The Drug Pipeline:
What’s in it and why it matters.
Introduction

For several years now, plan sponsors have become accustomed to relatively modest growth in drug spend. This modest growth was in part due to the introduction of lower cost, generic versions of a significant number of previous “blockbuster” medications such as Lipitor, Crestor, Plavix, and others (collectively known as “The Patent Cliff”). However, behind this wave of new generics was a trend toward higher cost, “specialty” drugs. Growth in one area was largely offset by savings in another for several years as we progressed through “The Patent Cliff”.

Today, it is safe to say that we have landed near the bottom of “The Patent Cliff.” New generics will continue to come to market, but few will have the impact of the blockbusters of the past few years. This means that growth in the use of these higher cost, specialty drugs will no longer be significantly offset by new generics coming to market. Plan sponsors realized this with the launch of several new drugs to manage Hepatitis C through 2013-2015, as well as other specialty drugs for multiple conditions.

Paying attention to what is coming in terms of new drug development is critical. This goes not only for promising pipeline agents, but also for pipeline failures as well, as these failures can often teach us lessons about other similar drugs in development.

This article will provide a glimpse into the pipeline over the next few years with a focus on potential new therapies for highly prevalent conditions, as well as expected developments in more mature markets.

The Pipeline

and Pooling/Stop-Loss

There is no question that specialty drugs require insurers to re-evaluate pooling thresholds, pooling charges, etc., especially when a drug is both expensive and used to treat conditions with high disease prevalence.

Understanding the new drug pipeline and the expected uptake of new drugs will not eliminate competitive pushback regarding increases to pooling charges and/or stop-loss charges. However, an understanding of the pipeline allows insurers to be better equipped to deal with these questions and validate their pricing policies.
Specialty Drugs
for Common Disorders

PCSK9 inhibitors for high cholesterol

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors) are a new class of biologic used to manage types of high cholesterol as a result of a genetic disorder, known as homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia. Currently, Repatha is available in the Canadian market and will soon be joined by Praluent. The idea of a specialty biologic to treat a genetic disorder at around $8,000 per year (for most claimants, but potentially higher in some cases) evolving into a treatment for a high prevalence condition, such as any plan member with high cholesterol, will cause concern for those involved with managing drug benefits.

It remains difficult to predict what the uptake of this class of drug might be, with estimates ranging over a large margin. Manufacturer estimates for the potential market of these drugs suggest 1,324 people per 100,000 covered lives; but the potential market could be much larger as new data becomes available.

Biologics for migraine

Seemingly on the heels of the launch of PCSK9 inhibitors for high cholesterol will be a new class of biologics known as Calcitonin Gene-Related Peptide (CGRP) inhibitors for the prevention of migraines.

The use of a biologic to treat migraine is not new. Botox received approval in Canada for the treatment of chronic migraine (defined as 15 or more days per month with headache lasting 4 hours a day or longer) in 2011.2

CGRP inhibitors, however, are being studied in a much broader population including both chronic migraine and episodic migraine with potentially no definition as to headache frequency or severity.

While the costs of these new biologics to treat migraines are not yet clear, they could potentially be similar to the annual treatment costs of PCSK9 inhibitors; although there may be potential cost offsets in terms of absenteeism, productivity loss and disability due to migraines. If not defined prior to the approval of these drugs in mid to late 2017, prior authorization criteria for these agents should be developed to quantify headache frequency and severity to ensure the cost effective use of these agents.

The most advanced biologics in this space include LY2951742 from Lilly3 and AMG334 being developed in partnership between Amgen and Novartis.4

Biologics for osteoarthritis

The use of biologic therapies for rheumatoid arthritis has been well established for several years with drugs such as Remicade, Inflectra, Enbrel, Humira and several others.

Rheumatoid arthritis (RA) is an autoimmune condition that affects only about 1% of the worldwide population.5 Osteoarthritis (OA) is a far more common condition, with nearly 1 in 2 people expected to develop symptomatic OA of the knee by age 85, and 2 out of 3 obese individuals expected to develop OA of the knee in their lifetime.6 Prevalence data such as this makes the potential costs of specialty biologics targeted to OA instead of RA particularly concerning.

