At the simplest level of drug plan design is the substitution of a brand drug with a generic drug. With a number of brand drugs losing patent protection over the last few years and drug system reform driving down the cost of generic drugs to levels of approximately 25% of the brand drug, the argument for mandatory generic drug substitution is strong. This has resulted in a number of group health insurance companies implementing mandatory generic substitution in all their drug plans. Essentially, this policy will result in an automatic price cut-back on a brand prescription whenever a new generic drug has been approved by Health Canada. The employer plan only pays for the cost of the generic drug even if the plan member decides to stay on their current brand treatment. While in theory this drug plan rule seems reasonable, there is a growing body of evidence that highlights the risks of applying this rule to all drug categories irrespective of drug formulation or health condition treated.

**Attention, please**

Not all drugs work the same way in each person. Furthermore, not all drugs are designed or formulated the same way. This is particularly true in the case of drugs used to treat mental health conditions such as depression and attention deficit hyperactivity disorder (ADHD).

Although behavioural modification is an important element of treatment, it alone is usually not effective in improving the core symptoms of ADHD. Generally, medication that acts as a stimulant is the most effective treatment for ADHD. Approximately 80% of people with ADHD respond to stimulant medication. 

**What is ADHD?**

ADHD is a biological condition of the brain that affects approximately 5% to 12% of children and persists into adulthood in 60% of patients. The prevalence of Adult ADHD is estimated to be 2% to 5%, which is similar to clinical depression, a mental health issue that is well-recognized in the workplace. The core symptoms of ADHD are inattention, impulsivity and hyperactivity. These symptoms can result in multiple areas of dysfunction relating to a person’s performance in the home, school, work and community. If poorly managed, ADHD can have serious consequences, including school failure, lower self-esteem, an increased risk of injury or accident and, ultimately, job failure and problems with relationships and substance abuse.
treatment. Psychostimulants affect areas of the brain that are believed to be important for concentration, weighing consequences, foresight and inhibiting actions—which appear to be under-aroused in a person with ADHD.

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In Canada, methylphenidate is the most commonly prescribed stimulant for ADHD and is available in various dosages and formulations. Before the introduction of Concerta® (methylphenidate hydrochloride extended release) in 2003, patients needed to take their medication two to three times a day. This posed significant compliance and adherence challenges for patients who had to take at least one of their doses during school or work hours. Concerta®, a multi-phasic, long-acting form of methylphenidate, was developed specifically to overcome these challenges and it uses a unique delivery system, ORal Osmotic (OROS) technology, that allows once-daily dosing. Concerta® is fast-acting, with an initial onset of action within one hour, and then provides continued release of the drug that lasts for 12 hours. This delivery technology has eliminated the need for a mid-day and late-afternoon dose.

In 2010, Health Canada approved a generic formulation, TEVA-methylphenidate ER-C, which was assessed to be bioequivalent to Concerta®. Interestingly, prior to the Health Canada approval, Teva had proven to the court that its product does not release methylphenidate from its dosage form in a sustained-ascending dose over time and therefore could not be said to infringe upon the Concerta® patent. Since then, there has been increasing evidence suggesting clinically meaningful differences between the two products, as well as abuse concerns due to differences in how the two products are manufactured.

Bioequivalence does not mean interchangeable

When Health Canada assesses a new generic drug for approval for use in Canada, it reviews studies conducted by the generic drug manufacturer to compare the generic drug to the brand drug for “comparative bioavailability.” These studies must show that the generic drug delivers the same amount of medicinal ingredient at the same rate and extent as the brand drug into the patient’s bloodstream. The term that is used to describe this is “bioequivalence.” However, what is not measured is how the drug affects the patient, which is referred to as “therapeutic equivalence.” Under Health Canada requirements, for a drug to be deemed bioequivalent, the amount of generic drug measured in the blood must be within a range of 80% to 125% of the brand drug for both the maximum concentration and total amount of drug delivered. For some drugs that are metabolized quickly from the body, have a narrow therapeutic effect range or have a complex profile with different levels of drug being delivered at different times of the day, this variance in drug can have a significant impact on how the drug works in each patient.

Although Health Canada has deemed Concerta® and TEVA-methylphenidate ER-C to be bioequivalent, provincial drug plan decision makers are not so quick in deeming the products to be interchangeable for the purpose of “generic substitution” rules. For example, in 2011, the Québec Conseil du médicament listed TEVA-methylphenidate ER-C in its RAMQ drug formulary but also stated that it “believes that certain differences between these two products could result in clinical differences and a greater potential for illicit use. As a precaution, considering that the consequences in destabilization in this disorder can be substantial, the Conseil du médicament did not want to apply the method of lowest price to the generic drug” (translated from French). 3

In addition, the U.S. Food and Drug Administration (FDA) is recommending additional bioequivalence metrics (beyond the standard metrics used by Health Canada) to evaluate generics to ensure therapeutic equivalence and interchangeability. No generic versions of Concerta® have yet been approved in the U.S.

