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Canadian Generic Pharmaceutical Association

Ensuring a Consistent Supply of Safe, Effective and High Quality Generic Medicines for Canadians

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Executive Summary

Ensuring a Consistent Supply of Safe, Effective and High Quality Generic Medicines for Canadians

The globalization of supply chains over the last two decades is changing how generic pharmaceutical companies operate and compete globally. Globalization of the pharmaceutical supply chain has the potential to reduce development and manufacturing costs, improve product quality, decrease time to market for generics, increase the variety and number of generics available on the market and reduce out-of-stock situations due to the increased flexibility to divert product from other markets. However, when a regulatory jurisdiction enforces changes to a product for a particular market, it introduces risks to the advantages recognized by globalization, the most significant of which is potential interruptions in supply. Although the benefits of globalization outweigh the risks, the risks and vulnerabilities must be identified and continually monitored and managed.

Mergers and acquisitions have significantly changed the face of the Canadian generic pharmaceutical industry over the last 10-15 years. Since 2009, compound annual growth has slowed to 0.4 percent (IMS Health Pharmafocus 2018). On average, generic manufacturers invest three to six years and an estimated four million dollars to bring a new generic drug to market (CGPA, 2012). Decreasing numbers of manufacturing sites, increasing costs of market access, decreasing payer reimbursement strategies, the fluctuating Canadian dollar and unique Canadian regulatory requirements, including patent protection laws, all combine to threaten the viability of the generic pharmaceutical industry in Canada. In order to stay competitive, Canadian companies must be able to operate within the global space.

While the manufacturing landscape has changed, the regulatory environment has not kept pace. The current global regulatory environment is evolving more slowly than the market driven globalization of pharmaceutical supply chains. While the regulatory framework in Canada continues to be focused on ensuring patient safety and product quality, the existing regionally centric regulations and guidelines/policies are impeding the realization of benefits from the globalization of supply chains. Developing and/or manufacturing a product specifically for the Canadian market is an increasingly unviable option from an economic perspective. There is an increased need for harmonization of regulations as well as consolidation of best practices in the review of submissions such that Canadian companies can leverage the benefits of global supply chains. While Health Canada has been participating in the International Generic Drug Regulators Programme, the Australia-Canada-Singapore-Switzerland Consortium and the US-Canada Regulatory Cooperation Council, all of which aim to promote collaboration and convergence of generic drug regulatory programs, more needs to be done.

This paper documents the challenges faced by the generic industry with the current regulatory environment as well as the impact of these challenges on patients and payers and seeks to identify solutions. Solutions founded in guidelines and policies can be a relatively quick fix, while those entrenched in legislation and regulations require longer term efforts and broader consultation with stakeholders.

This paper does not include an exhaustive list of challenges. What it seeks to do is highlight the need for global harmonization of regulations, policies and guidelines wherever possible.

Opportunity exists for the Canadian Generic Pharmaceutical Association (CGPA) and its members to work closely with Health Canada to develop and implement solutions not only for these challenges, but also solutions that will allow Canadian companies to maximize the realized benefits of the globalization of supply chains. Harmonizing regulations in Canada with other regulatory bodies can help generic manufacturers leverage the opportunities from globalization which ultimately benefits Canadian patients and government. The ability to leverage single product development and common bulk product will

decrease costs to industry, patients and payers and decrease the time to market. It will also increase the flexibility to divert product from one market to another to minimize the potential for drug shortages. It will encourage companies to launch products in Canada by streamlining the review process, ultimately resulting in a greater variety and number of generics in Canada.

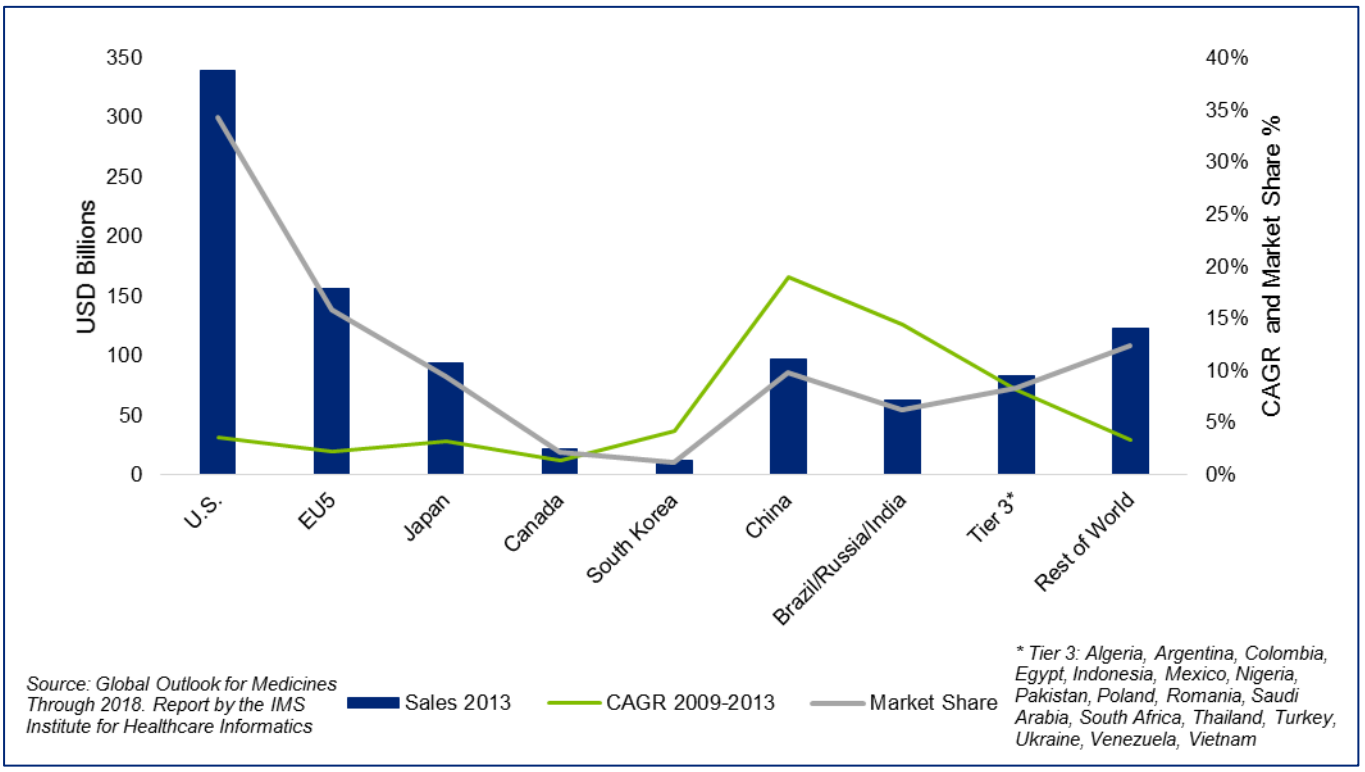
Fundamental to the discussion is the mandate of CGPA member companies to ensure a consistent supply of safe, high quality cost-effective medicines. However, in order to remain viable and competitive in today's global business environment, it is imperative to leverage global competencies wherever possible. While the required changes in regulations and/or policies and guidances must continue to focus on patient safety and product quality, they also must be based on science and facts. The benefits of globalization can be optimized with a regulatory framework that looks to the global environment and allows Canada to take advantage of the trend while minimizing the associated risks.

