THE SCHOOL OF PUBLIC POLICY

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Long-Acting Reversible Contraceptive Device Regulations: Lessons for Canada

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Capstone Approval Page

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Executive Summary

Unintended pregnancy rates in Canada have remained relatively stable over the past decade, even though contraceptive use has increased over the same time period. Given these statistics, it is possible that Canadians are using contraceptives inconsistently, or are using less effective contraceptive methods. For example, Long-Acting Reversible Contraceptives (LARC), such as intrauterine devices and subdermal implants, have the lowest failure rates of all currently developed reversible methods but are only used by less than five percent of female contraceptive users in Canada.

Several researchers and health care professionals have suggested that increasing LARC use could have a significant impact on reducing the unintended pregnancy rate, given their high efficacy rates and minimal room for user error. However, Canadian women have limited choices when it comes to LARC products, which may influence LARC uptake. For example, no type of subdermal implant is currently available on the Canadian market, and several types of intrauterine devices are also unavailable. While there are many market factors that may affect product variety in Canada, some researchers have determined that unnecessary regulatory hurdles are largely responsible for Canada's dearth of contraceptive products. The first step to increasing LARC uptake is to ensure that the Canadian regulatory system is properly equipped to attract and approve safe and effective LARC products.

This paper examines the regulatory process in some of Canada's peer countries—namely The United Kingdom, the United States, and Australia—in order to discover regulatory best practices for LARCs. This paper compares each country's classification system for LARCs, the overall pathway to regulatory approval, clinical trial requirements, post-market surveillance activities, and the transparency of each country's regulatory process.

After a review of the literature, it is evident that there are many lessons to be learned from other countries' experiences with LARC regulations. The overarching lesson is that it is imperative to include a number of voices in both the pre-market approvals process and in post-market surveillance. Academic researchers, doctors, medical professionals, consumers, distributors, manufacturers, government officials, and international regulators all have an important role to play in upholding safety and efficacy standards. In an increasingly globalized pharmaceutical industry, Canada would do well to increase participation from each of these groups in order to reduce unnecessary regulatory hurdles for manufacturers while simultaneously protecting consumers from unsafe devices.

The paper concludes with specific recommendations for Health Canada. If adopted, these recommendations will make Canada a more attractive market for LARC products while ensuring that the highest standards of safety and efficacy are upheld for Canadian contraceptive users. As a result, more LARC products will seek to enter the Canadian market, which will provide women with diverse needs and preferences with more options when it comes to selecting an effective contraceptive method.

I. Introduction

Despite the fact that contraceptive use has increased by 66 per cent over the past 10 years, unintended pregnancy rates in Canada have remained relatively stable over the same time period.[1] These statistics suggest that Canadians are either using contraceptives inconsistently or are choosing less effective contraceptive methods. Oral contraceptives are by far the most popular form of birth control in Canada, but other forms of contraception, such as intrauterine devices and subdermal implants, have much lower failure rates and are more cost effective in the long run.

One reason why Canadians may be choosing less effective forms of birth control is because some of the most effective contraceptive methods are currently unavailable in the Canadian market.[2] Multiple studies have found that Canadians consistently have access to fewer contraceptive products than women living in similar countries. For example, Canadians only had access to 35 per cent of the contraceptive products available worldwide in the early 2000s, compared with 58 per cent in the United States and 44 per cent in the United Kingdom.[3] More recent studies suggest that Canada continues to lag behind its peer countries in terms of contraceptive variety.[4]

Given everyone's unique body chemistry, and the fact that most contraceptives are designed for female use, it is imperative that women have access to a variety of contraceptive products so they can find a method that best aligns with their individual family planning needs.

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1. Lauren Vogel, "Canadian Women Opting for Less Effective Birth Control," *Canadian Medical Association Journal* 189, no. 27 (July 10, 2017).

2. Adriana Barton, "Stringent Health Canada Requirements Restrict Access to Hormonal Implants," *The Globe and Mai,* April 12, 2015, https://www.theglobeandmail.com/life/health-and-fitness/health/stringent-birth-control-requirements-keep-options-limited-for-canadians/article23882944/.

3. Dianne Azzarello and John Collins, "Canadian Access to Hormonal Contraceptive Drug Choices," *Journal of Obstetrics and Gynecology Canada* 26, no. 5 (2004).

4. Christine Troskie, et al, "Regulatory Approval Time for Hormonal Contraception in Canada, the United States and the United Kingdom, 2000-2015: A Retrospective Data Analysis," *Canadian Medical Association Journal* 4, no. 4 (November 3, 2016).

When contraceptive options are limited, women with diverse needs and preferences are left with less effective birth control methods, or sometimes no method at all.

The contraceptive disparity between Canada and other similar countries may be caused by unnecessary regulatory hurdles imposed by Health Canada, which make Canada an unattractive market for contraceptive manufacturers. Long-Acting Reversible Contraceptive (LARC) devices, such as intrauterine devices and subdermal implants, may be subject to particularly onerous regulatory hurdles since these contraceptives contain both drug and device components.

This paper will compare the regulatory procedures for LARC products in the United States, the United Kingdom, Australia, and Canada in order to determine regulatory best practices.[5] Like Canada, these countries have large developed economies with similar levels of resources devoted to health care.[6] The regulatory process in each country will be evaluated at the following stages: classification, the overall pathway to regulatory approval, clinical trials review, post-market surveillance, and regulatory transparency. Following a review of the literature, this paper will provide recommendations to Health Canada on how to improve Canada's regulatory process to ensure that women have access to an optimal variety of safe and effective long-acting reversible contraceptive choices. These recommendations are summarized in Table 1.

5. The United Kingdom's drug and device regulations are likely to change once the terms of Brexit are decided. The regulations discussed in this paper are current as of August 1, 2019.

