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Essay

Permissive regulation: A critical review of the regulatory history of buprenorphine formulations in Canada

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ABSTRACT

Suboxone (buprenorphine-naloxone) is an opioid product approved in the US and Canada for the treatment of opioid use disorder. The drug is considered an important response to the opioid overdose epidemic with consistent calls for wider prescribing and deregulation. The history of Suboxone regulation in Canada has not been critically examined. Part of the rationale for doing so stems from the US regulatory experience, with documented irregularities, or what some have called abuses, that support profit-making by Suboxone's manufacturers. This regulatory analysis allows us to determine how opportunities to address health crises through drug innovation are managed at a federal level. We used public drug and patent registries to critically examine Suboxone's Canadian history. First, we investigated Suboxone's entry into the Canadian market to understand how it achieved market exclusivity. Second, we examined Health Canada's risk mitigation process to address extramedical use and diversion to understand the intersection of regulation and brand promotion. Insights from these two analyses were then extended to the recent approval of two related buprenorphine-containing products and their specific pathways to Canadian market exclusivity. We identified inconsistencies in Suboxone's regulatory history that suggest Health Canada's functions of health protection and promotion were compromised in favour of an "innovations" agenda that supports profit-making. Despite six years of market exclusivity in Canada, there was no evidence suggesting Suboxone achieved formal exclusivity (i.e., through patent or data protection). Health Canada's process to address safety concerns of Suboxone were compromised by reliance on the manufacturer to carry out post-market education, allowing the manufacturer to create and market a branded "education" program for its product. Similar inconsistencies have afforded market exclusivity for two related products despite marginal innovation. These analyses reveal a case of permissive regulation, where principles of health protection are compromised by economic imperatives. Such a regulatory approach has the potential to adversely impact public health due to unnecessarily high costs for medicines deemed essential to stem a major health crisis. Alternative pharmaceutical policies are urgently needed to safely and efficiently expand treatment access for opioid use disorder.

Background

The role of pharmaceutical regulation is to protect the public from unsafe products, and this is a core activity within Health Canada's mission to support population health (Health Canada, 2011). However, regulation also has an effect on market access and drug prices (Gold et al., 2010). The regulatory role of Health Canada sits at the intersection of what Moran has called the three faces of the health care state: regulation, industrial development, and the management of distributional conflicts (Moran, 1995). This paper will critically examine the regulatory history of Suboxone (buprenorphine-naloxone), an opioid combination product used to treat opioid use disorder, and the newer long-acting buprenorphine formulation known as Sublocade. We propose this as a case of "permissive regulation", where an agenda that aims to promote drug innovation specifically by protecting market exclusivity and promoting private profit generation has compromised Health Canada's regulatory function, potentially adversely impacting drug pricing and drug access (Abraham & Davis, 2009).

The regulatory history of Suboxone in Canada has neither been well documented nor critically reviewed. It is imperative to do so for two reasons: the pride of place afforded to this drug in response to the opioid epidemic with related influential calls for deregulation and wider

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Suboxone prescribing (Ahamad et al., 2016; Fiscella et al., 2019) and the emergence of two new branded formulations of buprenorphine in Canada (The Ontario Drug Policy Research Network, The Office of the Chief Coroner for Ontario/Ontario Forensic Pathology Service, Public Health Ontario, Centre on Drug Policy Evaluation, 2020). In this paper, we will examine the Canadian history of Suboxone and illustrate similarities to the United States (US), where irregularities, or what some have deemed "abuses", of the pharmaceutical regulation process are already well documented (Haffajee & Frank, 2019, 2020, p. 496). These include the drug's initial pathway to market exclusivity through the "cost recovery" justification of the *Orphan Drug Act*; "product hopping" between therapeutically interchangeable formulations; and filing a sham citizen petition, ultimately denied by the US Food and Drug Administration (FDA), aimed at blocking generics by claiming safety concerns with tablet formulations (Haffajee & Frank, 2019, 2020). Given the same parent company operates in both countries, it likely used similar tactics in Canada. Likewise, FDA decisions hold substantial influence over those of the much smaller Health Canada (Lexchin & Kohler, 2011).

In this analysis, we will critically examine buprenorphine's Canadian regulatory history through three lines of questioning. What was Suboxone's initial entry into the Canadian market and how did it achieve market exclusivity for six years? Were there patent or data protections or simply a lack of generic competition? Second, how does Health Canada's risk mitigation process to address extramedical use and diversion of Suboxone accord with existing standards for the role of industry in continuing medical education? Third, how does this history for Suboxone compare to the recent approval of two buprenorphine-containing products also manufactured by Indivior that represent only "marginal innovations" (Kesselheim, 2010) and what are the implications for access and pricing? We will identify inconsistencies that suggest Health Canada's regulatory function has been compromised in favour of support for companies' profitability, even for drugs of high public interest. This is of particular importance because Health Canada has multiple roles within the Canadian health system. Besides pharmaceutical regulation, Health Canada also has an important role for health promotion and this agency has identified the Canadian crisis of opioid-related harms as a central concern on their agenda (Health Canada, 2022). Finally, we will suggest additional analyses to further substantiate these findings and identify possible rectifying policies.