Canadian Context

Companies must look at several factors when developing a business case and deciding whether to launch a new generic in a given market. Market size, existing competition, development and approval costs, regulatory hurdles, length of time to market and legal challenge costs must all be taken into consideration. Key barriers to Canadian market entry include increasing costs of drug development, regulatory approval, patent challenges and provincial formulary listings.

Canada is the 10th largest market for pharmaceutical drugs in the world. In 2013, total pharmaceutical sales in Canada represented 2.3% of the global market, while generic sales in Canada represented less than 2% of the global market. The top 5 pharmaceutical sales countries in 2013 were the U.S., Japan, China, Germany and France accounting for 62% or $615B in sales (IMS Institute for Healthcare Informatics, 2014). The breakdown in sales and growth rate is provided in Figure 1 below.

Figure 1: Global pharmaceutical sales and growth



The U.S. (population of 324M), is the largest market for pharmaceutical drugs and accounts for 34.4% of the global market. The EU is the 2nd largest market in the world with the top 5 markets in the EU (collectively known as EU5) consisting of Germany (population 82M), France (population 67M), Italy (population 61M), UK (population 65M) and Spain (population 46M) accounting for 15.8% of the market. As the market in Canada (population 36M) is significantly smaller than the U.S. and the EU5, generic drug manufacturers may determine that it is not economically viable to launch a generic in Canada if they are required to conduct product development and/or manufacture product batches specifically for the Canadian market, even though the product may already have been approved in a similar regulatory

jurisdiction. The costs for bioequivalence studies and clinical trials are significant and, given the limited market size in Canada, it may not always be the best investment for a generic manufacturer to introduce the drug into the Canadian market. Generic manufacturers in e.g. Spain (population closest to Canada), can access the entire European market with approval based on a single drug dossier making the return on investment worthwhile. The ability for Canadian generic manufacturers to take advantage of global product development and introduce drugs from other markets, such as the U.S. or EU, can result in an increased number of generic drugs becoming available in the Canadian market. In 2015, over 700 generic approvals were issued by the United States Food and Drug Administration (U.S. Food and Drug Administration, 2015) compared to 128 generic approvals by Health Canada (Health Canada, 2015).

Additionally, from a business perspective, as displayed in Figure 1, the compound annual growth rate (CAGR) in Canada has been relatively modest at 1.4% over 5 years, compared to the growth rates in the U.S. 3.6%, EU5 2.2% and emerging markets 13.6%. Add that to the fluctuating value of the Canadian dollar and the business case becomes even bleaker.

In addition to product licensing costs, Canada's unique patent regime, whereby brand name manufacturers have two sequential tracks of litigation for the same patent(s), places generic companies at significant and often catastrophic risk when entering the Canadian market. Companies can be sued for patent infringement under the *Patent Act* even after they have successfully challenged the same patent(s) under the *Patented Medicines Notice of Compliance Regulations*.

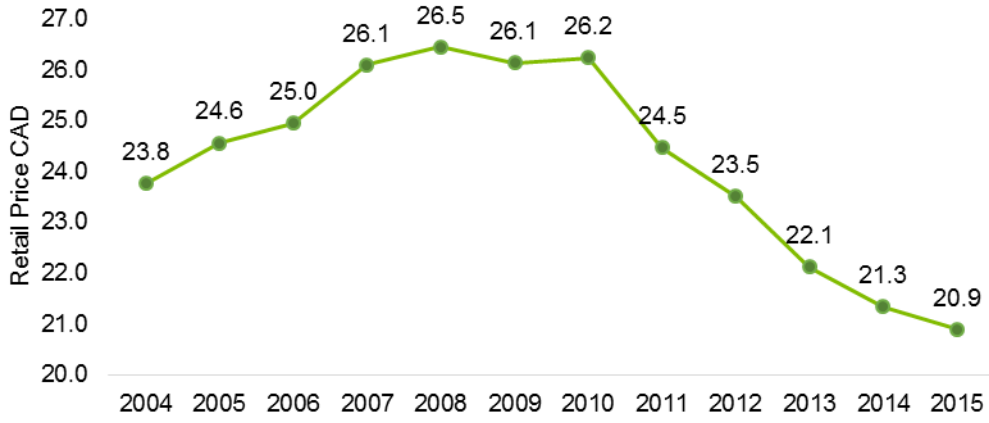
Once Health Canada issues a Notice of Compliance, the generic drug can be sold anywhere in Canada; however, in order to maximize sales and revenue the drug must be listed on the provincial formularies, in order for it to be eligible for reimbursement by the provincial government. The formulary specifies which drugs can be reimbursed and to what extent. For a generic drug to be added to a province's formulary, in addition to having a Notice of Compliance with a Declaration of Equivalence from Health Canada, it must meet the regulatory requirements of each individual province. Some provinces may require additional data and/or clinical trials even after the drug has been approved by Health Canada, which increases the cost of introducing a generic drug to the market, delaying patient access and savings to the province. In many cases, this can result in a generic manufacturer deciding not to introduce their generic drug in one or more provinces, or in some cases, not even filing for approval of the generic drug in Canada.

> *"There are significant opportunities to reduce regulatory barriers at Health Canada that needlessly inhibit both entry into the Canadian market and production in Canada for export. However, in addition, and perhaps more importantly, there is an unnecessary barrier in the Canadian Patent Act. More particularly, under U.S. law, a U.S. patent is not infringed by importation of a chemical made outside the U.S. by a process or from an intermediate patented in the U.S. However, in Canada, the case law holds that a Canadian patent is infringed by such importation. The Canadian Patent Act thus needs to be amended to provide that, as in the U.S., a Canadian patent on a process or intermediate is not infringed by importation of a chemical where the patented process or intermediate was not used in Canada."*
>
> Dr. Barry Sherman, Chairman Apotex Inc.

There has also been increased pressure on generic manufacturers to reduce the costs of generic drugs. The pan-Canadian Pharmaceutical Alliance (pCPA), established in 2010, utilizes the combined purchasing power of the provinces to achieve lower prices for both generic and branded drugs (The pan-Canadian Pharmaceutical Alliance, 2016). The average price of a generic drug prescription in Canada has decreased from $26.23 in 2010 to $20.92 in 2015 as shown in Figure 2 below (CGPA, 2015), while the cost of a brand name drug prescription has increased from $71.91 to $91.92 in the same timeframe. Thus, while generic drugs were dispensed to fill 68.6% of all prescriptions in 2015, they accounted for

only 22.0% of dollar purchases. The pressure on reducing costs is further magnified by the weakening Canadian dollar which increases the costs of generic drugs and/or materials which are manufactured outside of Canada. While sales volumes have been increasing year over year in Canada, sales revenues have remained stagnant and unchanged.

Figure 2: Average retail price* per prescription for generic drugs in Canada, 2004 - 2015



Source: The Canadian Generic Market, CGPA

** Average retail price is based on total price of prescriptions (price of drug plus any mark-ups and professional dispensing fees) divided by estimated prescriptions dispensed in Canadian retail pharmacies (excludes hospitals; includes retail new and refills).*

As a result of Canadian specific requirements which can prevent generic manufacturers from using global product development and/or common bulk product, the size of the Canadian market and decreasing listing prices from the provinces, making a strong business case to launch a generic in Canada is increasingly difficult. Generic manufacturers may decide not to introduce a generic alternative in the Canadian market even though they may supply a similar product in other jurisdictions. The CGPA and some of its member companies describe Canada as a complex market to access with challenging patent laws and one of the highest market entry costs for a small population base (Hollis & Grootendorst, 2012). Provided below are insights from senior executives of the CGPA member companies briefly describing the complexity of the Canadian market and some of the challenges experienced by the generic manufacturers.

