Generic Drug Repurposing in Canada

A Canadian Manufacturer’s Perspective

Pharmascience Inc.

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Executive Summary

- The COVID-19 pandemic has highlighted multiple and unprecedented challenges for the Canadian healthcare system, and the need for greater speed and flexibility in the provision of new therapeutic options for Canadians.

- New therapeutic solutions do not necessarily require the full development of novel drugs or vaccines. There are multiple examples of significant therapeutic developments made possible by developing new indications or adapted formulations of existing agents to serve new patient populations. This process is known as 'drug repurposing'.

- Soaring R&D costs and their impact on introductory prices of new drugs and reimbursement budgets are now recognized as a major health care problem. Repurposing is increasingly perceived as a potential solution to mitigate this negative impact on health systems.

- Interest for drug repurposing has been heightened by COVID-19. Examples of agents investigated for COVID-19 include colchicine, dexamethasone, isoquercitin, remdesivir, and fluvoxamine. In most cases, the development of effective COVID-19 vaccines eventually limited the use of these agents, but the COVID experience highlights the importance of drug repurposing, and the need for specific regulatory, HTA and commercial pathways enabling it.

- There are major barriers that have prevented generic companies from investing in repurposing and have limited the development of new indications for off-patent drugs. Without modifications of the Canadian regulatory, HTA and reimbursement pathways, it is most unlikely that the systematic industry effort required for repurposing to become a reliable contribution to therapeutic innovation will be possible.

- The development of pediatric drug formulations, a common example of repurposing, is particularly impacted by these barriers. The absence of approved pediatric formulations appears to be worse in Canada than in other comparable countries (US, UK, Europe, Australia)

- A national drug repurposing policy to enable the R&D and drug development efforts is therefore needed in Canada. It must be both federal and provincial/territorial in scope, as the effort requires both regulatory and pricing/reimbursement components, such as:

    1. Amended regulatory and HTA pathways specific to the approval and assessment of repurposed drugs.

    2. A distinct, defined pricing framework to adapt generic pricing grids to the need for additional R&D for repurposed drugs, including pediatric formulations.

3. A limited period of patent restoration, additional data protection and/or reimbursement exclusivity (3 years) for the new indication or formulation.

4. Revised submission fee schedules from Health Canada, CADTH and INESSS to incentivize repurposing, especially for pediatric formulations.

5. Targeted budgets from federal and provincial research funding agencies to fund drug repurposing trials done in Canada.

Introduction and Background
Drug Repurposing

The COVID-19 pandemic has highlighted multiple and unprecedented challenges for the Canadian healthcare system, and the need for greater speed and flexibility in the in the provision of new therapeutic options for Canadians. to fill the therapeutic gap experienced at the beginning of the pandemic, whether with novel. COVID has thus become a major call to action for health authorities to review and modernize our drug system to allow for more innovation, faster and at an affordable cost.

Pharmascience Inc. is a major player in Canada on the pharmaceutical scene. As the second largest Canadian-owned pharmaceutical manufacturer, the largest pharmaceutical employer in Quebec, a Top-50 Canadian R&D investor, and a global exporter, Pharmascience has the scope, size, capacity, and human resources and to offer a concrete contribution to the strengthening of Canada's pharmaceutical supply. The COVID experience has shown that this includes the facilitation of generic drug repurposing. The purpose of this position paper is to offer specific recommendations to federal and provincial health and economic development authorities based on this experience.

Pharmascience has been involved as a partner of a major not-for profit research institution (the Montreal Heart Institute Research Center) in two clinical trials involving an existing anti-inflammatory agent, colchicine, in new indications in cardiovascular medicine and in COVID-19. Our company has also conducted several development projects to repurpose established generic medicines in new pediatric formulations and indications to meet a largely ignored unmet patient need. This experience allows us to offer strategic recommendations to help foster more development initiatives for repurposed medicines in Canada, and to enhance Canada's capacity to generate such research to address unmet medical needs.

While our primary aim is to solve important health system needs, the reinforcement of Canada's R&D effort through the repurposing of existing drugs can also translate into significant innovation and economic development. This adds to the value of the following recommendations as a fertile ground for public policy improvement.

About Pharmascience

Since its founding in 1983, Pharmascience has experienced rapid growth and has gained a leadership position in the Canadian and international generic drug industry. This flagship Canadian pharmaceutical company has remained a family-owned business with its head office, and all of its R&D and manufacturing facilities located in Québec.