6. CIHI, "OECD Interactive Tool: International Comparisons—Peer Countries, Canada," *Canadian Institute for Health Information*, accessed June 30, 2019, https://www.cihi.ca/en/oecd-interactive-tool-peer-countries-can.

Table 1. Summary of Recommendations to Health Canada

Classification	1. Reclassify non-hormonal IUDs as Class IV medical devices.
Autonomy	2. Maintain Health Canada's independence as a national drug and medical device regulator.
Clinical Trials	3. Update Health Canada's guidance document on clinical trial requirements for hormonal contraceptives. Remove unnecessary requirements and harmonize guidelines with the EMA and FDA.
	4. Require manufacturers of Class III and IV contraceptive devices to test their products in healthy human subjects prior to market approval.
	5. Amend the *Medical Device Regulations* to require manufacturers of high-risk contraceptive devices to adhere to Good Clinical Practice when conducting investigational testing.
Post-Market Surveillance	6. Analyze post-market data when approving a drug or device that has a long market history in another comparable jurisdiction.
	7. Amend the *Medical Device Regulations* to require high-risk contraceptive device manufacturers to report foreign adverse events to Health Canada, regardless of whether or not the foreign regulator required the company to take corrective action.
	8. Require LARC manufacturers to submit periodic safety update reports to Health Canada at a predetermined interval. Independently assess each report, regardless of if the manufacturer believes the risk-benefit ratio has changed.
Transparency	9. Develop a user-friendly online portal for drug and device adverse event reporting. Launch an educational campaign in tandem to encourage spontaneous voluntary reporting.
	10. Release Summary Basis of Decision and Regulatory Decision Summary documents for all previously approved LARC products.
	11. Post negative decision summaries for all Class III medical devices so that women can know why certain non-hormonal IUDs are not available on the Canadian market.

Ia. Background

Pharmaceutical birth control has played a pivotal role in promoting gender equality for decades. Multiple studies have shown that when women are able to utilize effective contraception to choose if and when they become pregnant, they earn higher lifetime wages, attain higher education, and have more fulfilling careers.[7] Today, certain types of contraceptives are widely available on the Canadian market, yet more than half of Canadian women will experience an unintended pregnancy in their lifetime.[8] Unintended pregnancies can strain relationships and negatively impact both the mother's and the father's mental health.[9] There is also evidence to suggest that children borne out of an unintended pregnancy perform poorer in school and may lag behind their peers in terms of social and intellectual development.[10] Therefore, reducing the unintended pregnancy rate has important implications for equality as well as for long-term societal prosperity.

Table 2 lists the failure rates of common contraceptive methods, and their prevalence in Canada. There is a difference between the "typical use" and "perfect use" failure rates because most people do not consistently adhere to the method's compliance guidelines. The birth control pill, for example, must be taken at exactly the same time every day to be most effective, and transdermal patches must be replaced regularly.

7. Adam Sonfield et al, *The Social and Economic Benefits of Women's Ability to Determine Whether and When to Have Children,* (New York: Guttmacher Institute, March 2013).

8. Marina Adshade and Niko Bell, "Governments Should Fund Birth Control, As They Do HIV Prevention," *The Globe and Mail*, January 7, 2018, https://www.theglobeandmail.com/opinion/governments-should-fund-birth-control-as-it-does-hiv-prevention/article37521476/?utm_medium=Referrer:+Social+Network+/+Media&utm_campaign=Shared+Web+Article+Links.

9. Sonfield et al, *The Social and Economic Benefits,* 21.

10. Sonfield et al, *The Social and Economic Benefits,* 23-24.

Table 2. Contraceptive Failure Rates and Canadian Prevalence of Each Method[11]

Method	Typical Use*	Perfect Use*	Canadian Prevalence**[12]
No Method	85	85	14.9
Standard Days Method	24	5	6.0[13]
Ovulation Method	24	3	
Withdrawal	22	4	11.6
Male condom	18	2	53.4
Combination Pill	9	0.3	43.7[14]
Progestin only pill	9	0.3	
Transdermal Patch	9	0.3	1.2
Vaginal ring	9	0.3	0.6
Injection	6	0.2	2.4
Copper IUD	0.8	0.6	2.3
Female sterilization	0.5	0.5	6.0
Hormonal IUD	0.2	0.2	2.0
Vasectomy	0.15	0.1	7.4
Subdermal Implant	0.05	0.05	0.1

* Number of women out of 100 experiencing an unintended pregnancy during the first 12 months of use

** Percentage of sexually active Canadian women using each method of contraception

11. Adapted from James Trussel, "Contraceptive Failure in the United States," *Contraception* 83, no.5, (May 2011): 13.

12. Amanda Black, Qiuying Yang, Shi Wu Wen, Andre Lalonde, Edith Guilbert, and William Fisher, "Contraceptive Use Among Canadian Women of Reproductive Age: Results of a National Survey," *Journal of Obstetrics and Gynaecology Canada* 31, no. 7 (2009): 627, 632; may add up to more than 100 as women were able to report more than one method.