The *Roadblocks to Globalization* section highlights some the specific challenges experienced by the generic manufacturers supplying products to Canada, which prevent them from fully leveraging the benefits of a global supply chain.

"Due to the lack of regulatory harmonization between the different provincial, territorial and federal governments, Canada and its current health care system is one of the more difficult countries for the generic industry to operate in because of the complexity and costs of market access. Harmonizing regulations and working towards a more sustainable and predictable environment would be critical elements for the supply chain to deliver consistency, quality and dependability and ultimately better serve Canadian patients."

Larry MacGirr, Chief Operating Officer at Pharmascience Inc.

Global Environment

The globalization of supply chains has been a major focus in many boardrooms and executive meetings over the last two decades. This has been especially true in the generic pharmaceutical industry due to the perceived benefits of reduced product development and manufacturing costs, improved quality, decreased time to market and the ability to divert product from one market to another based on demand. However, in order to leverage the benefits of globalization, regulations and policies must be harmonized to the greatest extent possible.

Global pharmaceutical sales growth continues, spurred by an aging global population, lengthening life expectancy, continued emerging market expansion, chronic diseases and advances in science leading to improvements in treatments and technologies (Deloitte, Deloitte 2016 Life Sciences Outlook, 2016). IMS Health forecasts the total global market to grow from $989B in 2013 to $1,324B in 2018 (IMS Institute for Healthcare Informatics, 2014). Generic pharmaceutical sales are projected to increase from $267B to $442B during that same period, which is over 50% of the forecasted growth (IMS Institute for Healthcare Informatics, 2014). Generic drugs typically sell at significantly lower prices (ranges from 18% to 85%) than the brand equivalent and this lower pricing will help drive much higher unit growth for the generic industry.

Introduction on the global pharmaceutical supply chain

Supply chain management is the integration, planning, and management of all of the processes across the system of resources from the earliest raw material supplier through the sourcing, logistics, manufacturing, and distribution networks to the customer. The base of supply chain management is the efficient integration and planning of demand and supply across companies. Planning is not only at the tactical level, but also at the strategic level.

Strategic planning is the optimization of the supply chain and the associated resources and assets to ensure acceptable quality while maximizing efficiency. For example, a strategic analysis of the supply chain includes total landed cost of the network. The total landed cost includes all of the steps in producing and delivering a drug to the patient, including cost of raw materials, suppliers, manufacturing, transportation, etc. The analysis may result in the consolidation of supply across the network by closing under-utilized facilities, transferring the production to other facilities in the network or outsourcing to third-party service providers.

The globalization of generic drug supply chains starts early in the process and includes formulation development, sourcing of Active Pharmaceutical Ingredients (APIs), excipients and/or packaging materials and clinical trials necessary for filing for regulatory approvals. It also includes selection of manufacturing sites and equipment and process validation, as well as setting specifications for in process materials and finished products.

Globalization still requires that products and brands meet local regulations, but in an ideal world there would be harmonized regulations, policies and practices. For maximum efficiency and benefit, there would be no differences until the last steps in the supply chain. At the minimum, country specific packaging and labelling would be required to meet local language requirements. In actuality, the changes driven by regulatory jurisdictions can be much more significant and come much earlier in the supply chain. This adds complexity and significantly reduces supply chain flexibility.

Canadian specific requirements, appearing as early as the initial product development, currently prevent companies from fully leveraging the benefits of being an active participant in the global supply chain. Product development and/or batches manufactured specifically for Canada at the minimum, increase costs to industry, patients and payers and delay market access, and in the worst case scenario, prevent products from being launched in Canada or remaining on the market in Canada.

Supply chain trends

Some of the key supply chain trends in the pharmaceutical industry include:

1. The use of generic drugs has continued to rise as payers pursue avenues to reduce costs (Deloitte, Deloitte 2016 Life Sciences Outlook, 2016). In 2014, 23% of Canadian sales were from generics and accounted for 67% of the prescriptions. Prescription drug sales in Canada were $23.3B in 2013 with $5.3B in generic sales (CGPA, 2015). Generic drugs are expected to account for a larger share of total global market, increasing from 27% in 2012 to 36% by 2017 (Deloitte, Deloitte 2016 Life Sciences Outlook, 2016).

2. This rising demand for generic drugs and the loss of revenue from blockbuster patent expiries is also driving consolidation, with both research-based and generics companies looking for acquisitions of all sizes (Deloitte, 2015 Global life sciences outlook, 2015). The consolidation of companies can help drive growth as well as achieve operational efficiencies, which can reduce costs for developing and manufacturing drugs.

3. Generic manufacturers are under continual pressure to keep prices low even though the margins in many countries are very thin. In Canada, this has been further exacerbated in the last few years by the weakening Canadian dollar. The Canadian dollar against the US dollar has been reduced from almost parity in 2013 to 0.72 in 2016 or 28%, while against the Euro, it has declined from 0.73 to 0.65 or 11%, and against the Indian Rupee from 56.8 to 48.9 or 14%. There is additional pressure on costs due to increasing competition, decreasing provincial budgets, economic austerity-led efforts and collective purchasing agreements.

4. With U.S., Canadian and European market growth slowing, pharmaceutical companies are looking at emerging markets such as, China, India, Brazil and Russia for additional sources of revenue. Pharmaceutical companies have been moving towards single product development to be able to introduce similar drugs in multiple markets.

5. Generic manufacturers continue to leverage the benefits of global supply chains to meet the growing demand for products and to tightly control supply chain costs. Generic companies source raw materials from all over the world, while continuing to outsource manufacturing of APIs to contract suppliers, and consolidating their own networks to increase efficiency and reduce costs. Sourcing from and manufacturing by pharmaceutical companies in China and India has grown significantly since the late 1990s. For example, in 2004 China and India manufactured 49% of global API demand and by 2007, manufacturing of APIs in China and India had risen to 68% (Newport Horizon Sourcing, 2007). It is estimated that 80% of APIs, used worldwide are now manufactured in China and India (Van Den Bos, 2009).

6. Globalization is not limited to raw materials and APIs. Generic companies are also outsourcing manufacturing (compounding, encapsulation, fill and finish, etc.) and packaging to contract suppliers and consolidating their own networks to increase efficiency and reduce costs. Innovation, Science and Economic Development Canada, in a 2015 report, stated that from 2001 to 2013, Canadian exports of pharmaceuticals increased by 155% and imports increased by

96%. In 2013, more than half of Canadian pharmaceutical production was exported, and 62%, or $13.7B, of the Canadian pharmaceutical market was supplied by foreign imports (Innovation, Science and Economic Development Canada, 2015).

Benefits of global supply chains

There are many benefits of a global supply chain. The major benefits include:

1. Improved access: Global supply chains result in improved access to drugs for patients and faster speed to market. As Canada is the 10th largest market, many generic manufacturers are able to introduce generic drugs developed for the U.S. or EU (the two largest markets in the world) in Canada, which otherwise would not have been introduced, as the cost of developing and manufacturing the product exclusively for Canada would not have been financially feasible.

2. Consistent quality of generics: The production of generic drugs can be regulated and de-risked as a global supply chain can ensure the same quality and production values through a global network of manufacturers. The visibility and traceability that can be provided allow for a better generic with higher quality assurance.