Today, Pharmascience manufactures and markets over 2000 products from nearly 300 product families, in 20 different dosage forms. Pharmascience is the largest manufacturer of generic drugs in Québec and one of the largest in Canada. It is also an important manufacturer of branded drugs, through its Pendopharm division, and of consumer products. The company is also an important contract manufacturer and service provider, including product development and quality testing.

85% of the Pharmascience business is based in Canada. But the company also distributes its products in more than 50 countries across five continents. It creates more than 2550 jobs in Canada, directly, indirectly and through its induced contribution to the Canadian economy. As of July 2021, this includes 1,350 workers at the Montréal and Candiac manufacturing and R&D sites, and at the Dorval distribution centre. In 2019, Pharmascience ranked as the largest pharmaceutical employer, and 118th largest, overall, in Québec. The average salary of Pharmascience's employees is twice the Québec average. Moreover, these jobs are particularly productive, with GDP per job 1.5 times higher than the Québec average.

Pharmascience's operating activities contribute $355 million to Canada's GDP annually. They generate $42 million in gross annual tax revenue for Quebec and $27 million for the Government of Canada[1].

The company ranks amongst the Top-100 largest R&D investors, all sectors confounded, with 40-40 million dollars invested annually. Pharmascience R&D activities are entirely conducted in Canada.

1- Aviseo, 2022 - Study of Pharmascience's Economic Contribution and Positioning in the Pharmaceutical Industry.

Why is Drug Repurposing Important for our Health System?

- The discovery and development of novel therapeutic agents is a notoriously lengthy and comprehensive research process. Bringing an entirely novel therapeutic agent to market takes on the average more than 10 years at a cost of about 2,6 billion dollars. The COVID-19 pandemic has served as a reminder of the pressure to which health systems can be subjected when novel agents are urgently required to treat diseases for which no known therapy exists.

- Soaring R&D costs impact on introductory prices of new drugs, which have now reached unprecedented levels, and drug reimbursement budgets. High drug prices are now recognized as a major health care problem, notably by the World Health Organization. The notion of 'financial toxicity' has recently emerged in the medical literature, equaling the inability to pay for required drugs to a medical harm. Soaring drug costs directly challenge the sustainability of public and private drug reimbursement programs.

- New therapeutic solutions do not necessarily require the full development of novel agents. There have been multiple examples of significant therapeutic advances made possible by new indications or pharmaceutical formulations for existing agents. This process is known as 'drug repurposing'. Lower cost repurposed products are increasingly regarded as an attractive alternative for health care practitioners and drug system managers in terms of value for money.

- Since the development effort is limited to clinical trials in a new indication, or to new formulations, fewer and less extensive trials are required. This creates several major advantages:

    - **Speed** – the development of a new indication can be accomplished as fast as the duration of the pivotal trials, and much faster than the development time required for an entirely novel molecule.

    - **Known safety profile**. As the agent has already been used in clinical practice, its safety profile in conditions of real-world use is well known and requires less additional evidence generation.

    - **Cost** – repurposing is usually done from already genericized drugs, available at an affordable price and requiring much less additional development work. This makes the repurposed agent very attractive in comparison to high cost novel agents. Additional research costs required are only a fraction of the normal overall cost for an entirely novel agent.

    - **Research Independence** - Because repurposed products are generally on the market under different indications, independent researchers have the opportunity to create innovative trials generating new evidence, and

possibly intellectual property, without having to sign restrictive agreements with multinational companies who want to control the drug's development program. Clinical trials on repurposed products are done where the patients and investigators are located versus where multinational companies want them done. This would favor Canada greatly, with its rich network of clinical research institutions. Investigator independence is a major regulatory and HTA asset.

- Interest for drug repurposing has been heightened by COVID-19. Examples of agents investigated for COVID-19 include colchicine, dexamethasone, remdesivir, and fluvoxamine. In most cases, the development of effective COVID-19 vaccines eventually limited the use of these agents, but the COVID experience highlights the importance of drug repurposing, and the need for specific regulatory, HTA and commercial pathways enabling it.

- Unfortunately, despite these advantages, there continues to be few quality trials undertaken, with the proper size and methodology, to support repurposing. Major barriers to drug repurposing have prevented generic companies to invest in repurposing in Canada, thus limiting the development of new indications for off-patent drugs. Without modifications of some of Canada's regulatory, HTA and reimbursement pathways, it is most unlikely that the systematic industry effort required to make repurposing a reliable contribution to therapeutic innovation will be possible.