13. Combined total of women who reported using the "rhythm" and "natural family planning" methods.

14. Combined total of women who reported using an oral contraceptive method, not including emergency contraceptives.

Some of the most effective contraceptive methods—such as intrauterine devices and subdermal implants—are the most underutilized in Canada. Intrauterine devices (IUD) and subdermal implants belong to a class of contraceptives often referred to as Long-Acting Reversible Contraceptives (LARC), or "set and forget" methods. LARCs provide effective contraception for years at a time with minimal upkeep required by the user. Since "set and forget" methods require almost no maintenance after insertion, their "typical use" and "perfect use" failure rates are very similar. LARCs are particularly appealing because fertility returns to normal once the device is removed, they have very low failure rates with typical use, and they are the most cost-effective option in the long run.[15]

Indeed, several studies have suggested that increasing LARC use could have a profound impact on reducing the unintended pregnancy rate.[16] Additionally, professional medical associations also support increasing LARC use. For example, The American College of Obstetricians and Gynecologists endorses LARC products as a first-line contraceptive due to their superior effectiveness and high user satisfaction when compared with other reversible methods.[17] The Canadian Pediatric Society echoes this recommendation, and suggests that LARCs should be considered a "first tier" option when trying to prevent pregnancy, especially for adolescents.[18] Despite these professional endorsements, less than five per cent of Canadian

15. Ritu Joshi, Suvarna Khadilkar, and Madhuri Patel, "Global Trends in Use of Long-Acting Reversible and Permanent Methods of Contraception: Seeking a Balance," *International Journal of Gynecology and Obstetrics* 131 (September 30, 2015): 61-62.

16. P.D Blumenthal, A. Voedisch, and K. Gemzell-Danielsson, "Strategies to Prevent Unintended Pregnancy: Increasing Use of Long-Acting Reversible Contraception," *Human Reproduction Update* 17, no. 1, (July 15, 2010); Colleen McNicholas and Jeffrey F. Peipert, "Initiation of Long-Acting Reversible Contraceptive Methods (IUDs and Implant) at Pregnancy Termination Reduces Repeat Abortion," *BJOG: An International Journal of Obstetrics and Gynaecology* 119, (2012).

17. Committee on Gynecologic Practice Long-Acting Reversible Contraception Working Group, *Committee Opinion no. 642: Increasing Access to Contraceptive Implants and Intrauterine Devices to Reduce Unintended Pregnancy,* (Washington, DC: The American College of Obstetricians and Gynecologists, October 2015).

18. Canadian Paediatric Society, "Contraceptive Care for Canadian Youth," *Canadian Paediatric Society*, June 12, 2018, https://www.cps.ca/en/documents/position/contraceptive-care.

contraceptive users choose a LARC method, which is particularly low when compared to Scandinavian and Asian countries, where up to 40 per cent of women use LARCs.[19]

Canadian women may be less likely to choose a LARC product because many LARCs—including subdermal implants and many types of IUDs—are unavailable in Canada. Additional contributing factors may include prohibitive out-of-pocket costs, since LARC products tend have larger up-front costs than other contraceptives; limited insurance coverage, since some health plans do not include coverage for non-hormonal IUDs; lack of access to a medical professional since not all doctors are trained to insert LARCs; difficulty taking time off of work, since obtaining a LARC product typically requires at least two doctor's appointments and a rest period after insertion; and lack of information about contraceptive options. However, before policy makers can begin to address barriers to access, it is imperative to ensure that a variety of safe and effective LARC products are available in the Canadian market. Improving access to effective contraceptives starts with ensuring that Canada's regulatory system is properly equipped to approve and monitor the sale of LARCs.

Table 3 shows LARC use in Canada, the United States, Australia, and the United Kingdom, as well as the number of brands approved for use of each LARC method.

19. Kai J. Buhling, Nikki B. Zite, Pamela Lotke, and Kirsten Black, "Worldwide Use of Intrauterine Contraception," *Contraception* 89, (2014): 164.

Table 3. Contraceptive Prevalence

	Total Contraceptive Use*	Total LARC Use **	Total Hormonal IUD Use**	Total non-hormonal IUD use**	Total Contraceptive Implant Use**	Number of approved Hormonal IUDs	Number of approved Non-Hormonal IUDs	Number of approved implants
Canada[20]	65.2%	4.4%	2.3%	2.0%	0.1%	3	12	0
United States[21]	61.7%	11.6%	7.6%	2.7%	1.3%	4	1	2
United Kingdom[22]	73%	10%	6%	2%	2%	5	20	1
Australia[23]	66%	11%	5.6%	0.5%	4.9%	3	4	1

*as a percent of reproductive aged women **as a percent of female contraceptive users

20. Black et al., "Contraceptive Use Among Canadian Women," 632, 634; Canada, Government of Canada, "Search Results For: Levonorgestrel," *The Drug and Health Product Register,* accessed November 22, 2018; Canada, Government of Canada, "Device Name Results Summary: Intrauterine Device," *Medical Devices Active Licenses Search,* accessed November 28, 2016.

21. Megan L. Kavanaugh and Jenna Jerman, "Contraceptive Method Use in the United States: Trends and Characteristics Between 2008, 2012 and 2014," *Contraception* 77, no. 1 (January 2018): 10; Megan L. Kavanaugh, Jenna Jerman, and Lawrence B. Finer, "Changes in Use of Long-Acting Reversible Contraceptive Methods Among U.S. Women, 2009-2012," *Obstetrics and Gynecology* 126, no. 5 (November 2015): 920, 921, 924; Drugs@FDA: FDA Approved Drug Products, "Levonorgestrel," *U.S. Food and Drug Administration,* accessed June 30, 2019, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process; Drugs@FDA: FDA Approved Drug Products, "Copper," *U.S. Food and Drug Administration,* accessed June 30, 2019, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process; Drugs@FDA: FDA Approved Drug Products, "Etonogestrel," *U.S. Food and Drug Administration,* accessed June 30, 2019, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

22. David Cibula, "Women's Contraceptive Practices and Sexual Behaviour in Europe," *The European Journal of Contraception and Reproductive Health Care* 13, no. 4, (2008): 367; Mary Harding, "Intrauterine System," *Patient,* last modified October 30, 2017, https://patient.info/sexual-health/long-acting-reversible-contraceptives-larc/intrauterine-system; Hayley Willacy, "Intrauterine Contraceptive Device," *Patient*, last modified May 21, 2019, https://patient.info/doctor/intrauterine-contraceptive-device-pro?fbclid=IwAR3jdvW2RQYxddpFy4SZs7LwEUgjftCIDii3NW20tjgrX_8WUvfm1MbpW-I#nav-5; Mary Harding, "Contraceptive Implant," *Patient*, last modified October 30, 2017, https://patient.info/sexual-health/long-acting-reversible-contraceptives-larc/contraceptive-implant.