Suboxone's initial entry and rise to fame for opioid use disorder

Suboxone, buprenorphine-naloxone as a soluble sublingual tablet or film, has risen to become first line therapy for opioid use disorder in Canada (Bruneau et al., 2018). As the epidemic of opioid-related harms has continued to grow, Suboxone has been referenced by major federal and provincial documents as a key part of the crisis policy response (Canadian Centre of Substance Use and Addiction, 2017; Ontario Newsroom, 2016). Although approved for the treatment of opioid use disorder, buprenorphine is an opioid and has a well-documented history of misuse (Campbell & Lovell, 2012). Suboxone's co-formulation with naloxone is meant to address this. As a strong opioid antagonist, naloxone should block the effects of buprenorphine if the co-formulated drug is injected or snorted instead of absorbed under the tongue. Yet, at the time of approval in the US and Canada, there was no good evidence that this co-formulation was effective at reducing this risk. Nearly twenty years on, this assumption is increasingly being questioned (Blazes & Morrow, 2020).

Reckitt Benckiser, primarily a household consumer products company, initially held the rights to the formulation before selling worldwide licensing to Schering Plough in 1997 (Fig. 1) (Campbell & Lovell, 2012). With increasing revenues from the lucrative US market, Reckitt Benckiser bought back most of the rights by 2010 and ultimately created Indivior in 2014 as a pharmaceuticals-focused spin-off with Suboxone as its primary holding. Suboxone (buprenorphine-naloxone) and its related formulation, Subutex (buprenorphine), were approved for marketing in the US in 2002, with a full seven years of market exclusivity, although all relevant patents for these drugs had expired. Reckitt Benckiser achieved market exclusivity for these products under the *Orphan Drug Act's* cost recovery principle, granted, albeit rarely, to manufacturers who demonstrate "no reasonable expectation" to recoup developing and marketing costs (Wellman-Labadie & Zhou, 2010). This was despite the high and rising prevalence of opioid use disorder in the US and despite development costs having been publicly funded through the National Institutes of Health and National Institute on Drug Abuse (Campbell & Lovell, 2012). Since 1983, only three drugs have been granted orphan exclusivity based on cost recovery, Suboxone and Subutex being two of them (Chua & Conti, 2019). In 2012 alone, Suboxone generated $1.55 billion in the US (Wellman-Labadie & Zhou, 2010) – a perfect example of a blockbuster "orphan drug", but the only one to achieve this through the *Orphan Drug Act's* cost recovery principle (Chua & Conti, 2019).

Suboxone's market exclusivity in Canada

Suboxone was approved in Canada on May 18, 2007, and was marketed shortly thereafter (Health Canada, 2015). The first generic version, by Mylan, was approved on July 4, 2013, followed by Teva (May 2014), Actavis Pharma (April 2016), Pharmascience (August 2017), and Taro (June 2021). Thus, Suboxone had more than six years of exclusivity in Canada (Fig. 1). Unlike the US, it appears Suboxone achieved market exclusivity in Canada without formally applying for it, which raises concerns around drug regulation, innovation, and access.

There are two legal pathways to exclusivity in Canada (Grootendorst et al., 2012). The first is through patents, by which pharmaceutical manufacturers typically achieve 20 years of exclusivity from the time of patent filing in Canada. This patent protection is intended to drive pharmaceutical innovation by providing a window for manufacturers to recoup development costs. However, Health Canada's Patent Register identifies no current or past patents related to buprenorphine-naloxone tablets (Government of Canada et al., 2011). The second pathway to market exclusivity, which can overlap with the first, is through Health Canada's granting of data protection for innovative drugs. Given that clinical trials required for market approval can consume much of the patent period, this pathway prevents generic producers from using the incumbent's clinical data for a period of six years and prevents marketing of a bioequivalent generic for eight years. To gain market access during this six-year period, a manufacturer would have to carry out their own clinical trials. This is usually considered cost prohibitive by generic firms even though they may submit data from clinical trials conducted outside of Canada (Health Canada, 2009). Again, a search of Health Canada's Register of Innovative Drugs shows no data protections assigned to buprenorphine-naloxone tablets (Health Canada, 2020b; Herder, 2013). Unlike the FDA's "Orange Book", which outlines the exclusivity allowances for all approved drugs, Health Canada offers no transparent listing beyond the Patent Register and the Register of Innovative Drugs, which in this case offer no insight into a mechanism for exclusivity.

Without patent or data protection, it is likely that Suboxone achieved market exclusivity due to a lack of generic competition. No generic manufacturer applied for regulatory approval in Canada until after the first generic approval in the US in 2013 (Health Canada, 2015). With uncertainty over profitability in a smaller market, industry is sometimes hesitant to submit drugs to Health Canada for regulatory review – Suboxone's approval in Canada was five years after the US – especially when the path to reimbursement appears complicated because of differences across provinces (Roberts et al., 2015). Whatever the underlying reasons, access to drugs in Canada may be delayed and prone to high pricing given limited competition from generic firms.