The Specific Case of Pediatric Formulations

- Despite the general acknowledgement that children require care standards adapted to their unique needs, there are remarkably few drugs formulated specifically for the pediatric population in Canada. An essential component of patient care, drug therapy, continues to be poorly adapted to the needs of sick children.

- Most drugs administered to children are compounded by pharmacists or parents from adult dosage forms. The resulting formulations do not meet Health Canada's Good Manufacturing Practices (GMPs). Quality controls for compounded products are weaker than for commercially prepared products. Consequently, their stability, potency, uniformity, microbial sterility, and bioavailability are less certain, and significant concentration-related or dosing errors can occur. Compounding is only accepted in Canada in the absence of an approved manufactured product approved by Health Canada.

- The absence of approved pediatric formulations appears to be worse in Canada than in other comparable countries (US, UK, Europe, Australia). Drug manufacturers are introducing fewer pediatric formulations in Canada than in these countries. This situation is unanimously described as problematic by health care practitioners (pediatricians, pharmacists, nurses) and organizations advocating for child health care. It results in significant barriers to optimal drug therapy in children.

This Canadian gap appears to result primarily from numerous economic barriers and market disincentives that prevent pediatric formulations from being offered commercially.

- The size of pediatric drug markets, regardless of the disease treated, is usually small. New drugs are rarely developed primarily for pediatric indications, and most of the usage is off label. Most drugs needed in pediatric care are off patent. This makes additional R&D investments by manufacturers risky, especially if one considers that off patent adult drugs are available at low generic prices that were not established to provide a R&D incentive, like those of patented medicines. If prices of pediatric formulations are benchmarked against those of high-volume adult generics, the resulting introductory price of the new formulation may well not yield a viable margin to cover the additional development and commercialization costs.

- The barriers to pediatric formulations development are essentially the same as those preventing generic molecules repurposing. Removal of those barriers would directly favor the development of pediatric formulations.

Pharmascience and Drug Repurposing

- Over the past 5 years, Pharmascience has gained significant experience through several repurposing projects that have allowed us to identify the main existing regulatory, HTA or reimbursement barriers to drug repurposing, including pediatric drugs, and to offer solutions.

Colchicine Projects

- Pharmascience has been involved in two major repurposing clinical trials conducted at the Montreal Heart Institute (MHI) Research Center by Dr. Jean-Claude Tardif, Principal Investigator.

- The COLchicine Cardiovascular Outcomes Trial (COLCOT I) has demonstrated that the anti-inflammatory drug colchicine at a dose of 0.5mg daily, in a novel extended-release formulation, in addition to standard of care, led to a significantly lower risk of ischemic cardiovascular events than placebo in 4,745 patients with a recent myocardial infarction followed for a median of 23 months. Results from COLCOT I were presented at the American Heart Association (AHA) late-breaking scientific sessions on November 16, 2019. They were published the same day in the *New England Journal of Medicine (NEJM)*.

  (Tardif J-C, Kouz S, Waters D, et al. *N Engl J Med* 2019. Available at www.nejm.org)

- Two more sub-analyses of the COLCOT I trial were presented during the 2020 session of the European Society of Cardiology (ESC). They were aimed at determining the impacts of time-to-treatment on colchicine response post MI, and whether genetic markers hold the potential to identify patients likely to benefit from colchicine treatment. One has been published.

  (Bouabdallaoui, N. Tardif J-C, Waters D, et al. *European Heart Journal* (2020) 00, 1–8 doi:10.1093/eurheartj/ehaa659)

- A New Drug Submission based on these data was approved by Health Canada on August 27, 2021.

- A second colchicine trial was initiated by the MHI Research Center and Dr. Tardif on March 23, 2020, with a purpose to test whether colchicine therapy may minimize the 'cytokine storm' observed in severe COVID-19 complications and to investigate if short-term treatment with colchicine reduces death rate and lung complications related to COVID-19. COLCORONA is an international randomized, double-blind, placebo-controlled study conducted in 6000 patients. This trial was funded by the Québec Ministry of Health and Social Services. The study was published in the Lancet Respiratory Medicine on May 27, 2021.