In another case, the FDA recently (October 2, 2012) mandated the removal of a generic version of Wellbutrin XL 300 mg (bupropion hydrochloride) manufactured by Impax Laboratories, Inc., and marketed by Teva Pharmaceuticals USA, Inc., as it was deemed to be not therapeutically equivalent to the brand drug.4 The withdrawal occurred when the bioequivalence tests failed between the two products at the 300 mg dose. The original bioequivalence tests used for approval were only done on the 150 mg dose and the results were extrapolated to the 300 mg format since this methodology was based on the FDA’s guidance at the time the products were approved. The FDA has since determined that this approach is no longer appropriate to establish bioequivalence of 300 mg bupropion hydrochloride extended-release tablets to Wellbutrin XL 300 mg, and is revising its guidance on how to conduct bioequivalence studies for extended-release products in the future.

These developments in the U.S. highlight the fact that current bioequivalence test results may not always translate to therapeutic equivalence.
Abuse potential reduced
Although methylphenidate is widely accepted as an effective treatment for ADHD, there are still concerns about the abuse potential of the drug. Recent studies, including studies conducted in Canada, demonstrate that stimulant abuse, misuse and diversion are problems, particularly among university students and young adults, but also in grade-and high-school children. Overall, that data suggest that there is a tremendous amount of pressure on children, adolescents and adults with ADHD, who are prescribed stimulant medications, to divert their medications.

Changes in ADHD medication therapies can have high patient and societal costs, (therefore) consultation with all who are involved in the care of the ADHD patient is essential before modifying drug therapy.

These concerns are addressed in the way Concerta® is designed and manufactured. The unique delivery mechanism of Concerta®, which includes a thick resin to hold the drug, minimizes the ability to crush the hard tablet into a powder, which could then be inhaled or dissolved in water and injected intravenously like currently available prescription stimulant medications. In fact, data show that Concerta® is less abused and/or misused than other stimulants. So much so that Concerta® is the only long-acting ADHD medication in Alberta that does not require a triplicate prescription (a safety measure to track the use of narcotics).

Real-world evidence
There has been growing evidence that suggests that the bioequivalence results from Concerta® and the generic drug may not translate into therapeutic equivalence. In other words, TEVA-methylphenidate ER-C may not predictably produce the same clinical effects as Concerta®. Two recent Canadian studies in pediatric and adult patients with ADHD show that Concerta® and TEVA-methylphenidate ER-C may not be interchangeable. In a pediatric study, the author concluded that the generic drug “does not appear to be clinically equivalent to Concerta®,” and recommends that since “changes in ADHD medication therapies can have high patient and societal costs, consultation with all who are involved in the care of the ADHD patient is essential before modifying drug therapy.” In the adult ADHD study, the authors concluded that due to the clinically and statistically significant differences in the outcomes measured, as well as the greater rates of discontinuation in the generic drug group, “health authorities should be careful before considering the reimbursement of that generic product since the specificity of the medication has to do more with the delivery system than the therapeutic agent.”

Both studies indicated that the two products may differ not only in effectiveness but also in their side-effect profiles. These observations are supported by a review of the Health Canada database, Canada Vigilance Adverse Reaction Online Database and the prescription claims data from IMS Health. The analysis confirmed that the incidence of adverse drug reactions is significantly greater, up to 60-fold higher, for the generic drug compared to Concerta®.

To further support these findings, surveys of 335 community pharmacists in Ontario and 145 community pharmacists in Québec have illustrated the real-world experiences at the pharmacy counter when patients are switched from Concerta® to TEVA-methylphenidate ER-C has been reported by both groups of pharmacists. In Ontario, switching was reported to be one of the most common reasons for reporting an adverse drug reaction. In Québec, two-thirds of the 145 pharmacists surveyed reported an adverse drug reaction as a result of switching from Concerta® to TEVA-methylphenidate ER-C.
**What do the experts say?**

Experts in the treatment of ADHD have begun to reflect these differences in ADHD treatment guidelines. The CADDRA (Canadian ADHD Resource Alliance) ADHD Practice Guidelines from 2011 reflect concerns that current standards for measuring bioequivalence between Concerta® and TEVA-methylphenidate ER-C may not reflect clinical equivalence of these drugs.14

Ensuring optimal ADHD treatment, whether it is for a child or an adult, is in the best interest of the patient, the family and the employer. In an era of growing sensitivities on long-term plan sustainability and affordability, cost-containment measures, such as mandatory generic substitution, are being implemented more broadly. However, haste for immediate cost savings must not be at the expense of thoughtful plan designs that optimally balance short- and long-term costs with benefits for the employee and the plan sponsor.

**REFERENCES**

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