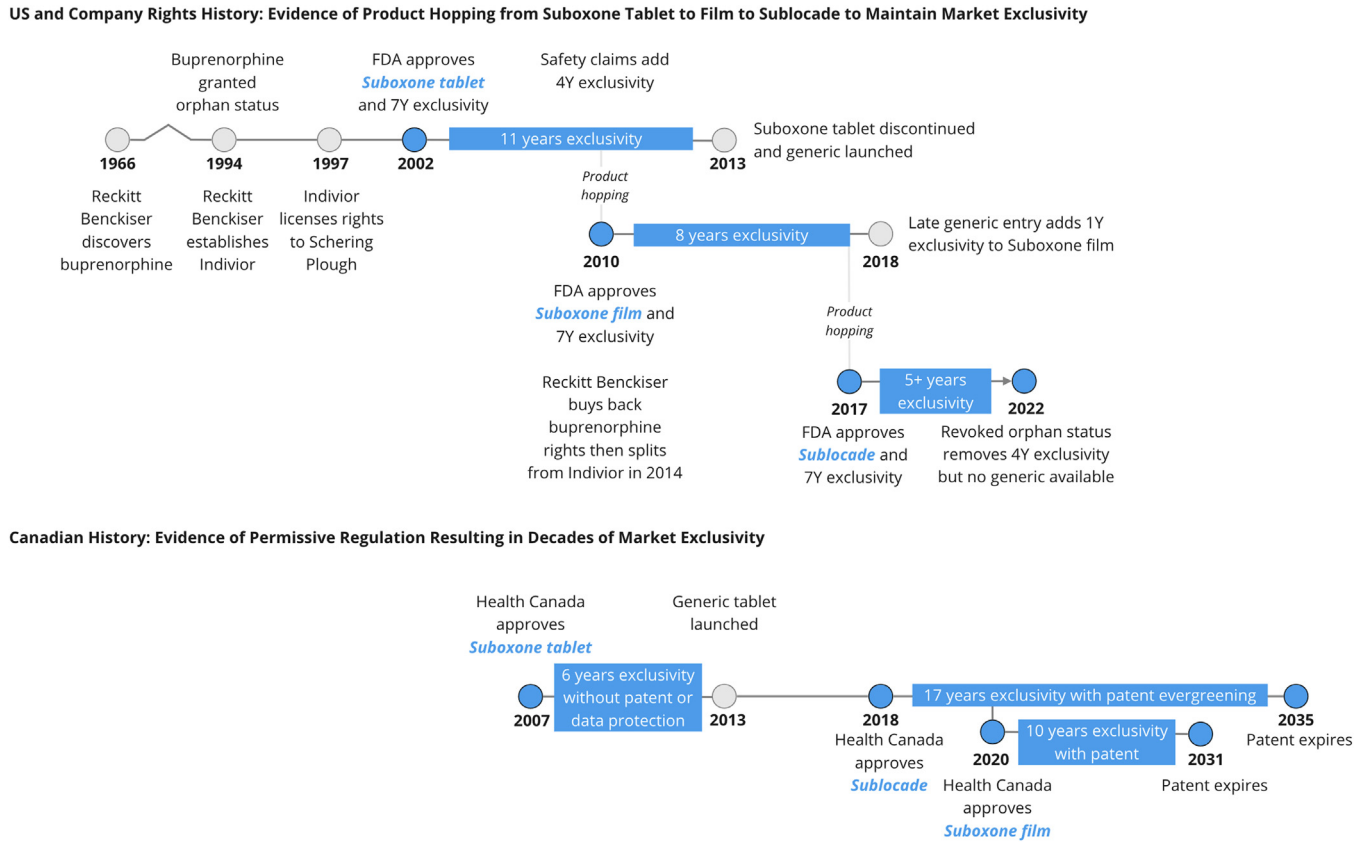

Fig. 1. Regulatory History of Suboxone in the US and Canada.

The Suboxone education program: risk mitigation or promotion?

New opioid drug submissions seeking approval in Canada must include a risk management plan (RMP) (Health Canada, 2018). The RMP describes a series of activities (e.g., pharmacovigilance, clinician education) carried out by the manufacturer to maintain safe use of the drug. As part of the RMP, manufacturers are required to encourage clinicians to participate in an accredited educational program. However, a clear example of permissive regulation is Suboxone's branded, unaccredited "education" program for its product. This program is outlined on the product monograph, a Health Canada-approved scientific document describing the drug properties, conditions of use, and indications, that is intended to be "devoid of promotional material" (Health Canada, 2020a): The "Suboxone Education Program" is described as having four key components:

- "training of the prescribing physicians in the use of SUBOXONE® sublingual tablets;
- maintenance of a list of SUBOXONE® Education Program trained physicians;
- daily dosing supervised by a healthcare professional, progressing to unsupervised administration as the patient's clinical stability permits;
- take-home doses once the patient has sufficient clinical stability and is able to safely store SUBOXONE®. Take-home doses should be assessed and reviewed on a regular basis" (Indivior UK Limited, 2017)

The Suboxone Education Program, which is a highly unusual inclusion in a Canadian pharmaceutical product monograph, flouts Canadian continuing medical education standards by including the brand name in the very title of the program (Canadian Medical Association, 2007). There is little to no evidence to support continuing medical education that is developed and provided by the manufacturer as an effective intervention for reducing risk. In fact, as evidenced by fentanyl, another opioid, manufacturer-sponsored educational programs often contain marketing messages promoting a more favourable view of the product (Infeld et al., 2019). Indivior appears to further cross the line between education and promotion by titling the educational program as "Suboxone CME" (Indivior UK Limited, n.d.). By using the phrase "CME", this program takes on the imprimatur of accredited continuing medical education programming without actually being accredited or even able to meet standards of accreditation due to direct industry involvement (Sud et al., n.d.).

In the US, buprenorphine had been regulated federally and all clinicians needed to complete an 8-hour training before prescribing. But Health Canada chose to delegate prescribing regulation to each province, leading to inconsistent standards. In many provinces, physicians are required to complete approved education before prescribing buprenorphine, where the Suboxone Education Program, although unaccredited, is the required program or at least one of the several approved programs (Government of Canada et al., 2018). The blurred boundaries between regulation, prescriber education, and promotion is a common concern even outside of this therapeutic area (Downie et al., 2017; Steinman et al., 2006).