3. Optimization of supply chain costs: Generic manufacturers can utilize global product development and global manufacturing to reduce the costs of developing and manufacturing country-specific generic drugs. This ultimately benefits patients, government and private companies paying for the generic drugs.

4. Reduction in out-of-stock situations: Generic manufacturers have the flexibility to divert product from other markets that can reduce or eliminate a drug shortage, provided that these products are approved in Canada.

The benefits of global supply chains far outweigh the risks, especially for Canadian patients. Global supply chains result in improved access of drugs to patients, consistent quality, reduction in development and manufacturing costs and reduction and/or elimination of out-of-stock situations.

Roadblocks to Globalization

The pharmaceutical industry's supply chains have become global over the last 20 years, however, the regulatory environment has not. Supply chains now reach around the world, with manufacturers sourcing raw materials, including APIs, from suppliers located in various regulatory jurisdictions. Additionally, there has been a consolidation of development and manufacturing sites for generic drug manufacturers with often one site becoming responsible for developing and manufacturing drugs for the global market.

This section highlights some of the challenges experienced by the generic companies that supply products to Canada and which prevent them from fully leveraging the benefits of a global supply chain. Suggested solutions to resolve these challenges are also discussed in this section. The challenges are categorized into one of the five following steps:

1. Securing APIs
2. Testing, Manufacturing and Production
3. Bioequivalence Studies and Clinical Trials
4. Provincial Drug Listing
5. Distribution

Securing Active Pharmaceutical Ingredients (APIs)

This is the first step in the supply chain and includes sourcing the API from an external supplier or manufacturing the API in-house. The majority of the APIs are provided by suppliers located in China and India. The API supplier must adhere to Good Manufacturing Practices (GMP), while the API must meet the specific quality standards.

Inconsistencies with how inspection results from different regulatory authorities are applied by Health Canada to foreign sites has the potential to disrupt supply

Health Canada has been inconsistent in how it interprets and acts on inspection results from different regulatory authorities for API and finished dosage form manufacturing sites. It is often not clear to generic manufacturers what compliance actions will be taken and why. In some cases, "terms and conditions" have been added to the Drug Establishment License (DEL), such as testing of product by an independent third-party. The DEL holders are often unclear as to what steps they need to take to remove these conditions and what the timelines are. In other cases, the compliance action taken by Health Canada can be more extreme than that taken by the country that has physically inspected the site.

There have been instances where Health Canada has banned the product from being sold in Canada due to inspection findings from the United States Food and Drug Administration (USFDA). Meanwhile, the USFDA has not imposed any restrictions on continued import and sale of the product in the U.S. market. As a result of the lack of clarity on why Health Canada's actions differs from those of other regulators, it takes an unpredictable amount of time and effort for the generic manufacturers to resolve these issues. During this time, they are unable to sell the particular generic drug in Canada and are at risk of losing their market share to other generic drugs or branded drug products and paying penalties to their contracted customers.

Health Canada is trying to protect Canadian patients by taking compliance actions; however, the unpredictability and lack of transparency for these actions is causing disruption in the industry. These actions have several possible impacts, including interrupted access for Canadian patients, reduction in the number of generic drugs available in the market, increased costs to industry (e.g. third-party testing, loss and disposal of product that has passed its expiry date) and in some cases, increased amount spent on a particular type of drug as the only option available may be the branded drug product.

Case Study

This example is for a generic drug used to treat symptoms of migraine headaches. The market size was approximately $6.1M with approximately 67% captured by the generic drug manufacturers and 33% belonging to the branded drug company as of October 2014.

Issue: The API site for one of the generic manufacturers was inspected in November 2014 by USFDA for GMP compliance. USFDA issued a Warning Letter to this site, however no compliance actions were taken in the U.S., and the product remained on the market. On the other hand, based on the warning letter from the USFDA, Health Canada asked the generic manufacturer to voluntarily quarantine all drugs containing the API manufactured at this site. Furthermore, Health Canada also requested the API site to voluntarily stop shipping their product to Canada. Despite numerous requests for clarification by the Canadian Generic Pharmaceutical Association (CGPA) on behalf of the generic manufacturers' on what steps were needed to lift the restrictions, none were provided by Health Canada.

Impact on patients: As of January 2016, the branded drug company has regained significant market share and has now captured 87% of the market while the generic drug manufacturers' market share has declined significantly to only 13%. As the branded drug product now has majority of the market, the result is that patients, governments and insurance companies are spending more on prescription drugs since the generic drug price is on average 41% of the price of the branded drug product.

Suggested solution: Health Canada's actions should be consistent with those of their trusted regulatory partners. If actions are taken to restrict products or facility activities, Health Canada should publish clear guidelines on what needs to be done to lift the restrictions.

Testing, Manufacturing and Production

This step involves establishing the processes for manufacturing the generic drug while meeting all quality requirements. Once the generic drug is ready to be launched in the market, the drugs are manufactured either by the generic drug company or one of its contract manufacturers.

With increasing competitiveness in the Canadian marketplace, decreasing list prices from provinces and the increasing importance of supply reliability, there is a growing need for generic manufacturers to maximize supply chain efficiencies. For global generic manufacturers, this can be achieved by supplying drugs to Canada utilizing common global bulk drug product. However, due to Canadian specific requirements, in many instances generic manufacturers are unable to supply products to Canada from the global bulk lots. The specific challenges that prevent the use of global bulk lots are identified in this section.

Tighter in-process control specifications compared to other jurisdictions prevent the use of a global bulk drug substance or a global bulk drug product, thereby increasing costs to manufacture drugs and delaying market entry

In many cases, Health Canada sets tighter in-process control specifications compared to the in-process control specifications determined by the manufacturer based on process validation studies. These tighter in-process control specifications have been observed in the following areas:

1. Blend uniformity limits and requirement of individual vs. mean results: The blend uniformity acceptance criteria for Health Canada are not aligned with international tolerances and are not based in law.
2. Weight variation limits for tablets and capsules: Generic manufacturers are routinely requested to tighten the acceptance criteria for "Uniformity of Mass" for tablets to ± 3%. It is stated that these limits are regarded as the "industrial standard" for weight variation for tablets weighing more than 100 mg and are achievable for products with a robust process using modern tablet press.
3. Impurity limits: Health Canada has been inconsistent in selecting pharmacopeial monographs for establishing impurity limits. The practice appears to be the selection from the pharmacopeia which has the tightest limits, while other regulatory authorities accept limits based on any of the major pharmacopeias, e.g. U.S., British, European, or Japanese.
4. Particle size: Particle size requirements can be different in Canada compared to other jurisdictions.

As a result of Canadian specific requirements, generic manufacturers are unable to use the global bulk drug substance or global bulk drug product to supply the Canadian marketplace, while these same bulks are utilized in products sold in other markets such as the EU and U.S. In such cases, the generic manufacturer will have to run a Canadian specific batch to make the generic drug or in some cases, may decide not to release a product for Canada even though it sells the same product in other markets around the globe. This can result in fewer generic drugs in the marketplace, thereby reducing competition for that particular type of drug. Secondly, if there are only a limited number of suppliers for a particular medicine, it exposes Canada to an increased risk of drug shortage.