A new class of biologics known as Nerve Growth Factor Inhibitors (NGFs) has been in development for several years and was regarded as a likely blockbuster with a potential market for chronic pain of over US$11 billion per year.7 However, signals of potential nervous system changes and joint degradation led the US Food and Drug Administration (FDA) to put a hold on trials, thus suspending development.7,8

The clinical hold imposed by the FDA on agents in this class was lifted in 2015,8 allowing development of these drugs to continue. However, it is likely that drugs in this class will undergo a heightened level of scrutiny by regulatory bodies such as the FDA and Health Canada due to past safety concerns. It is unclear at this point whether these drugs may be eventually approved for sale. For now, this class of drugs provides a useful example why interruptions or discontinuations in clinical research need to be monitored.
New Developments
in More Mature Markets

Hepatitis C

New drugs for Hepatitis C, with their high cure rate, have taken the industry by storm since the approval of Sovaldi by Health Canada in 2013. Subsequent launches of additional Hepatitis C therapies such as Harvoni, Holkira Pak, Technivie and others have only added to the attention received by these new drugs.

Although pharmacy claims data suggest that the initial warehousing of patients and resulting rush of claims and claimants may be waning, there continues to be several new drugs in development for this condition.

Most new therapies for Hepatitis C (HCV) have focused on the most common forms of the disease. Genotype 1 HCV accounts for approximately 60% or more of HCV cases in Canada, with genotypes 2, 3 and 4 making up almost all of the rest. With extremely high cure rates (90% or more) associated with new HCV therapies for these most common genotypes, it is not anticipated that many of those who have recently received treatment will require subsequent retreatment for HCV. There does, however, remain a need for HCV therapies targeted to the more rare forms of the disease—genotypes 5 and 6.

These new therapies appear to offer similarly high cure rates to other recent therapies, and competitive pressures may mean pricing similar to or slightly less than other agents in the class.

While the new drug pipeline does contain several new therapies for HCV, the most common forms of HCV are well served by existing therapies with extremely high cure rates. One drug of interest in the near term HCV pipeline is Gilead’s combination of sofosbuvir (already in Sovaldi and Harvoni) with a new antiviral known as velpatasvir, which is expected to be approved to treat all genotypes of HCV. This agent could be seen by mid-2016. Although a significant advance for the less common forms of HCV, the impact of this and other new HCV therapies may be low given the availability of existing therapies, with extremely high cure rates, for the most common forms of the disease.
Oncology (cancer)

The oncology pipeline receives much attention and contains a significant number of drugs in development. However, new cancer therapies often generate questions regarding the high cost of these products versus the small prolongation of life that these therapies sometimes offer.13

The oncology pipeline is particularly rich, and a full discussion of it is beyond the scope of this article. There are, however, some common themes that are worth mentioning.

Immunotherapies

Immunotherapies are an exciting area of drug development showing promise in many forms of cancer. Instead of targeting the tumour itself, these drugs work by stimulating the body’s natural immune system to fight the cancer.14

Two such drugs have recently been launched in Canada: Opdivo (currently approved for unresectable metastatic melanoma and non-small cell lung cancer) and Keytruda (currently approved for unresectable metastatic melanoma). In metastatic melanoma, this new class of drugs has been shown to significantly improve one year survival versus existing chemotherapy with far fewer adverse events.14

This class of drugs is also being studied for other types of cancer, with approvals expected in 2016 for Opdivo in kidney cancer.15 Other uses for this new class of cancer therapies include colorectal cancer, lymphoma and other solid tumors.16

Combination therapies

Another potential area of interest for payers involves using combinations of existing specialty drugs versus solo usage of individual drugs. While treatment of metastatic melanoma is being improved by the use of immunotherapies, it is also being improved by the use of these combination therapies.