Poor clinical practices both for chronic pain and substance use disorders have resulted from insufficient medical education (Lynch, 2011). Industry promotions under the guise of medical education have been implicated in the rise of opioid analgesic prescribing and its attendant harms (Persaud, 2014; Van Zee, 2009). Furthermore, funding non-industry education programs has been a key part of governments' responses to the opioid crisis in both Canada and the US (Canadian Centre of Substance Use and Addiction, 2017; Kahn et al., 2019). Specifically at the regulatory level, the US instituted the opioid analgesic Risk Evaluation and Mitigation Strategy (REMS) as an important federal opioid crisis response. This extensive REMS program, comparable to Health

Canada's RMP, was meant to limit industry influence by creating a pool of funds at arm's length from industry to support the development and evaluation of opioid analgesic and chronic pain management continuing education programs. However, a recent evaluation of the REMS program demonstrated poor adherence to industry disclosure guidance and poor evaluation methodologies leading to an inability to assess the program's impact on risk reduction (Heyward et al., 2020). Likewise, the program has been criticized for selecting content that favours industry agendas (Lurie, 2018).

In a systematic review of continuing medical education programs for buprenorphine and methadone prescribing, we identified only one study that examined effects on diversion and extramedical use (Lofwall et al., 2011). This one study, funded by Reckitt Benckiser, only examined changes in prescriber knowledge and attitudes and not changes in prescriber performance or patient health outcomes. Taken together, the absence of evidence of any benefit to patient health and concerns about messaging that is favourable to industry, support the contention that the regulatory requirement by Health Canada for the Suboxone Education Program reinforces product promotion rather than risk minimization.

Reformulating and repackaging, but no rebranding – extending Suboxone's market exclusivity

In 2009, Suboxone's "orphan drug" exclusivity was set to expire in the US (Fig. 1) (Barenie et al., 2021). Yet Reckitt Benckiser allegedly engaged in "product hopping", a scheme aimed to extend market exclusivity via a new formulation of buprenorphine-naloxone – also branded as Suboxone but reformulated as a sublingual film instead of a tablet (Barenie et al., 2021; Federal Trade Commission, 2021). As the exclusivity period for the tablets was ending, the company claimed to the FDA that the tablet carried an excessive risk of pediatric overdose, since tablets were dispensed as multiple doses in a bottle, while the film was individually wrapped making it harder for a child to accidentally consume multiple films (Haffajee & Frank, 2020). The company also claimed the film would address the diversion risk of the tablets, but the evidence is inconclusive (Lofwall & Walsh, 2014). Under this guise of safety, Reckitt Benckiser pulled its sublingual tablets from the market, making the film the only available formulation. The claims of safety and diversion risk were contested by both public defenders and generic manufacturers, who ultimately won out (Federal Trade Commission, 2021). But the legal wrangling delayed generic market access for the buprenorphine-naloxone tablets until 2013 – enabling a full four years of billion-dollar sales for Reckitt Benckiser (Barenie et al., 2021).

By 2018, the film's market exclusivity (now sponsored by Indivior) was also successfully challenged by Mylan and Dr. Reddy's of India (Office of the Commissioner, 2018). Mylan settled with Indivior, but Dr. Reddy's went on to successfully market the film and penetrate the lucrative US market. This successful challenge by generics was publicly celebrated by the US Health and Human Services Secretary, Alex Azar, who highlighted the importance of increasing access to buprenorphine-naloxone (US Department of Health and Human Services, 2018). In his statement, he announced: "[We] are so pleased that the FDA has approved generic versions of one medication-assisted treatment option. These approvals will help increase competition, lower cost, and save lives, advancing [Health and Human Services]'s priorities to lower drug prices and combat the opioid epidemic."

This US history is highly relevant to regulation in Canada. Suboxone film was approved in Canada in July 2020 and the online Suboxone Education Program was correspondingly updated on December 20, 2020, suggesting this will continue to be an important part of the regulatory approval (Indivior UK Limited, n.d.). The Canadian Agency for Drugs and Technologies in Health (CADTH), a national health technology assessment agency, reviewed the film and identified no safety advantages compared to the tablet (Canadian Agency for Drugs and Technologies in Health, 2014). Importantly, the tablet and film share a product monograph which documents identical dosing and safety information for the two formulations. Thus, Suboxone film is therapeutically interchangeable with the tablet, demonstrating questionable innovation.

There are conflicting interests of affording market exclusivity as a pathway to innovation versus ensuring public access to affordable life-saving therapies (Abraham & Davis, 2009; Hollander, 2006). In the case of the Suboxone film, there is no clear innovation as compared to the tablet regarding safety, efficacy, or convenience (Canadian Agency for Drugs and Technologies in Health, 2014). Patents, in and of themselves, are poor proxies for health innovation (Kapczynski et al., 2012). Furthermore, court rulings in the US found the manufacturer wrongfully attempted to delay generic competition, costing Reckitt Benckiser $1.4 billion USD in fines, one of the largest settlements in pharmaceutical opioid history (The United States Department of Justice, 2019). Likewise, there is already active generic manufacturing of the film formulation for the much larger US market. Given the substantial public interest at stake, it is incumbent on Health Canada, outside of its regulatory role and in collaboration with other federal agencies, to identify pathways to help procure additional supplies, in turn, lowering costs. This may include interventions such as developing public manufacturing capacity or facilitating compulsory licensing. The latter in particular has a history of use and acceptance for promoting public interest since the rise of patent protections. Indeed, some scholars have argued that compulsory licensing does not substantially impede innovation (Chien, 2003; Eggertson, 2020).