(https://doi.org/10.1016/S2213-2600(21)00222-8)

- Both trials are cutting edge, state-of-the art clinical studies whose clinical, public health and pharmacoeconomic impacts on health systems could be groundbreaking, either by further reducing cardiovascular morbidity and mortality in a large patient population at low cost, or by offering effective therapy to pre-empt the most damaging complications of COVID-19.

Pediatric Projects

- In recent years, Pharmascience has invested in the development of pediatric formulations, a therapeutic area that has largely been underserviced by the pharmaceutical industry for economic reasons. In the current conditions in Canada, markets for pediatric drugs are too small, and regulatory and reimbursement barriers too important to allow for a reasonable return on the development investments required.

- Yet, the lack of pediatric formulations is a critical gap in our healthcare system. Children with serious diseases requiring drug therapy are being treated with adult dosage forms unsuited to their age, weight and condition. Adult dosage forms must be reconditioned by pharmacists or by parents or caregivers to allow for their administration to children. The resulting forms usually do not meet Canadian Good Manufacturing Practices (GMP) requirements and may represent a risk to the safe and effective administration of these drugs to young children.

- The main reason why manufacturers do not develop pediatric forms are economic. Most (98%) drugs identified by pediatricians as missing a pediatric formulation are off patent. They all do require significant development in formulation research, manufacturing, and in the preparation of scientific submissions to Health Canada as well as Health Technology Assessment (HTA) authorities such as CADTH and INESSS. For drugs for which there is no exclusivity, these costs become an unsurmountable barrier. Hence the decision by most manufacturers not to invest in pediatric drug development in the Canadian market.

- Pharmascience has nevertheless chosen to venture at its own risks in the development of 3 new pediatric formulations for a cardio-vascular drug, amlodipine (oral solution), and for the anti-epilepsy drug levetiracetam (oral solution and parenteral pediatric solution). All three projects have led so far to regulatory approvals in Canada, but none has resulted until now in listings on public formularies.

Removing Drug Repurposing Barriers

- Making drug repurposing possible on a larger scale in Canada and aligning it with drug system needs will require a concerted effort of manufacturers and of the federal and provincial/territorial jurisdictions to remove the main barriers that have so far prevented repurposing to contribute as much as it can to patient health care. Considering the substantial contribution of repurposing to affordable innovation for health care managers, it would be a major missed opportunity if this effort was not undertaken.

- The main barriers to repurposing, from a researcher's or drug developer's vantage point, are the following:

    1. Poorly adapted regulatory and HTA pathways.
    2. Low price of generic drugs fails to incentivize drug manufacturers' investment.
    3. No or limited intellectual property protection.
    4. Disproportionate regulatory and HTA fees.
    5. Scarce clinical trial funding available.

- **Regulatory and HTA pathways are not adapted to repurposed drugs**

    Neither regulatory nor HTA pathways and data requirements are adapted to drug repurposing. The combination of poor commercial exclusivity, low prices and scarce research funding makes it virtually impossible for a drug developer to meet the full scope of data requirements from Health Canada, CADTH or INESSS for a repurposed drug, for which, in the best of circumstances, few quality clinical trials will be available. Specific pathways must be designed to allow for repurposing to be undertaken systematically by industry.

    Recommendation: new regulatory and HTA pathways must be designed jointly by Health Canada, CADTH and INESSS to reduce redundant regulatory approvals HTA barriers faced by repurposing.

- **Low price of generic drugs fails to incentivize drug manufacturers' investment**

    The price of generic drugs in Canada is set by pricing frameworks negotiated between Canadian jurisdictions responsible for drug reimbursement and industry. Current frameworks are based on the cost of bringing a new generic drug on the market within approved indications and dosage forms. This determines the type of development investments required (i.e. formulation of the new agent, bioequivalence, manufacturing scale up, regulatory approval, formulary listing,

etc.) and defines the manufacturing cost of the product. Any additional development activity, such as funding of clinical trials, regulatory costs of getting a new indication approved, HTA submissions or commercial communication to health care practitioners about the new indication, falls outside of this cost structure and must be recouped through revised pricing to make the effort commercially viable.

Failing to meet that requirement will result in new indications for repurposed drugs being sought at a commercial risk for the developer. Without an adapted pricing framework for repurposed drugs, no systematic effort will be undertaken by industry to support repurposing. The consequence will be that the use of generic drugs outside of their original indications will be left to non-evidence based, off-label use by practitioners. As evidence-based use of repurposed generics has the potential to be provide highly cost-effective innovation for drug systems, major opportunities will be lost to strengthen the sustainability of these systems.