23. Juliet Richters et al., "Contraceptive Practices Among Women: The Second Australian Study of Health and Relationships," *Contraception* 94, (June 2016): 550-551; ARTG Search, "Intrauterine Drug Delivery System," *Australian Government Department of Health Therapeutic Goods Administration*, accessed June 30, 2019, https://tga-search.clients.funnelback.com/s/search.html?query=intrauterine+drug+delivery+system&collection=tga-artg; ARTG Search, "Intrauterine Device," *Australian Government Department of Health Therapeutic Goods Administration,* accessed June 30, 2019, https://tga-search.clients.funnelback.com/s/search.html?query=%22intrauterine+device%22&collection=tga-artg&start_rank=1; ARTG Search, "Subcutaneous Implant," *Australian Government Department of Health Therapeutic Goods Administration,* accessed June 30, 2019, https://tga-search.clients.funnelback.com/s/search.html?query=%22subcutaneous+implant%22&collection=tga-artg.

Of particular interest is the subdermal implant, a matchstick-sized rod inserted into the upper arm. The implant is a combination medical device that releases hormones to prevent egg fertilization and is effective for up to 5 years. The device has been safely administered in over 80 countries for years and is particularly popular among teenagers.[24] Subdermal implant use is so low in Canada because no version of the device is currently approved for sale.[25]

Also missing from the Canadian market are a variety of IUDs. Intrauterine devices are inserted into the uterus by a doctor, and are effective for up to 10 years, depending on the model. IUDs are sorted into three main categories: copper-containing devices (non-hormonal IUDs), hormone-releasing intrauterine systems (hormonal IUDs), and IUDs made of plastic or steel (inert IUDs). There are 3 different brands of hormonal IUDs available in Canada, 12 copper IUDs, and no inert IUDs.[26] However, the number of approved devices does not necessarily imply product variety. Of the 12 copper IUDs approved for use in Canada, four are generic versions of previously approved devices. [27] Furthermore, all IUDs in Canada are T-shaped. The United Kingdom, by comparison, has U-shaped, frameless, and spherical IUDs, which were all designed to try and mitigate some of the adverse side effects that accompany traditional T-shaped devices.[28] The shape and size of a uterus can vary from woman to woman, so selecting the right size of IUD can reduce the risk of uterine perforation or dislodgement.[29] Additionally, hormonal

24. Adriana Barton, "Stringent Health Canada Requirements Restrict Access to Hormonal Implants," *The Globe and Mail,* April 12, 2015, https://www.theglobeandmail.com/life/health-and-fitness/health/stringent-birth-control-requirements-keep-options-limited-for-canadians/article23882944/.

25. Subdermal implant use is not set at 0% because some women receive the implant abroad prior to coming to Canada.

26. Inert IUDs are not marketed for sale in any of these four countries and have decreased in popularity in other countries in recent years. Therefore, inert IUDs will generally not be discussed in this paper.

27. Generic pharmaceuticals and medical devices have the same effectiveness as their brand name counterparts but are sold at a fraction of the price. See Laura Ruth, "The Future of Devices is Generic," September 23, 2011, https://www.mddionline.com/future-devices-generic.

28. David Delvin, "Contraceptive Coils (IUDs)," *Net Doctor,* May 17, 2016. https://www.netdoctor.co.uk/conditions/sexual-health/a2212/contraceptive-coils-iuds/.

29. Dirk Wildemeersch, "New Intrauterine Technologies for Contraception and Treatment in Nulliparous/Adolescent and Parous Women," *Facts, Views, and Vision in Obstetrics, Gynecology and Reproductive Health* 1, no. 3 (2009): 225-226.

IUDs release varying levels of hormones, which comes with a range of advantages and disadvantages depending on a woman's individual body chemistry. For example, the higher the hormone dosage, the more likely a LARC product is to stop a woman's menstrual cycle.[30] Depending on a woman's preferences and pre-existing conditions, this could be considered a benefit or a disadvantage. Non-hormonal IUDs can also differ by the amount of copper wire covering the device, which affects its failure rate.[31] A copper IUD's failure rate decreases as more copper is added to the surface area of the device, but menstrual bleeding has also been known to become heavier as the copper content increases. Women with low iron stores who opt for a non-hormonal IUD may prefer an IUD with a lower copper content to reduce menstrual blood loss.[32]

It is important for women to have a variety of LARC products to choose from so that they can determine with their doctors which option will work best for their individual needs and preferences. Additionally, encouraging competition among LARC manufacturers may also lower prices, which is especially important for women who need to pay out of pocket for contraceptives.[33]

The variety of contraceptives that a woman can choose from fluctuates widely depending on which country she lives in.[34] There are several reasons why a medicine may be available in one country but not another, even when both countries have similar safety standards. For example, the manufacturer may decide not to apply for approval in a particular region if they

30. NHS Direct Wales, "Intrauterine System (IUS)," *NHS Direct Wales,* last modified April 5, 2016. https://www.nhsdirect.wales.nhs.uk/encyclopaedia/i/article/intrauterinesystem(ius).

31. Bliss Kanershiro and Tod Aeby, "Long-Term Safety, Efficacy, and Patient Acceptability of the Intrauterine Copper T-380A Contraceptive Device," *International Journal of Women's Health* 2 (August 9, 2010).