For several years, BRAF inhibitors such as Zelboraf and Tafinlar have been commonly used in the management of metastatic melanoma with a particular genetic mutation (BRAF V600 mutation-positive).17 More recently, another class of drugs known as MEK inhibitors (eg. Mekinist) has also been used to treat the same cancer. Both BRAF Inhibitors and MEK inhibitors are considered high cost drugs.

Most recently, Health Canada has approved combination therapies involving BRAF inhibitors and MEK inhibitors. While these new regimens extend survival by several months, they effectively double the cost of treating this cancer by combining these agents.18

Subsequent entry biologics (SEB) or biosimilars

For years, plan sponsors and insurers have seen drugs like Remicade, Enbrel and Humira firmly entrenched at or near the top of their “Top DIN lists.” In fact, these drugs have been around long enough that they are at or near the end of their patent lives. However, under Canada’s current regulatory framework, these drugs will not see the generic competition we are accustomed to for more traditional drugs. Instead of “generic” versions of these molecules, we will see what are known as “subsequent entry biologics” (SEB) or “biosimilar” versions of the original biologics.
Although not the first SEB launched in Canada, Inflectra (infliximab) was launched as a biosimilar version of Remicade in March 2015\textsuperscript{19} with approval for most of the indications for which Remicade was approved. While Inflectra will not be considered “interchangeable” with Remicade in the same sense that traditional generics may be interchangeable with their brand counterparts, public and private plans in Canada have started to list Inflectra in a manner that requires plan members starting infliximab for the first time to use Inflectra instead of Remicade for the conditions where Inflectra was approved by Health Canada.\textsuperscript{20,21,22} Other SEBs approved by Health Canada include Omnitrope (a biosimilar version of human growth hormone), Basaglar (a biosimilar version of Lantus insulin) and Grastofil (a biosimilar version of Neupogen).

The next major SEB expected to come to the Canadian market may be a biosimilar version of Enbrel. While this case is still before the courts,\textsuperscript{23} this SEB could be launched by one or more manufacturers by the end of 2016 or in early 2017. A biosimilar version of Humira may follow in 2018.

While pricing discounts for SEBs versus innovator biologics are variable for the small number of SEBs to date, most offer a discount versus the innovator product. While savings may be limited to the number of new plan members initiating therapy, SEBs do offer potential future savings, and knowledge of the SEB pipeline is particularly useful in gauging potential offsets to higher cost market entries.

**Generic pipeline**

While the bulk of the “Patent Cliff” is largely behind us, new generics are important to monitor going forward. As previously mentioned, subsequent entry biologics will not be generically interchangeable with their original counterparts. However, there are specialty non-biologic drugs that will eventually lose patent coverage and open the door to generic competition; for example, Gleevec (a drug used to treat leukemia and other cancers), became generic in 2013.

While the generic pipeline for 2016 and 2017 is relatively thin versus the years of the “Patent Cliff,” major traditional generic launches expected in 2016 include generic versions of Cymbalta (for depression and fibromyalgia), and Tiazac XC (for hypertension). In 2017, we can expect generic versions of Olmetec (for hypertension), Exjade (for chronic iron overload) and Vimpat (for epilepsy), among others.\textsuperscript{24}

High cost drugs that could see generic launches in 2016 include Alimta (cancer), Kivexa (HIV), Iressa (cancer), and Volibris (pulmonary arterial hypertension). High cost generic launches in 2017 could potentially include Viread (HIV), Reyataz (HIV), and Kaletra (HIV).\textsuperscript{22}
Conclusion

The end of the “Patent Cliff”, and the increase of SEBs and specialty drugs in the pipeline, will create new financial pressures for plan sponsors and insurers. Historically, the ‘complexity’ of a disease (e.g., cancer) often dictated the cost of treatment. The pipeline drugs currently in development are now significantly more expensive, regardless of whether they treat common medical conditions (e.g., migraines) or more complex diseases. Cost pressures from these new therapies will only increase, and plan sponsors and insurers must remain vigilant in monitoring the pipeline in order to prepare and adjust their benefit plans to best respond to potential market disruptions.

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