Recommendation: A distinct, defined pricing framework to adapt generic pricing grids to the need for additional R&D for repurposed drugs. This framework would define conditions that must be met by the manufacturer (quality of clinical and pharmacoeconomic data, and of health outcomes). If these conditions are met, incremental pricing could be negotiated. This is in some ways comparable to the policy adopted by the pCPA for biosimilar drugs to incentivize biosimilar makers to introduce their products in Canada in a market that had previously failed do so.

- **No or limited Intellectual Property Protection (IPP)**

Most repurposing candidates are off patent drugs, and therefore can be manufactured by whoever meets Health Canada's bioequivalence, labelling and Good Manufacturing Practices (GMP) standards. Enforceability of patents sought for the new indication is unclear. Therefore, there is no guaranteed period of commercial exclusivity allowing the drug developer to recoup R&D investments required by the repurposing of a molecule. Some of these investments can be significant. For instance, good quality, Phase 3 randomized controlled clinical trials must be done in large populations to sustain Level 1 efficacy and safety evidence. The cost for such trials is high. Furthermore, the drug may need to be reformulated to adapt to the new patient population's needs, such as children, also at a cost to the developer. And lastly, launching a new indication requires a commercial strategy in which company resources must be invested. None of these investments are factored into the price of a generic product supplying established demand for approved indications. Any manufacturer venturing into repurposing must ensure that these additional investments are recouped.

Recommendation: A grant of additional patent restoration or additional data protection, similar to those allowed in the USA or in some European countries would be consistent with the objective to incentivize repurposing. A limited period of reimbursement exclusivity (3 years) for the new indication should be offered to manufacturers undertaking generic drug repurposing or introducing pediatric formulations to compensate for the lack of IPP. Authority should be provided in provincial regulations overseeing public drug program management.

- **Disproportionate, poorly adapted regulatory and HTA fees**

  Both regulators and health technology assessors charge submission review fees in Canada for manufacturers going through these processes. These fees have been designed primarily for new patented drugs with market exclusivity (often commanding high prices). They can total hundreds of thousands of dollars for a given drug development project. These fees are not adapted to the market reality of repurposed drugs. When markets are small, such as for new pediatric formulations, review fees can be totally disproportionate and take away the full profitability of the new product for extended periods of time (1-2 years). This constitutes an acute pain point of the Canadian drug system, often leading to 'no submission' or 'no launch' decisions.

  Recommendations: new submission fee schedules should be considered by Health Canada, CADTH and INESSS to allow for reduced fees to incentivize repurposing, especially for pediatric formulations, where the problem is most acute.

- **Scarce clinical trial funding available.**

  Expensive clinical research, such as well-designed randomized, controlled Phase 3 clinical trials, is unlikely to be undertaken by drug manufacturers in the absence of patent or regulatory data protection. The risk not to recoup the required investments and commercialize at a loss is too great. This significantly limits the sources of clinical trials funding for repurposed indications of old drugs, shifting the primary funding role from industry to public research funding agencies.

  Recommendation: Federal and provincial agencies responsible for research funding (CIHR, FRQS) should have dedicated budget envelopes to fund drug repurposing trials and to ensure the generation of high-quality clinical evidence by Canadian research institutions. Such evidence would allow Canadian HTA agencies to offer evidence-based recommendations to payers on the clinical effectiveness and value for money of repurposed drugs.

Summary of Recommendations

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1. A limited period (3 years) of patent restoration, and/or reimbursement exclusivity for the new indication should be offered to manufacturers undertaking generic drug repurposing to compensate for the lack of IPP. This would put Canada on par with other developed countries

2. A specific pricing framework should be defined by the pan Canadian Pharmaceutical Alliance (pCPA) on behalf of jurisdictions to adapt generic pricing grids to repurposed drugs, similar to the policy adopted by the pCPA for biosimilar drugs.

3. Federal and provincial agencies responsible for research funding should have dedicated budget envelopes to fund drug repurposing trials and to ensure the generation of high-quality clinical evidence by Canadian research institutions.

4. New regulatory and HTA pathways must be designed jointly by Health Canada, CADTH and INESSS to reduce redundant regulatory approvals and HTA barriers faced by repurposing.

5. New submission fee schedules should be considered by Health Canada, CADTH and INESSS to allow for reduced fees to incentivize repurposing, especially for pediatric formulations, where the problem is most acute.