32. AT Andrade and Orchard E. Pizarro, "Quantitative Studies on Menstrual Blood Loss in IUD Users," *Contraception* 36, no.1 (1987).

33. Chintan V. Dave, Abraham Hartzema, and Aaron S. Kesselheim, "Prices of Generic Drugs Associated with Numbers of Manufacturers," *The New England Journal of Medicine* 377, no. 26 (December 28, 2017): 2597-2598.

34. See Table 3.

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deem their product unprofitable due to small market size or lack of demand. High application fees or onerous regulatory requirements may also deter a manufacturer from bringing its product to a particular country if the regulatory burden is too large relative to the size of the potential market.

Canada has long faced criticism that its regulatory guidelines have deterred a number of new medicinal products from entering the country. A 2004 study surveyed sponsors of 12 contraceptive products that were approved in the United States, Europe, and Australia to find out why these products were not also available in the Canadian market. The survey found that 11 of the 12 products were unavailable because of the Canadian regulatory environment, Health Canada rejections, or inactivity in the review process.[35] Although these products were approved by regulatory bodies in other jurisdictions with similar safety standards and procedural requirements, these products were held up in the Canadian approval process.

More recently, a 2016 study found that Canadian women wait longer for novel contraceptive methods and have fewer contraceptive options than women in the United States and the United Kingdom.[36] The study defined a contraceptive as "novel" if the product involved "either a new active ingredient…or a new drug delivery system."[37] The reason for the lag in contraceptive approvals is two-fold: manufacturers delay their application to Canada after first receiving approval elsewhere, and the time between the initial application and final approval is longer in Canada than in other jurisdictions.[38] Additionally, some manufacturers view Canada as an unprofitable market, so they never seek Health Canada approval. As a result, Canadian women are left with fewer contraceptive options.

35. Azzarello and Collins, "Canadian Access to Hormonal Contraceptive Drug Choices," 497.
36. Troskie et al., "Regulatory Approval Time."
37. Troskie, et al, "Regulatory Approval Time," 655-656.
38. Troskie, et al, "Regulatory Approval Time," 655-656.

Given Canada's relatively small market size, drug and device manufacturers often seek market approval in other larger markets prior to seeking Health Canada approval. However, the time-to-approval period in Canada is five times longer for contraceptives than for other drug products.[39]

There may be room for regulatory adjustments in the Canadian contraceptive approvals process to ensure that women have timely access to a range of contraceptive options, especially LARCs. However, when evaluating medical regulations, it is important to balance the need for consumer choice with the need for stringent safety and efficacy requirements. This is especially true in the wake of the breast implant scandal, which was unveiled as part of a larger initiative of investigative journalism examining the global implants industry.[40] The investigation revealed that a popular brand of textured breast implants was linked to several complications, including a rare type of cancer. It also revealed that implant manufacturers presented sparse clinical trial data to regulators, which allowed unsafe devices to enter the market.[41] The implant scandal highlights the need for medical devices to undergo rigorous safety testing, which until recently, was not required by many regulatory bodies. Furthermore, regulatory documents are often not publicly accessible, making it difficult for patients to learn more about medical devices. Patients rely on their doctors to reassure them that a device is safe; however, this becomes problematic when doctors are given inaccurate or incomplete information. Post-market surveillance requirements were often lax or voluntary, meaning that reports of medical device malfunctions were kept confidential or were never filed. Given the heightened public awareness surrounding the dangers

39. Azzarello and Collins, "Canadian Access to Hormonal Contraceptive Drug Choices," 496.

40. Hilary Osborne, "From Orange Bags to Essure: Why We're Examining the Implants Industry," *The Guardian,* November 25, 2018, https://www.theguardian.com/society/2018/nov/25/from-orange-bags-to-essure-why-were-examining-implants-industry.

41. Hannah Devlin, Hilary Osbourne, and Caelainn Barr, "Breast Implants Study Reveals Serious Safety Concerns," *The Guardian*, November 26, 2018, https://www.theguardian.com/society/2018/nov/26/breast-implants-study-reveals-serious-safety-concerns.

of insufficient regulatory policy, it is imperative that drug and medical device regulations balance the need for open competition with high safety standards.

Ib. Methodology

To conduct the research for this study, I utilized qualitative methods, including a review and analysis of key policy documents, legislation, and academic literature from Canada, the United States, the United Kingdom, and Australia. As previously discussed, these jurisdictions were selected because like Canada, these countries have large developed economies with similar levels of resources devoted to health care.[42] Examining regulatory procedures in these jurisdictions is particularly topical because all four of these countries is either currently, or has already, re-evaluated their medical device directives in light of the breast implant scandal.[43]

In order to determine gaps in Canada's regulations, I compared and contrasted five main stages of the regulatory process with each comparator jurisdiction. These five stages include: classification, an overview of the regulatory process, clinical trials review, post-market surveillance, and transparency of the regulatory process. I identified the regulatory process in each comparator jurisdiction by analyzing publicly available information on government websites and referencing the relevant legislation in each country. After noting the differences between each jurisdiction and Canada, I determined which gaps were the most concerning by consulting academic literature. Additionally, I noted best practices accepted by international tribunals for medical device and pharmaceutical regulations and noted where Canada had not yet adopted these practices.

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42. CIHI, "OECD Interactive Tool: International Comparisons—Peer Countries, Canada," *Canadian Institute for Health Information*, accessed June 30, 2019, https://www.cihi.ca/en/oecd-interactive-tool-peer-countries-can.

43. Sasha Chavkin, "The Implant Files Sparked Reform Around the World. Here's Why We're Still Reporting," *ICIJ*, February 27, 2019, https://www.icij.org/investigations/implant-files/the-implant-files-sparked-reform-from-around-the-world-heres-why-were-still-reporting/; Will Fitzgibbon, "Australia Announces Medical Device Action Plan to Address Patient Concerns," *ICIJ*, April 8, 2019, https://www.icij.org/investigations/implant-files/australia-announces-medical-device-action-plan-to-address-patient-concerns/.