> "*As a result of the unique regulatory environment, the Canadian generic drug market offers very special challenges for global manufacturers wishing to introduce new products to benefit Canadian patients. Generally speaking, very few (e.g. less than 10%) of Sandoz's global products are approved in Canada with the same specifications as used by other major highly regulated jurisdictions (e.g. U.S., EU). Health Canada routinely requests tighter testing limits or additional manufacturing controls than are required for those countries. This means that Sandoz oftentimes need to manufacture and test Canadian specific batches for most of their global products, adding unnecessary costs, complexity and risk of supply interruption. While this is a burden for global pharmaceutical companies doing business in Canada, it also poses a significant risk for the long-term sustainability of the Canadian healthcare system. Some important global, high-quality generic products are simply not approvable under the conditions requested by Health Canada, while many of those generic products that are approved are unsustainable in Canada's current market conditions.*"
>
> Len Arsenault, Vice-President, Scientific Affairs at Sandoz Canada Inc.

Case Study

Generic drug: This example is for an aqueous injectable solution used as an anaesthetic agent. Currently, there are 2 products in the market, one of which is a branded drug while the other is a generic

drug. The total market size is $4M, with 90% captured by the branded product and 10% by the only approved generic manufacturer. There is another generic manufacturer that supplies the same product in the EU, U.S. and Australia but is currently unable to supply in the Canadian market due to the tighter in-process controls in Canada.

Issue: The generic manufacturer used the EU dossier to support an Abbreviated New Drug Submission (ANDS) in Canada. All aspects of the application were accepted, except one area. The Therapeutic Products Directorate (TPD) did not accept the formulation overage that had been accepted by the EU and other regulators. The generic manufacturer provided justification but ultimately had to accept a tighter range proposed by TPD or not receive the approval. As a result, the generic manufacturer would be forced to manufacture three Canadian specific validation lots and Canadian specific commercial lots. Given the size of the Canadian market, this is not economically justifiable. Therefore, the generic manufacturer was unable to launch an approved product even though there is only one other generic in the market.

Impact on patients: There is only one generic drug in the market which reduces competition and hence keeps the generic drug prices high. This drug is mostly used in a hospital setting and thus is fully paid for by Canadian taxpayers. The lack of multiple generics results in a higher cost to public budgets. Also, if the current market leading drug manufacturer was to experience disruption in supply, there could be a drug shortage, if the only alternate drug supplier is unable to meet patient demands.

Suggested solution: In-process specifications should be determined by the manufacturer based on process validation studies. Policies with respect to in-process control specifications should be consistent with global standards. This will allow generic manufacturers the ability to use the same global bulk drug substance and bulk drug product in Canada, which would still provide the acceptable level of quality, and would be beneficial to the smaller Canadian market.

Practice requiring the generic drug to match the branded drug with respect to scoring of tablets increases costs to manufacture drugs

Generic manufacturers have a practice of matching the appearance of the generic drug with the corresponding branded drug. It is believed, that this practice helps with the acceptance of the product by patients. Although there is no specific regulation that requires generics to match branded drugs with respect to scoring (or any other physical characteristic), Health Canada has recently been enforcing this as a requirement. This can make it difficult for global companies to take advantage of supply chain efficiencies if the global generic differs with respect to scoring compared to the Canadian generic.

Maintaining Canadian specific tablet tooling increases costs and requires that global manufacturing facilities produce specific batches for Canada. This can interrupt production for several hours before and after the manufacture of the Canadian batch in order to change tablet punches in the corresponding tablet press, complete appropriate cleaning and room setup and then produce a small run specific to the Canadian requirements. With increased demand for product from a limited number of facilities, moving to a common tablet trade dress significantly improves manufacturing and quality control efficiency, and better ensures product supply as the Canadian market needs can oftentimes be met with a portion of a larger global batch. Scheduling a Canadian specific batch will often times be adjusted to allow for production of another market's product with much larger volumes and greater profit margins.

Case Study

Generic drug: The example generic drug is used for the treatment of high blood pressure. The market size is approximately $37M, with 80% of it captured by the branded drug.

Issue: The Canadian Reference Product (branded drug product) for this drug does not have a score. The global bulk drug product produced by the generic manufacturer for other markets is scored. While Health Canada has no specific regulation or policy prohibiting such scoring of the tablets, it has become the practice in recent years to require the generic to match the reference product. This makes it very difficult for global companies to benefit from efficiencies and furthermore puts supply in Canada for these products at risk since the alternative is scheduling a Canada specific batch (which may exceed the actual needs for Canada), stopping production, retooling the tablet presses, requalifying these changes then cleaning and repeating these processes once the Canadian batch is produced.

One of the generic manufacturers filed a product variation as Supplemental New Drug Submission with inclusion of scoring the tablet as the major change proposed. Health Canada did not accept these changes and issued a Notice of Non-compliance, even though there is no specific regulation or policy prohibiting such scoring.

Impact on patients: If the generic manufacturer could use its global product, the cost of the generic drug in Canada can be reduced, as can the costs and delays to the manufacturer thereby resulting in savings for the patients and/or provincial governments.

Suggested solution: Health Canada should demonstrate flexibility by permitting scoring for generic tablets (when not on the reference product) where 1) the split tablet halves (or quarters) correspond to a recommended dose or available strength, and 2) the split tablet halves meet content uniformity requirements for full tablets.

Bioequivalence Studies and Clinical Trials

This step involves obtaining approval from Health Canada on the bioequivalence of the generic drug with the brand name drug. The submission should prove that the generic drug is bioequivalent to the brand-name drug in dosage form, strength, route of administration, performance characteristics and intended use (CGPA). At first, it may not seem appropriate to include a section on bioequivalence and clinical trials in a report on global supply chain however, in the generic pharmaceutical industry, the supply chain actually starts at the time of development, with formulation and clinical trials. The total cost of introducing a product into a country is a major consideration. If additional cost or time is introduced during these phases, a generic drug may never be introduced into Canada, negatively impacting the market and supply chain.

Non-Canadian Reference Products are allowed only in very limited circumstances thus adding costs and delaying or preventing generic drug introduction in Canada

Canada is the 10th largest market for prescription drugs in the world and represents 2.3% of the market. Contrast this with the U.S., which accounts for 34.3% of the market and EU5 consisting of Germany, France, Italy, UK and Spain which account for 15.8% of the market (IMS Institute for Healthcare Informatics, 2014). In many cases, a generic drug manufacturer may decide not to introduce a drug into the Canadian market if it is required to perform bioequivalence studies using a Canadian Reference Product as the business case might not be favourable due to high costs and a limited Canadian market compared to the U.S. or the EU. As a result, in such instances Canadian patients may be limited to branded drug products which have higher costs compared to generic drugs.

Currently there are very limited instances where non-Canadian Reference Products are allowed to be used as comparators in studies. Increasing the possibilities of using non-Canadian Reference Products will result in additional introduction of generic drugs as it will decrease the development costs for introducing a generic drug into the Canadian market. This will allow generic manufacturers to take advantage of global development and introduce a drug in Canada which they may have already introduced in the U.S. or EU. This helps the Canadian public as they will have more access to generic drugs as well as a reduced risk of drug shortages because of the presence of multiple suppliers.

Case Study

Generic drug: This generic drug is a dry powder inhaler used to treat asthma and chronic obstructive airway disease. Currently there is only one brand product with no generic competition in the Canadian market. The total market size is approximately $188M annually.