If there is failure to intervene at the federal level, then provincial drug reimbursement programs can help reduce costs by declining to cover the full cost of the brand product. This is, in fact, what happened with branded formulations of the opioid analgesic oxycodone, known as OxyContin and OxyNEO in Canada (Canadian Agency for Drugs and Technologies in Health, 2015). When OxyContin's exclusivity period was set to expire, Purdue Pharma pulled it from the market and reformulated and patented the same drug as OxyNEO (Gomes et al., 2018, 2017). This reformulation came in a "tamper-resistant" form that was meant to deter injecting or snorting the drug. Health Canada approved OxyNEO, but most drug benefit programs refused to reimburse the full cost. Cheaper generic formulations without "tamper-resistance" became available for therapeutic use in Canada.

Reformulating and rebranding

In a further pivot from Suboxone tablets, Indivior also focused its attention on Sublocade (buprenorphine without naloxone), which is injected once monthly. Initially in the US, this formulation was intended to have market exclusivity, under *Hatch-Waxman* data protection legislation, for three years (until 2021). However, in a highly unusual move, the FDA granted Sublocade orphan drug status based on the original orphan ruling for Subutex (tablet formulation of buprenorphine without naloxone) from 1994 (Fig. 1). In 2020, however, both the data protection and orphan drug exclusivities were successfully challenged in court by another company, resulting in the expiry of Sublocade's US market exclusivity on November 30, 2020 (U.S. Food and Drug Administration, n.d.). The FDA went so far as to also rescind Subutex's original 1994 orphan drug status, stating that the use of the cost recovery principle was based on faulty assumptions from Reckitt Benckiser (Chua & Conti, 2020).

Canada, however, has a different story. Sublocade was approved in November 2018 and is covered under a patent which was filed in June 2011 and thus does not expire until 2031. An additional patent for a minor expansion in therapeutic indication was granted in June 2019 and is set to expire in 2035, extending Sublocade's exclusivity by four years. This suggests a practice of patent evergreening, a technique for delaying generic competition (Stanbrook, 2013). Similar to Suboxone, a "Sublocade Training Program" was created by the manufacturer and recommended by authoritative substance use institutions (British Columbia Centre on Substance Use, 2020). In its review of various buprenorphine formulations, CADTH determined that Sublocade demonstrated efficacy

versus placebo in treating opioid use disorder, but it did not identify any comparative effectiveness trials to other buprenorphine formulations or other treatments. As such, CADTH recommended Sublocade for public formulary coverage, but at a 73% discount from the proposed $550 CAD (~$440 USD) per month cost (Canadian Agency for Drugs and Technologies in Health, 2019). However, each province can choose whether to follow the recommendation. Ontario, the most populous province in the country, chose to cover the full cost of this medication, but at an unknown price (Drug Programs Policy and Strategy Branch Ontario Public Drug Programs, 2016).

This highlights the same dilemma as with Suboxone film and identifies a need for Health Canada to publicly clarify exclusivity status similar to what the FDA publishes in the Orange Book. It appears as if Indivior has market exclusivity for injectable buprenorphine and that at least some public insurers are willing to pay the full cost for the drug. Thus, Health Canada's decision to approve patent-protected formulations of buprenorphine puts an undue burden on the provincial public insurers, and thus ultimately Canadians, to pay for an "innovation" that is at best marginal and which the US regulatory regime has deemed as not worth protecting. In this case, Health Canada has an opportunity to reduce opioid overdose deaths in this country by implementing policy to encourage or otherwise facilitate the entry of lower-cost options.

Areas of further study

Future studies could deepen this analysis by analyzing additional data sources, if they become available. First, as of 2019, Health Canada has committed to releasing anonymized clinical data and other regulatory submission materials used to inform drug approvals and other regulatory activities. This includes retroactively releasing information upon request. Accessing documentation relevant to the regulatory approvals process, in particular, Health Canada's interpretation of the submitted data, may help to understand whether Suboxone was granted market exclusivity, on what justification, and specifics of the RMP. These could be requested through an Access to Information request, though it is unclear what information would be released and when. Finally, it would be useful to examine provincial utilization of buprenorphine-naloxone to estimate the excess financial and health costs incurred due to exclusivity.

Conclusions

The ability of pharmaceutical companies to highlight innovation and manipulate drug regulation is not unique to Canada. Permissive regulation, whereby regulators fail to uphold their technical standards against the interests of the manufacturer, have been reported in both the US and Europe (Abraham & Davis, 2009; Hollander, 2006). In beginning to document the history of Suboxone regulation in Canada, we have identified several inconsistencies that seem to favour a particular innovations agenda of market exclusivity and product promotion over core regulatory functions of protecting public safety. This view of "innovation" conflicts with alternative views that stress the accessibility of effective health technologies. An innovations agenda, while perhaps important to the Canadian government and to the larger "health care state", is not central to the expressed mission of Health Canada (Eren Vural et al., 2021). And indeed, Health Canada has made public proclamations and taken other initiatives to address opioid-related harms in Canada. This analysis suggests that Health Canada's principles are being compromised by industrial and economic development objectives – potentially to the detriment of public health due to unnecessarily high costs for medicines deemed essential to stem a major health crisis. This is especially important when the value of market exclusivity in delivering effective and accessible health technologies is itself under scrutiny (Barenie et al., 2021; Chapman et al., 2019).