The recommendations for Health Canada were developed with two main policy goals in mind: Reducing the unnecessary regulatory burden for LARC manufacturers, given current practices in other leading jurisdictions, and upholding an internationally-accepted standard for safety and efficacy of approved contraceptive products.

I conducted semi-structured interviews with experts in pharmaceutical policy to receive feedback on the proposed recommendations to Health Canada. Ethics approval for this project was obtained from the University of Calgary Conjoint Faculties Research Ethics Board. Interview participants were identified from a literature review on pharmaceutical and medical device policy in Canada and were recruited through targeted email invitations.

The research findings and recommendations are discussed at each stage of the regulatory process, starting with classification.

II. Classification

Depending on the country, LARC products are either regulated as pharmaceuticals, medical devices, or a combination of the two, referred to as combination products. The regulatory guidelines—and therefore the safety and efficacy requirements—differ for each product depending on how it is classified. LARC products, like all contraceptive products, may also have additional regulatory requirements in certain jurisdictions on top of standard pharmaceutical regulations to provide an additional level of safety.[44] While there has been some effort to standardize the way that medical products are classified across jurisdictions, regulations for medical devices, including combination products, continue to differ across the globe.

44. L. Mastroianni, PJ Donaldson, TT Kane, "Regulation and Contraceptive Development," *Developing New Contraceptives: Obstacles and Opportunities*, Washington, DC: National Academies Press (1990); Bureau of Metabolism, Oncology and Reproductive Sciences, "Guidance for Industry: Clinical Development of Steroidal Contraceptives Used by Women," *Government of Canada,* October 29, 2002.

IIa. Canada

Both hormonal and non-hormonal IUDs take the form of a small rod, which is inserted by a doctor into the uterus. The progestin released in hormonal IUDs prevents pregnancy by preventing ovulation and thickening the cervical mucus, thus blocking sperm from reaching an egg. The hormones in a subdermal implant prevent pregnancy in the same way, the only difference being that the implant is placed in the upper arm instead of the uterus. The way that copper IUDs prevent pregnancy is not universally understood; the product information in different countries list varying reasons for how the device prevents pregnancy. In Canada, package inserts for non-hormonal IUDs generally attribute its contraceptive properties to the copper component, which acts as a spermicide within the uterus.[45]

In Canada, both hormonal and non-hormonal IUDs are subject to the *Food and Drugs Act*, but because the two products prevent conception through different mechanisms, they are subject to different sets of regulations.

Health Canada defines a combination product as "a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or device), such that the distinctive nature of the drug component and the device component is integrated into a singular product."[46] Since hormonal IUDs combine a drug component (levonorgestrel) and a device component (the plastic frame) into a single product, they are considered a drug/medical device combination product.[47] Under this definition, a non-hormonal IUD would not be considered a combination product since the copper wire, on its own, is not considered a drug in Canada.

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45. Bayer Canada, *Intrauterine Device: Nova-T Model Cu 200 Ag* (Mississauga, ON: Bayer Inc., July 2, 2015).

46. Canada, Health Canada, *Drug/Medical Device Combination Products* (Ottawa, ON: Health Canada, 2006): 1.

47. Alain Musende, *Health Canada's Regulatory Oversight Medical Devices Advertising* (Ottawa, ON: Health Canada, Government of Canada, May 10, 2016): 30-31.

Prior to 2006, combination devices in Canada were required to comply with to two sets of regulations: the drug component needed to satisfy the *Food and Drug Regulations,* and the device component needed to satisfy the *Medical Device Regulations*.[48] This meant that because hormonal IUDs contain a regulated reproductive drug, they were required to obtain approval as both a medical device and as a pharmaceutical, while non-hormonal IUDs only needed to obtain approval as a medical device.[49] It is important to understand the regulatory history of combination devices because it was through this system that the first hormonal IUD in Canada received approval in 2001.

While medical devices in Canada were typically approved in under six months, it could take years for a new drug to get regulatory approval from Health Canada.[50] Because combination devices had to go through two sets of regulations, approval time was substantially longer for hormonal IUDs than it was for copper IUDs.[51] In order to "ensure timely access to drug/medical device combination products," Health Canada made revisions to their policy in 2006 so that the entire combination product would only be subject to either the *Food and Drug Regulations* or the *Medical Devices Regulations*, depending on the product's primary mode of action.[52]

Since hormonal IUDs achieve their primary purpose (contraception) through its drug component, hormonal IUDs are now regulated as drugs and fall under the directive of the *Food and Drug Regulations*.[53] Although subdermal implants are currently not approved for use in Canada, they would likely also fit into this category.[54] Since copper IUDs do not contain a drug

48. Canada, Health Canada, *Drug/Medical Device Combination Products*, 1.
49. Musende, *Health Canada's Regulatory Oversight,* 30-31.
50. Anne Snowdon, Richard Zur, and Jeremy Shell, *Transforming Canada Into a Global Centre for Medical Device Innovation and Adoption* (London, ON: Richard Ivey School of Business, June 2011): 26.

51. Anne Snowdon et al., *Transforming Canada,* 26.
52. Canada, Health Canada, *Drug/Medical Device Combination Products,* 1.
53. Canada, Health Canada, *Drug and Medical Device Combination Product Decisions* (Ottawa, ON: Health Canada July 21, 2014); Canada, Government of Canada, "Search Results For: Levonorgestrel."
54. Canada's *Drug and Medical Device Combination Product* Decisions document lists "implants who primary purpose is to release a drug" as combination products that have been classified as drugs.

component, they are regulated strictly as medical devices and therefore are subject only to the *Medical Device Regulations*. This means that hormonal and copper IUDs are approved by different regulatory bodies within Health Canada and are subject to different regulatory requirements.