Issue: A generic manufacturer is pursuing a generic drug development program for the U.S. market. The research and development (R&D) investment is substantial and involves the development of both the device and formulation. The manufacturer would like to leverage this development and introduce the same drug into the Canadian market. However, there two challenges: 1) Health Canada's current regulatory framework would prevent the generic manufacturer from leveraging the clinical studies and in-vitro testing conducted for the U.S. market as they allowed to use foreign reference product in very limited circumstances, and 2) Health Canada does not have final guidances on to the regulatory requirements for the submission of generic inhalation products. As the costs for conducting bioequivalence studies and clinical trials with a Canadian Reference Product are significant, the manufacturer currently intends to file an Abbreviated New Drug Submission (ANDS). The outcome of the ANDS submission is not yet known as it has not been filed by the generic manufacturer.

Impact on patient: There are no generic alternatives in the market which reduces competition and subjects patients and payers to the high cost of the branded drug product.

Suggested solution: Health Canada needs to further expand the boundaries of regulatory convergence (as supported by sound scientific principles) to enable additional introduction and availability of generic drugs to Canadians. Expanding the use of non-Canadian Reference Products for clinical studies and in-vitro testing will enable generic companies to take advantage of global product development, and in many cases, eliminate the need for an additional study for approval in Canada. Such an approach would be less cost-prohibitive for Canadian generic companies to obtain approvals and market globally approved products in Canada.

Lack of generic drug pathway in Canada for certain complex molecules results in generic drugs not being introduced in the market

There are many instances where Health Canada has not developed a generic drug pathway for complex molecules or mixtures. As a result, many of the generic drug companies are unable to introduce generic drugs into the market, even though patents have expired and generic alternatives have been introduced in other jurisdictions such as the U.S. and/or EU. In these cases, Health Canada adopts a "wait and see" approach to observe what regulatory bodies in other jurisdictions are doing. Once regulatory bodies in other jurisdictions have provided a pathway, Health Canada seems to choose the most conservative option, including requesting clinical end point studies that can be cost-prohibitive. As a result, many of the generic manufacturers decide not to introduce the drug into the Canadian market, which could have a significant cost to the Canadian public. The brand name drugs are more expensive than generics, and

having only one supplier for a particular type of drug also exposes Canada to risk of drug shortages due to lack of options.

Health Canada should be more proactive with establishing a generic drug pathway for complex molecules. This can be achieved by establishing a framework for introducing such generic drugs or following the lead from other regulatory bodies such as the USFDA in establishing regulatory pathways for generic drugs.

Case Study

Generic drug: There are currently ten Health Canada approved medications used for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). One of these non-biologic medications has no launch constraints such as patents or data exclusivity and could be potentially introduced in the Canadian market by the generic drug companies. The approximate market size for this drug is currently $83M.

Issue: Health Canada currently does not have a generic regulatory pathway for the introduction of this generic drug into the market due to the complexity of identifying if the medicinal ingredient in the generic drug is the same as the branded product. Health Canada has requested a clinical end point study, meanwhile, the USFDA has provided a regulatory pathway for introducing the generic drug by defining the requirements for proving the sameness of the molecule to the brand drug product which does not require a clinical end point study. As a result, the generic manufacturers in the U.S. are able to file for approval and introduce this generic drug into the market while they are unable to do so in Canada.

Impact on patients: Currently there is only one brand drug product in the marketplace and hence no competition in the market. Once a generic is introduced into the market, the potential savings can be approximately 45%, assuming the volume for the drugs sold remain the same, and typical pricing for generics applies.

Suggested solution: The generic industry and Health Canada should review the science for clarity and understanding. Health Canada should investigate the USFDA pathway for approval to determine acceptance for Canada.

> *"If Health Canada continues to insist on Canadian specific requirements, the higher cost of goods for a Canadian developed product versus the cost of a product developed for global consumption will result in a reduction in the number of generic filings. Further to this, Health Canada has started to see the impact and at a recent meeting inquired from industry as to the "reasons" for the reduced number of submissions received."*
>
> Naguib Fahmy, Head of Mylan Canada Gx at Mylan Pharmaceuticals ULC

Identical Medicinal Ingredient policy limits the ability to use common product development to avoid patent infringement requiring Canadian specific development

Health Canada currently has a requirement that the generic drug must have Identical Medicinal Ingredients with respect to salts when compared to the branded drug product. Hence, if a generic drug has different salts or complexes compared to the branded drug product, it is not considered identical and therefore not approved as bioequivalent. There is a similar requirement in the U.S. for same salts, but if the salts in the generic drug are not the same, there is a pathway for generic manufacturers in the U.S. to obtain approval via interchangeability rating; this pathway does not exist in Canada. As a result of this requirement, it prevents generic manufacturers from introducing a global product into the Canadian market. This can either result in generic manufacturers deciding to not introduce a generic drug into the Canadian market or to make a Canadian specific drug for the Canadian market. This also exposes

Canada to drug shortages, if there is a disruption in supply as generic manufacturers cannot divert their global product into the Canadian market.

There is an opportunity for Health Canada to revise the Identical Medicinal Ingredient policy and allow the use of different salts and other chemical forms of the same active moiety in the generic drug compared to the branded drug product.

Case Study

Generic drug: This example is for a drug used as an anti-depressant. Currently, there is one brand product in the market and one generic manufacturer that is currently involved in litigation with the brand company.

Issue: One of the generic manufacturers has introduced the generic drug in Australia but is unable to do so in Canada due to the Identical Medicinal Ingredient requirement. The product introduced in Australia has a different salt compared to the brand product in Canada. The cost of standalone product development for Canada is not financially feasible, hence the generic manufacturer has decided not to introduce this drug in Canada. As a result, there will be only one generic drug product in Canada, thereby reducing competition.

Impact on patients: There will be only one generic drug in the marketplace competing with the brand drug product which will keep the prices higher. The addition of one or more generic drugs will result in costs savings as competition will cause prices to fall. Additionally, with only two suppliers in the marketplace, it exposes Canada to potential drug shortage situations.

Suggested solution: The Identical Medicinal Ingredient policy is another opportunity for industry and Health Canada to openly review the science, to investigate other regulatory agencies' policies and pathways for approvals, and to determine the viability of accepting these policies for Canada.

Provincial Drug Listing

Once the generic manufacturer has obtained approval from Health Canada, the generic drug can be sold across Canada. The cost of drugs is covered by a hybrid of public and private health coverage. In 2014, $12.1B (42%) of non-hospital prescribed drug spending was financed by the public sector, $10.3B (35.8%) by private insurers and $6.4B (22.2%) by Canadian out-of-pocket expenditures (Kuchenreuther, 2015). However, for the drug to be reimbursed by the province, it must be added to the provincial formulary which is maintained by each province and specifies which drugs will be reimbursed and to what extent (Business Monitor International, 2016). The generic manufacturer must submit an application to each of the provinces and territories for it to be added to their formularies.

Provincial requirements of additional testing can prevent addition of generic drugs to the provincial formulary

All provinces in Canada maintain a drug formulary and a drug must be added to this formulary for patients to receive reimbursement from the province. For a generic drug to be added to a province's formulary, it must obtain an approval from Health Canada followed by an individual approval from the province. The Therapeutic Products Directorate (TPD) of Health Canada is responsible for reviewing the science and issuing (or refusing to issue) a Notice of Compliance (NOC). Once the NOC is received, the drug can be

sold anywhere in Canada. This process involves a detailed review of chemistry and manufacturing data and evaluation of bioequivalence data of the generic drug with the standard reference (brand name) drug. Once a generic drug has been approved by Health Canada, the manufacturer must then submit an application to each province for inclusion in the province-specific drug formulary. Approval of the province-specific application allows substitution of the branded drug product with the generic drug.