Importantly, the opportunity exists to rectify the imbalance between innovation and public health related goals in the context of regulatory treatment of the Suboxone film and Sublocade reformulations. Three specific policies that Health Canada can implement to address the identified concerns are: first, and in keeping with the practices of the US FDA, to publish the exclusivity status (and the regulatory justification for such exclusivity) for all approved drugs; second, to put in place safeguards to ensure that an RMP serves a *bona fide* patient safety purpose and that educational materials are independent of the manufacturer instead of protecting a company's market advantage; and, third, to develop criteria for weighing public interest against exclusivity rights and a set of policy options to rectify imbalances. The first policy can be implemented immediately, provided resources are in place to articulate the regulator's justification for exclusivity. The second is more complex as discerning whether safety versus market advantage is the primary purpose of an RMP will involve tracking the RMP over time. One proposed solution may be establishing a similar process to the US, where prospective generic manufacturers can submit its REMS through a separate review process (Haffajee & Frank, 2020). Again, it will be essential for Health Canada to devote resources to monitoring RMPs to ensure they are not undue barriers to generic entry. Finally, the third policy could be modelled upon the new compulsory licensing mechanism that was temporarily put into place in order to help address the COVID-19 pandemic (Legislative Services Branch, 2021). Instead of having to demonstrate good faith efforts to secure a voluntary license from the patent holder, under this mechanism, the Minister of Health can initiate the application for a license provided that the Chief Public Health Officer of Canada believes there is a "public health emergency that is a matter of national concern." The ongoing opioid overdose crisis easily meets this threshold and has even been identified as such in the Chief Public Health Officer's Report on the State of Public Health in Canada (Public Health Agency of Canada, 2021). The only change that is required to re-introduce this mechanism into force, in turn enabling compulsory licensing of Suboxone and Sublocade formulations, is to repeal the September 30, 2020 expiry date pertaining to this provision.

While other reforms and changes to Health Canada's practices may be needed to fully restore the regulator's consumer protection role, these three policy actions will help address the specific concerns raised by Health Canada's mishandling of buprenorphine formulations to date.

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Declarations of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abraham, J., & Davis, C. (2009). Drug evaluation and the permissive principle: Continuities and contradictions between standards and practices in antidepressant regulation. *Social Studies of Science, 39*(4), 569–598.

Ahamad, K., Kerr, T., Nolan, S., & Wood, E. (2016). *Moving towards improved access for evidence-based opioid addiction care in British Columbia.* http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Publications/Epid/Other/05_Moving_Towards_Improved_Access_for_Evidence-Based_Opioid_Addiction_Care.pdf

Barenie, R. E., Sinha, M. S., & Kesselheim, A. S. (2021). Factors affecting buprenorphine utilization and spending in Medicaid, 2002-2018. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 24*(2), 182–187.

Blazes, C. K., & Morrow, J. D. (2020). Reconsidering the usefulness of adding naloxone to buprenorphine. *Frontiers in Psychiatry /Frontiers Research Foundation, 11*, Article 549272.

British Columbia Centre on Substance Use. (2020). *Sublocade (extended-release buprenorphine) information* https://www.bccsu.ca/wp-content/uploads/2020/05/Bulletin-Sublocade_0520.pdf.

Bruneau, J., Ahamad, K., Goyer, M.-È., Poulin, G., Selby, P., Fischer, B., … Wood, E.CIHR Canadian Research Initiative in Substance Misuse. (2018). Management of opioid use disorders: A national clinical practice guideline. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne, 190*(9), E247–E257.

Campbell, N. D., & Lovell, A. M. (2012). The history of the development of buprenorphine as an addiction therapeutic. *Annals of the New York Academy of Sciences, 1248*, 124–139.

Canadian Agency for Drugs and Technologies in Health. (2014). *Buprenorphine/naloxone (suboxone) film versus buprenorphine/naloxone tablets for the treatment of opioid addiction: Comparative safety* https://www.cadth.ca/media/pdf/htis/feb-2014/RB0642%20Suboxone%20Final.pdf.

Canadian Agency for Drugs and Technologies in Health. (2015). *Prescribing and dispensing policies to address harms associated with prescription drug abuse* https://www.cadth.ca/sites/default/files/pdf/ES0291_Prescription_Drug_Abuse_e.pdf.

Canadian Agency for Drugs and Technologies in Health. (2019). *CADTH Canadian drug expert committee recommendation (final)* https://www.cadth.ca/sites/default/files/cdr/complete/SR0579%20Sublocade%20-%20CDEC%20Final%20Recommendation%20June%2021%2C%202019_for%20posting.pdf.

Canadian Centre of Substance Use and Addiction. (2017). *Joint statement of action to address the opioid crisis: A collective response* https://www.ccsa.ca/sites/default/files/2019-04/CCSA-Joint-Statement-of-Action-Opioid-Crisis-Annual-Report-2017-en.pdf.

Canadian Medical Association. (2007). *Guidelines for physicians in interactions with industry* https://policybase.cma.ca/documents/policypdf/PD08-01.pdf.

Chapman, S. R., Aladul, M. I., & Fitzpatrick, R. W. (2019). Lost cost savings to the NHS in England due to the delayed entry of multiple generic low-dose transdermal buprenorphine: A case scenario analysis. *BMJ Open, 9*(8), Article e026817.

Chien, C. (2003). Cheap drugs at what price to innovation: Does the compulsory licensing of pharmaceuticals hurt innovation? *Berkeley Technology Law Journal /Boalt Hall School of Law, University of California, Berkeley, 18*(3), 853–907.