Canada categorizes medical devices into four classes based on the risk associated with their use, with Class I presenting the lowest risk, and Class IV presenting the highest risk. The higher the risk class, the more regulatory oversight required for market approval. Since the copper IUD is "invasive via a body orifice" and remains in the body "for 30 consecutive days or longer", it is considered a Class III medical device, according to Canada's guidelines.[55]

IIb. United Kingdom

When Canada decided to subject combination products to only one set of regulations, it did so in part to align itself more closely with what was being done in the European Union.[56] As a result, the classification process for combination devices is similar in the United Kingdom and Canada, since the United Kingdom generally follows the European Union system of drug and medical device classification.[57]

Like Canada, the United Kingdom classifies non-hormonal IUDs as medical devices, and hormonal IUDs as combination products. The European Union goes one step further to define hormonal IUDs as "integral" combination products because the medicinal product and device form a single integrated product. Integral combination products are subject to different regulatory requirements than co-packaged combination products, that is, devices whose

55. Canada, Health Canada, *Guidance Document: Guidance on the Risk-Based Classification System for Non-In Vitro Diagnostic Devices (Non-IVDDs),* (Ottawa, ON: Health Canada, June 12, 2015): 7.

56. Canada, Health Canada, *Drug/Medical Device Combination Products,* 1.

57. United Kingdom, Medicines and Healthcare Products Regulatory Agency, "Medical Devices: How to Comply With the Legal Requirements," *Government of the United Kingdom*, last modified February 26, 2019, https://www.gov.uk/guidance/medical-devices-how-to-comply-with-the-legal-requirements; The United Kingdom's drug and device regulations are likely to change once the terms of Brexit are decided. The regulations discussed in this paper are current as of August 1, 2019.

medicinal products are separate items contained in the same package.[58] Subdermal implants are also considered Integral Combination Products. Integral combination products are regulated as either drugs or devices depending on their principle intended action. Since the principle intended action is achieved by the medicine component, both hormonal IUDs and subdermal implants are regulated as medicines under Directive 2001/83/EC and Regulation No 726/2004.[59]

Like Canada, the European Union has four classes of medical devices, but they are labelled as Class I, IIa, IIb, and III. The requirements for each class are similar to Canada's requirements, although devices are not always placed into the same corresponding class. [60] For example, some Class I devices in Canada are considered Class IIa in the EU. While Canada's Class III is similar to Europe's Class IIb, non-hormonal IUDs are regulated as Class III in both jurisdictions.[61] Despite the same class title, the regulatory requirements differ, since Class III in the EU generally corresponds to Class IV in Canada.[62]

Non-hormonal IUDs are also listed under Rule 14 of the EU Medical Devices Guidance Document, which states that "all devices used for contraception" are considered Class IIb devices, "unless they are implantable or long-term invasive devices, in which case they are Class III." [63] Contraceptive intrauterine devices are then listed as fitting into this category. The

58. European Medicines Agency, "Medicinal Products that Include a Medical Device ('Combination Products')," *European Medicines Agency*, accessed July 15, 2019, https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices#medicinal-products-that-include-a-medical-device-('combination-products')-section.

59. European Medicines Agency, "Medical Devices," *European Medicines Agency*, accessed July 4, 2019, https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices.

60. Canada, Life Sciences Branch, Industry Canada, *Quality System Requirements for Medical Devices: Reference Guide for Manufacturers selling Medical Devices in Europe, Canada, and the United States, 2005 Version,* (Ottawa, ON: Industry Canada, 2005): 66.

61. Canada, Life Sciences Branch, Industry Canada, *Quality System Requirements,* 46, 66; European Commission, DG Health and Consumer, *Medical Devices: Guidance Document—Classification of Medical Devices,* (Brussels: European Commission, June 2019): 46; Canada, Health Canada, *Guidance Document: Guidance on the Risk-Based Classification System,* 1.

62. Canada, Life Sciences Branch, Industry Canada, *Quality System Requirements,* 66.

63. European Commission, DG Health and Consumer, *Medical Devices,* 47.

document also clarifies that "intrauterine contraceptives whose primary purpose is to release progestogens [hormonal IUDs] are not medical devices."[64]

IIc. The United States

Like the European Union and Canada, the United States regulates combination devices as either drugs or medical devices, depending on the product's primary mode of action.[65] What sets the United States apart, is that it regulates all LARCs—including non-hormonal IUDs—as drugs.

The prevailing cause for the classification difference dates back to the Dalkon Shield fiasco of the 1970s. The Dalkon Shield was an inert, plastic intrauterine device made roughly in the shape of a beetle. It was marketed as a safer alternative to the birth control pill, and quickly grew to dominate the IUD market. However, due to serious design flaws and insufficient safety testing, it caused tens of thousands of women to suffer from a range of complications including sepsis, sterility, pelvic inflammatory disease, and even death.[66] The device was removed from the American market four years after its debut and caused demand for other types of safer IUDs to plummet.[67]

In the wake of this crisis, the Food and Drug Administration (FDA) was given wider authority through the *Medical Device Amendment* to regulate and approve medical devices before they entered the market.[68] With this new authority, the FDA determined that all intrauterine devices, including those that "incorporate heavy metals, drugs, or other active

64. European Commission, DG Health and Consumer, *Medical Devices,* 47.

65. Federal Drug Administration, Office of Combination Products, *Frequently Asked Questions About Combination Products* (Silver Spring, MD: Office of Combination Products, last modified February 15, 2018): 4; the United States also has its own category for Biologics.