The provincial drug listing process varies from province to province. In some provinces, the generic drugs are listed in the formulary within days, while in others it could take several months to a year.

There are cases where the province is reluctant to accept the bioequivalence determination by Health Canada and choose to operate their own complex regulatory systems with expert communities (CGPA, National Interchangeability For Generic Pharmaceutical Products). This not only results in additional time to add the generic drug to the formulary, but also in some cases may require a manufacturer to conduct further testing on the generic drug. Conducting additional testing specifically for certain provinces does not add any additional value if Health Canada has approved a generic drug. A manufacturer may decide not to add the drug to the formulary as the costs for adding it to the provincial formulary (as a result of additional tests required) would make the business case for introducing the drug into the province unfeasible.

Not adding a generic drug to the provincial formulary has several disadvantages. It limits the access of patients to less expensive drugs with similar effectiveness. Secondly, if there are no other generics in the marketplace, it limits competition for the branded drug company. Lastly, only having one supplier could increase the chance of a drug shortage if there is a disruption in supply.

It is Health Canada's responsibility to determine if a generic drug is bioequivalent to a branded drug product. Additional requirements for testing at the province level should not be required.

> *"Some provinces continue to conduct a separate bio-study review for generic pharmaceutical products even though Health Canada has completed a detailed review of the bio-study and has approved these products in Canada. This seemingly bureaucratic requirement is a needless waste of resources creating delays in approval of federally approved generic pharmaceutical products at the provincial level which then translates into delays for tax payers in these provinces to receive cost savings to their provincial drug plan."*
>
> Doug Sommerville, Senior Vice President, General Manager at Teva Canada Limited

Case Study

Generic drug: This challenge is highlighted by an example where the generic drug manufacturer decided not to apply to the Ontario formulary for listing of their drug, even though this drug is approved by Health Canada. The generic manufacturer has a topical antibiotic used for the treatment of acne vulgaris. The market in Ontario is approximately $700K and consists of one branded drug and two generic drugs. The two generic drugs available are not listed in the Ontario formulary.

Issue: One of the generic drug manufacturer's product was approved by Health Canada in accordance with the TPD Guidelines on Aqueous Solutions. The Abbreviated New Drug Submission (ANDS) was approved based on pharmaceutical equivalence only and an in-vivo clinical study was not required. After receipt of Notice of Compliance from Health Canada, this product was submitted for listing in the Ontario formulary but the application was rejected as a comparative in-vivo study against the Canadian Reference Product was required. An in-vivo study would require conducting a clinical study with a clinical end point and would cost approximately $2M, while the total market size for this type of drug is approximately $700K. Hence, the generic manufacturer decided it did not make financial sense to proceed forward with the application in Ontario. This generic drug has been added to all other provincial formularies but is currently not listed on the Ontario formulary. At present, there are no generic drugs in the Ontario formulary.

Impact on patients: There are two major impacts for not adding a generic drug to the provincial formulary. Firstly, branded drugs are more expensive than generic drugs; hence, there is an additional cost to the Ontario government and/or patients for using the branded drug. Assuming the market share for the generic drugs in Ontario (approximately 17% by volume) was similar to the market share nationally excluding Ontario (approximately 69% by volume), the total spent on these type of drugs would decrease by at least 13% based on 2015 volumes and the current pricing of drugs. Secondly, if there was a disruption in the supply of the branded drug, there could be a drug shortage as the current generic drugs are not interchangeable with the branded drugs. The bigger issue is that generic companies are continually evaluating the risks of being added to the provincial formularies and the time/costs involved in being added. If they believe that the risk is too great (either not being added or taking excessive time to be added), they may elect to not file for approval in Canada.

Suggested solution: Provinces should accept Health Canada's assessment of whether a generic drug is bioequivalent to a branded drug product. Additional testing requirements by some provinces makes the process inconsistent, increases paperwork and timelines for adding a drug to the provincial formulary. As demonstrated above, in some cases, the manufacturer may decide not to add the drug to the formulary due to these requirements, or in other cases may not even file for approval in Canada.

Note that the Ontario government recently approved Ontario Regulation 201/96 made under the Ontario Drug Benefit Act ('ODBA Regulation') and Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act ('DIDFA Regulation'). The amendments came into force on October 1, 2016.

These amendments will, along with other improvements, allow products with a Declaration of Equivalence designation from Health Canada to be reviewed under the faster, streamlined drug submission process and will not be required to conduct any further tests in order to be approved for addition to the Ontario Drug Benefit Formulary.

Thus, while the case study presented above prevented patients and Ontario taxpayers from benefiting from safe, effective, lower-cost generic prescription medicines in the past, the Ontario government's recent regulatory amendments address this problem.

Distribution

This is the final step in the supply chain and involves the distribution of the drugs to the patients and handling of drug shortages by Health Canada, manufacturers, pharmacies and hospitals.

Adequately defining drug shortages and identifying root causes presents challenges to a continuous supply chain

Drug shortages occur due to various reasons and can have a significant impact on patients, pharmacists and prescribers. The risk of a drug shortage is further exacerbated when there are limited suppliers for a particular drug in the market. In many cases, generic manufacturers may decide not to introduce a particular drug in Canada even though they may sell the product in other global markets such as, U.S., EU or Australia, due to the various challenges identified earlier. In these instances, there could be drug

shortages if the branded drug company or the generic drug suppliers in the market incur any issues such as: supply disruption from the API site, manufacturing issues, etc.

Over the years, Health Canada has taken steps to improve the process for handling drug shortages; however, there is additional improvement required. There needs to be clearer definitions on what constitutes a drug shortage and which suppliers should report to Health Canada when they believe there may be a disruption in supply. Health Canada should be more transparent, like the USFDA in drug shortage scenarios, take the lead in coordinating actions among stakeholders and continue to work cooperatively with the generic manufacturers to resolve drug shortage scenarios.

Case Study

Generic drug: The generic drug is used for the treatment of epilepsy and mania. There are eight additional variations of the generic drug that are approved in Canada. However, there was critical shortage of this medically necessary drug since all manufacturers, including the brand, were out of stock. Although there are other potential substitutes (i.e. eight other products that can be used for epilepsy and nine other products that can be used to treat mania), it should be noted that, the treatment for epilepsy and mania is very sensitive, with patient-specific dosages and it can be very dangerous for the patient to substitute their medications.

Issue: The only generic manufacturer for the particular variation of the drug had proposed minor changes to the manufacturing process and had data which demonstrated that the proposed changes would have no impact on the product performance. The generic manufacturer wanted to release the product as soon as possible and considered these changes as Annual Notification. However, upon discussions with TPD, the generic manufacturer was requested to file a supplement which would have to be reviewed and approved by Health Canada before the product was released to the market. Although an expedited review was completed, it delayed the release of the product to the market.

Impact on patient: The generic drug is used to treat epilepsy as well as to stabilize mood of the patient, and due to its sensitivity it was considered a very serious drug shortage that could put patient lives at risk. Patients were asked to switch to one of eight other potential variations of the generic drug; however, switching drugs would be very difficult for the patient and in some cases not even possible.

Suggested solution: Drug shortage guidelines should be consistent and clearly understood. Health Canada should provide central coordination of drug shortages to minimize impact on patients. Additionally, further dialogue with Health Canada should be conducted to work with them to agree on how risk- and science- based principles, on which the guidance is built, should be applied when assessing post approval changes to generic drugs.

Discussion and Next Steps

Ensuring a consistent supply of safe, effective and high quality generic medicines for Canadians.