Chua, K.-P., & Conti, R. M. (2019, July 26). Orp*han drugs for opioid use di*sorder: An *abuse of the orphan drug a*ct. https://www.healthaffairs.org/do/10.1377/hblog20190724.795814/full/

Chua, K.-P., & Conti, R. M. (2020, March 5). *Revocation of orphan drug designation for extended-release buprenorphine injection: Implications and next steps*. https://www.healthaffairs.org/do/10.1377/hblog20200302.846103/full/

Downie, J., de l'auteur(e), T. L. T., & Herder, M. (2017, April 25). *Regulatory risk mismanagement and the abortion pill*. https://policyoptions.irpp.org/fr/magazines/avril-2017/regulatory-risk-mismanagement-and-the-abortion-pill/

Drug Programs Policy and Strategy Branch Ontario Public Drug Programs. (2016). *Ontario drug benefit formulary/comparative drug index* (Edition 42) https://www.health.gov.on.ca/en/pro/programs/drugs/formulary42/summary_edition42_20161011.pdf.

Eggertson, L. (2020). *Canada can override patents to combat drug, equipment shortages during the pandemic* April 2. CMAJ News https://cmajnews.com/2020/04/02/covid-patent-1095862/.

Eren Vural, I., Herder, M., & Graham, J. E. (2021). From sandbox to pandemic: Agile reform of Canadian drug regulation. *Health Policy, 125*(9), 1115–1120.

Commission, Federal Trade (2021). *FTC returns nearly $60 million to those suffering from opioid addiction who were allegedly overcharged in suboxone film scheme* May 10. Federal Trade Commission https://www.ftc.gov/news-events/news/press-releases/2021/05/ftc-returns-nearly-60-million-those-suffering-opioid-addiction-who-were-allegedly-overcharged.

Fiscella, K., Wakeman, S. E., & Beletsky, L. (2019). Buprenorphine deregulation and mainstreaming treatment for opioid use disorder: X the X waiver. *JAMA Psychiatry, 76*(3), 229–230.

Gold, E. R., Kaplan, W., Orbinski, J., Harland-Logan, S., & & N-Marandi, S. (2010). Are patents impeding medical care and innovation? *PLoS Medicine, 7*(1), Article e1000208.

Gomes, T., Jain, S., Paterson, J. M., Sketris, I., Caetano, P., & Henry, D.Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. (2018). Trends and uptake of new formulations of controlled-release oxycodone in Canada. *Pharmacoepidemiology and Drug Safety, 27*(5), 520–525.

Gomes, T., Mastorakos, A., Paterson, J. M., Sketris, I., Caetano, P., Greaves, S., & Henry, D.Canadian Network for Observational Drug Effect Studies Investigators. (2017). Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone: A time series analysis. *CMAJ Open, 5*(4), E800–E807.

Government of Canada, Health Canada, Health Products, Food Branch, Therapeutic Products Directorate, Office of Patented Medicines, Liaison, Patents, & Liaison. (2011, August 22). *Patent register - Drug products* https://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp.

Government of Canada, Works, P., Government Services Canada, Public Services, Canada, P., Integrated Services Branch, & Gazette, C.. (2018, March 7). *Regulations amending the narcotic control regulations and the new classes of practitioners regulations (Diacetylmorphine (Heroin) and Methadone): SOR/2018-37* https://gazette.gc.ca/rp-pr/p2/2018/2018-03-21/html/sor-dors37-eng.html.

Grootendorst, P., Bouchard, R., & Hollis, A. (2012). Canada's laws on pharmaceutical intellectual property: The case for fundamental reform. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne, 184*(5), 543–549.

Haffajee, R. L., & Frank, R. G. (2019). Generic drug policy and suboxone to treat opioid use disorder. *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics, 47*(4_suppl), 43–53.

Haffajee, R. L., & Frank, R. G. (2020). Abuses of FDA regulatory procedures - The case of Suboxone. *The New England Journal of Medicine, 382*(6), 496–498.

Health Canada. (2011, October 12). *About mission, values, activities* https://www.canada.ca/en/health-canada/corporate/about-health-canada/activities-responsibilities/mission-values-activities.html#what.

Health Canada. (2015, June 18). *Drug product database: Access the database* Drug Product Database: Access the Database https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html .

Health Canada. (2018). *Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products: Guidance for industry*. Health Canada https://play.google.com/store/books/details?id=ObFfuwEACAAJ.

Health Canada. (2020, November 1). *Product monographs: Frequently asked questions* Product Monographs: Frequently Asked Questions https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph/frequently-asked-questions-product-monographs-posted-health-canada-website.html#a2.1 .

Health Canada. (2020, November 27). *Register of innovative drugs* https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/register-innovative-drugs.html.

Health Canada. (2022, March). *Federal actions on opioids to date*. Federal Actions on Opioids to Date https://www.canada.ca/en/health-canada/services/opioids/federal-actions/overview.html.

Herder, M. (2013). When everyone is an orphan: Against adopting a U.S.-styled orphan drug policy in Canada. *Accountability in Research, 20*(4), 227–269.

Heyward, J., Olson, L., Sharfstein, J. M., Stuart, E. A., Lurie, P., & Alexander, G. C. (2020). Evaluation of the extended-release/long-acting opioid prescribing risk evaluation and mitigation strategy program by the US food and drug administration: A review. *JAMA Internal Medicine, 180*(2), 301–309.

Hollander, I. (2006). Viagra's rise above women's health issues: An analysis of the social and political influences on drug approvals in the United States and Japan. *Social Science & Medicine, 62*(3), 683–693.

Indivior UK Limited. (n.d.). *Suboxone Training Program*. Retrieved September 16, 2021, from https://www.suboxonetrainingprogram.ca/en/

Indivior UK Limited. (2017). *Product monograph including patient medication information* https://pdf.hres.ca/dpd_pm/00041074.PDF.

Infeld, M., Bell, A., Marlin, C., Waterhouse, S., Uliassi, N., & Fugh-Berman, A. (2019). Continuing medical education and the marketing of fentanyl for breakthrough pain: Marketing messages in an industry-funded CME module on breakthrough pain. *World Medical & Health Policy, 11*(1), 43–58.

