. Vitrakvi® (laroctretinib), which has yet to be approved by Health Canada, is indicated for the treatment of solid tumours with a mutation of the NRTK fusion gene. This mutation is quite rare, with 2,500 to 3,000 new cases reported in the US each year. (Equivalent Canadian statistics are not available.) However, despite a predicted low utilization, its cost of almost $400K per year per patient could severely impact private plans.

Treatments for rare diseases are also an important focus area in the pipeline. More than 25 drugs for these complex and life-threatening conditions are either in Phase III studies or under regulatory review. Gene-based therapies are also in development in this field.

Of note, the most expensive drug ever commercialized is scheduled for approval in 2019 in the United States. Zolgensma® (onasemnogene abeparvovec) is seeking approval for the treatment of spinal muscular atrophy Type 1. This drug would be administered just once, at the considerable price of USD$2M. The only drug currently approved for SMA is Spinraza™, which needs to be taken long-term, at the cost of $700K for the first year and around $350K in subsequent years. Zolgensma would be a direct competitor to Spinraza and, given the fact that the administration is likely to be in a hospital setting, its approval could potentially be beneficial for private payers that currently pay for Spinraza.

Refer to Appendix for a listing of possible near-term approvals of new brands.