In the prior section, *Roadblocks to Globalization*, several case studies were detailed that are inhibiting the generic pharmaceutical industry, the payers and the patients from fully realizing the benefits of a globalized pharmaceutical supply chain. These benefits include, improved access to a wider variety of drugs for patients, faster speed to market, optimization of supply chain costs and reduction or elimination of out-of-stock situations due to the ability to divert product from other markets.

Regulatory agencies, including Health Canada, play an important role in the supply chain, in overseeing patient safety and product quality. The implications of globalized supply chains have been the topic of numerous papers, discussions, and focus groups, by regulatory agencies and legislators around the world. New legislation has been enacted in several countries to ensure product quality and patient safety across the globalized supply chains.

Health Canada realizes the importance of and need for regulatory convergence and is taking steps towards it. Health Canada is a member of the International Generic Drugs Regulators Programme (IGDRP) which consists of 19 agencies and organizations, including the FDA and EU regulatory authorities. The IGDRP was established to promote collaboration and convergence in generic drug regulatory programs in order to address the challenges posed by increasing workloads, globalization and complexity of scientific issues (International Generic Drug Regulators Programme, 2016). Some of the objectives of IGDRP include greater alignment of regulatory approaches and technical requirements as well as enabling greater inter-agency collaborations. Health Canada is also a member of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium which was established in 2007 to promote greater regulatory collaboration and alignment of regulatory requirements (Department of Health, Therapeutic Goods Administration, 2016). The rise of globalization and innovations has increased the need for regulatory convergence and communication between the different regulatory bodies. Health Canada's participation in such organizations is a great initiative and will help facilitate regulatory convergence in the Canadian environment.

The press is also playing a role in public, agency and legislator opinions about the globalization of supply chains and the implications of the increasing percentage of production in emerging markets, especially in Canada. Recently, the Canadian Institutes of Health Research in collaboration with the Health Products and Food Branch Inspectorate and Policy and Strategic Planning Division, Health Canada conducted a Best Brains Exchange entitled: "Quality of drugs manufactured in emerging economies: Are cost containment strategies heightening the likelihood of substandard drugs in Canada". The background document included over ten references from news reports in 2014 and 2015 scrutinizing Health Canada and questioning the quality and safety of drugs manufactured outside of Canada (Canadian Institutes of Health Research, 2016).

The generic pharmaceutical industry must continue to work with Health Canada to ensure patient safety and product quality, while maximizing the benefits of a global supply chain. Together, they will need to educate the press and ultimately the public on the need for globalization and the benefits of it.

Health Canada is already looking to the future, and continues to focus on safety and quality, while basing their work on science, and considering solutions across the country and the world. From the Health Canada web-site:

*"*Health Canada's Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs and medical devices for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations (Health Canada)."

Health Canada also states that to achieve their goals, they "[Rely] on high-quality scientific research as the basis for [their] work." The agency states their future as: "Health Canada believes that prevention and health promotion can hold healthcare costs down and improve quality of life in the long term. To this end, the Department is committed to meeting the challenges of tomorrow by supporting research and fostering partnerships with researchers across the country and the world (Health Canada)."

CGPA, as the industry representative, should facilitate discussions with Health Canada and ultimately work toward solutions that will allow Canadian patients, payers, and the generic industry to realize the benefits of supply chain globalization, including working toward solutions for each of the case studies identified in this paper.

Conclusion

With the increasing globalization of supply chains, countries, including Canada, cannot afford to act in isolation. In order to reap the benefits of a global supply chain, laws, interpretative documents and best practices must be harmonized wherever possible.

As the 10th largest market for pharmaceuticals in the world and with generic sales accounting for less than 2% of global sales, Canadian companies must be able to leverage global product development and common bulk product in order to remain viable and competitive.

Patient access to a consistent supply of safe, efficacious high quality medicines at competitive prices is dependent upon Canadian companies' ability to leverage global competencies and find alternative sources of comparable medicines when interruptions in the supply chain occur.

Downward pricing pressures from payers (average price of generic drugs decreased from $26.24 in 2010 to $20.90 in 2015) require industry to find additional resources in economies of scale.

Other barriers to market, such as Canadian specific requirements (not justified by safety and/or science), additional provincial listing requirements and complex patent laws with high costs and liability have the potential to prevent companies from bringing new generics to the Canadian market or to remain on the Canadian market.

Health Canada, together with the provincial and territorial health authorities, have an opportunity and an obligation to further improve the existing regulatory framework to encourage and promote the introduction of new generic drugs into the market and to help ensure that they stay on the market based upon patient demand.

Health Canada and the Canadian Generic Pharmaceutical Association need to continue to work together to align the regulations and guidelines in Canada with the international community in order to maximize the benefits of a global supply chain, while maintaining patient safety and product quality. This will enable generic manufacturers to introduce more generic drugs into the market which will ultimately result in savings to Canada's healthcare system.

References

Business Monitor International. (2016). *Regulatory Development - Canada - Q2 2016.* Business Monitor International.

Canadian Institutes of Health Research. (2016). *Quality of drugs manufactured in emerging economies: Are cost containment strategies heightening the likelihood of substandard drugs in Canada?*

CGPA. (2012). *Generic Prescription Drug Development.*

CGPA. (2015). *The Canadian Generic Market.* Retrieved from http://www.canadiangenerics.ca/en/advocacy/docs/CanadianGenericMarket_2015.pdf

CGPA. (n.d.). *National Interchangeability For Generic Pharmaceutical Products.* Toronto. Retrieved from http://www.canadiangenerics.ca/en/advocacy/docs/National_Interchangeability.pdf

Deloitte. (2015). *2015 Global life sciences outlook.* Deloitte.

Deloitte. (2016). *Deloitte 2016 Life Sciences Outlook.* Deloitte.

Department of Health, Therapeutic Goods Administration. (2016). *Australia-Canada-Singapore-Switzerland (ACSS) Consortium*. Retrieved from https://www.tga.gov.au/australia-canada-singapore-switzerland-acss-consortium

Health Canada. (2015). *Health Canada New Drug Authorizations: 2015 Highlights.*

Health Canada. (n.d.). *Therapeutic Products Directorate.* Retrieved from About Health Canada: http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php

Hollis, A., & Grootendorst, P. (2012). *Tendering Generic Drugs: What are the risks?*

IMS Health. (2014). *MIDAS.*

IMS Institute. (2014). *Global Outlook for Medicines Through 2018.* Parsippany.

IMS Institute for Healthcare Informatics. (2014). *Global Outlook for Medicines Through 2018.* Parsippany.

Innovation, Science and Economic Development Canada. (2015). *Life Sciences Industry.* Retrieved from Pharmaceutical Industry Profile: https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html

International Generic Drug Regulators Programme. (2016). *About us*. Retrieved from https://www.igdrp.com/

Kuchenreuther, M. (2015). Market Access Outlook for Canada. *Pharmaceutical Technology*.

Newport Horizon Sourcing. (2007).

The pan-Canadian Pharmaceutical Alliance. (2016). Retrieved from The Council of the Federation: Canada's Premier: http://www.pmprovincesterritoires.ca/en/initiatives/358-pan-canadian-pharmaceutical-alliance

U.S. Food and Drug Administration. (2015). *Office of Generic Drugs (OGD) Annual Report for 2015.*

Van Den Bos, J. (2009). *Globalization of the Pharmaceutical Supply Chain: What are the Risks?* Health Watch.

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