Kahn, N., Chappell, K., Regnier, K., Travlos, D. V., & Auth, D. (2019). A collaboration between government and the continuing education community tackles the opioid crisis: Lessons learned and future opportunities. *The Journal of Continuing Education in the Health Professions, 39*(1), 58–63.

Kapczynski, A., Park, C., & Sampat, B. (2012). Polymorphs and prodrugs and salts (oh my!): An empirical analysis of "secondary" pharmaceutical patents. *PloS One, 7*(12), e49470.

Kesselheim, A. S. (2010). Using market-exclusivity incentives to promote pharmaceutical innovation. *The New England Journal of Medicine, 363*(19), 1855–1862.

Legislative Services Branch. (2021, June 30). Patent act https://laws-lois.justice.gc.ca/eng/acts/P-4/page-4.html.

Lexchin, J., & Kohler, J. C. (2011). The danger of imperfect regulation: OxyContin use in the United States and Canada. *The International Journal of Risk & Safety in Medicine, 23*(4), 233–240.

Lofwall, M. R., & Walsh, S. L. (2014). A review of buprenorphine diversion and misuse: The current evidence base and experiences from around the world. *Journal of Addiction Medicine, 8*(5), 315–326.

Lofwall, M. R., Wunsch, M. J., Nuzzo, P. A., & Walsh, S. L. (2011). Efficacy of continuing medical education to reduce the risk of buprenorphine diversion. *Journal of Substance Abuse Treatment, 41*(3), 321–329.

Lurie, J. (2018). *Doctors receive opioid training. Big pharma funds it. What could go wrong?*. Mother Jones http://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/.

Lynch, M. E. (2011). The need for a Canadian pain strategy. *Pain Research & Management: The Journal of the Canadian Pain Society = Journal de La Societe Canadienne Pour Le Traitement de La Douleur, 16*(2), 77–80.

Moran, M. (1995). Three faces of the health care state. *Journal of Health Politics, Policy and Law, 20*(3), 767–781 discussion 783-5.

Office of the Commissioner. (2018, June 14). *FDA approves first generic versions of Suboxone sublingual film, which may increase access to treatment for opioid dependence* https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-versions-suboxone-sublingual-film-which-may-increase-access-treatment?utm_campaign=06142018_PR_Suboxone%20sublingual%20film&utm_medium=email&utm_source=Eloqua.

Ontario Newsroom. (2016, October 12). *Ontario taking action to prevent opioid abuse*. Queen's Printer for Ontario https://news.ontario.ca/en/release/42168/ontario-taking-action-to-prevent-opioid-abuse.

Persaud, N. (2014). Questionable content of an industry-supported medical school lecture series: A case study. *Journal of Medical Ethics, 40*(6), 414–418.

Public Health Agency of Canada. (2021, December 12). Full report: A vision to transform Canada's public health system Full Report: A Vision to Transform Canada's Public Health System https://www.canada.ca/en/public-health/corporate/publications/chief-public-health-officer-reports-state-public-health-canada/state-public-health-canada-2021/report.html .

Roberts, E. A., Herder, M., & Hollis, A. (2015). Fair pricing of "old" orphan drugs: Considerations for Canada's orphan drug policy. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne, 187*(6), 422–425.

Stanbrook, M. B. (2013). Limiting "evergreening" for a better balance of drug innovation incentives. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne, 185*(11), 939.

Steinman, M. A., Bero, L. A., Chren, M.-M., & Landefeld, C. S. (2006). Narrative review: The promotion of gabapentin: An analysis of internal industry documents. *Annals of Internal Medicine, 145*(4), 284–293.

Sud, A., Strang, M., Buchman, D., Spithoff, S., Upshur, R., Webster, F., & Grundy, Q. (n.d.). How the Suboxone Education Program presented as a solution to risks in the Canadian opioid crisis: a critical discourse analysis [Under review]. BMJ Open.

The Ontario Drug Policy Research Network, The Office of the Chief Coroner for Ontario/Ontario Forensic Pathology Service, Public Health Ontario, Centre on Drug Policy Evaluation. (2020). Preliminary patterns in circumstances surrounding opioid-related deaths in Ontario during the COVID-19 pandemic https://www.publichealthontario.ca/-/media/documents/o/2020/opioid-mortality-covid-surveillance-report.pdf?la=en.

The United States Department of Justice. (2019). Justice department obtains $1.4 billion from Reckitt Benckiser group in largest recovery in a case concerning an opioid drug in United States history July 11 https://www.justice.gov/opa/pr/justice-department-obtains-14-billion-reckitt-benckiser-group-largest-recovery-case.

US Department of Health and Human Services. (2018). *HHS Secretary Azar Praises FDA approval of generic drugs for treating opioid dependence* June 14 https://public3.pagefreezer.com/browse/HHS.gov/31-12-2020T08:51/https://www.hhs.gov/about/news/2018/06/14/hhs-secretary-azar-praises-fda-approval-generic-drugs-treating-opioid-dependence.html.

U.S. Food and Drug Administration. (n.d.). *Orange book: Approved drug products with therapeutic equivalence evaluations*. Retrieved September 16, 2021, from https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=209819&Appl_type=N

Van Zee, A. (2009). The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *American Journal of Public Health, 99*(2), 221–227.

Wellman-Labadie, O., & Zhou, Y. (2010). The US orphan drug act: Rare disease research stimulator or commercial opportunity? *Health Policy, 95*(2–3), 216–228.