66. Robin Marantz Henig, "The Dalkon Shield Disaster," *The Washington Post,* November 17, 1985, https://www.washingtonpost.com/archive/entertainment/books/1985/11/17/the-dalkon-shield-disaster/6c58f354-fa50-46e5-877a-10d96e1de610/?noredirect=on&utm_term=.6de909f65bb4.

67. Henig, "The Dalkon Shield Disaster."

68. Susan Bartlett Foote, "Loop and Loopholes: Hazardous Device Regulation Under the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act," *Ecology Law Quarterly* 7, no.1 (March 1978).

substances" should be regulated as drugs.[69] Since the FDA's drug regulations are more stringent than device regulations, some health care professionals postulate that policy makers decided to mandate drug classification for all IUDs as a catch-all way to prevent another Dalkon Shield disaster.[70]

Only one brand of non-hormonal IUD is currently available in the United States, the ParaGard. The package insert for the ParaGard states that its contraceptive effectiveness is only "enhanced" by the copper in the device.[71] This view attributes the device's contraceptive properties mainly to the presence of the polyethylene frame in the uterus—not the copper.[72] If the device achieves its most important therapeutic action (contraception) primarily through its device component, then according to the guidance documents published by the Office of Combination Products, the entire combination product *should* be regulated as a medical device. However, the Patient Info portion of the Approval Package for the ParaGard in the United States further states that "how the IUD prevents pregnancy is not completely understood," which may have made its classification difficult.[73]

Regardless of the method's true primary mode of action, the Code of Federal Regulations explicitly states that "intrauterine devices for human use for the purpose of contraception that incorporate heavy metals, drugs, or other active substances" will be regulated as drugs.[74] Since

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69. "Food and Drugs," *Code of Federal Regulations*, title 21 (2019): 23, https://www.govinfo.gov/content/pkg/CFR-2019-title21-vol5/pdf/CFR-2019-title21-vol5.pdf.

70. Caroline Beaton, "Why Does America Have Fewer Types of IUDs Than Other Countries?" *The Atlantic*, April 18, 2017, https://www.theatlantic.com/health/archive/2017/04/why-america-has-fewer-iuds-than-other-countries/523077/.

71. CooperSurgical, *ParaGard Intrauterine Contraceptive* (Trumbull, CT: Cooper Surgical, Inc., January 2018): 1.

72. Joseph B. Stanford, Rafael Mikolajczyk, "Mechanisms of Action of Intrauterine Devices: Update and Estimation of Postfertilization Effects," *American Journal of Obstetrics and Gynecology* 187, no. 6 (December 2002).

73. Center for Drug Evaluation and Research, *Approval Package For Application Number 18-680 ParaGard Copper T Model TCU 380A Intrauterine Contraceptive* (Silver Spring: MD, Federal Drug Administration, November 15, 1984).

74. "Food and Drugs," *Code of Federal Regulations*, title 21 (2019): 23.

copper is an "active substance" and is also sometimes considered a "heavy metal", copper non-hormonal IUDs fall into this category.

For combination products whose classification has not been predetermined through legislation—such as subdermal implants—the Office of Combination Products is responsible for assigning the product to the primary regulatory agency that best aligns with the product's primary mode of action. The product will then follow its assigned agency's application type for premarket review and must adhere to the other regulatory standards relevant to that agency. The primary agency may also consult with other centres during the review of the combination product.[75] Since the subdermal implant's primary mode of action is caused by its drug component, its primary agency is the Center for Drug Evaluation and Research (CDER), with the Center for Devices and Radiological Health (CDRH) consulting on the safety of the device component. Thus, all intrauterine devices and subdermal implants are subject to the same regulatory process in the United States.

IId. Australia

Hormonal and non-hormonal IUDs are both considered combination products in Australia.[76] Like all other jurisdictions discussed so far, a combination product in Australia is classified as a device if it does not achieve its primary intended action through its drug component, and is regulated as a medicine if it does. [77] As such, hormonal IUDs and subdermal implants are regulated as drugs since they prevent conception through their pharmacological components. In fact, hormonal IUDs are marketed as "intrauterine drug delivery systems," to

75. KJ Lauritsen and T Nguyen, "Combination Products Regulation at the FDA," *Clinical Pharmacology and Therapeutics* 85, no. 5 (May 11, 2009): 469.

76. Australia, Department of Health, Therapeutic Goods Administration, *Australian Medical Devices Guidance Document Number 35: Device—Medicine Boundary Products* (Symonston, Australia: Therapeutic Goods Administration, November 2005): 11-12; Australia's drug and medical device regulations and classification systems are currently under review.

77. Australia, Department of Health, Therapeutic Goods Administration, *Australian Medical Devices Guidance Document.*

further clarify that the device component mainly serves as a means to deliver the drug in the uterus.

Publicly available product information for copper-bearing non-hormonal IUDs in Australia credit the device's contraceptive properties to "a pronounced sterile inflammatory reaction, which takes place as a result of a foreign body response in the uterus."[78] This explanation clearly aligns with Australia's decision to regulate non-hormonal IUDs as devices, since the polyethylene frame—not the copper—is listed as the primary mode of action used to prevent pregnancy. The presence of a foreign body in the uterus is also listed as one of ways the Mirena hormonal IUD prevents pregnancy, but its contraceptive properties are largely credited to the presence of levonorgestrel.[79]

Since non-hormonal IUDs are considered medical devices, they also are sorted into a risk class. Australia's medical device classification system is similar to the European Union's, by labelling each class as I, IIa, IIb, or III, with the class number increasing with the level of risk.[80] Under Rule 5.2(2), *Devices for Contraception or Prevention of Sexually Transmitted Diseases*, non-hormonal contraceptive intrauterine devices are listed as Class III because they are an implantable or invasive device intended for long-term use.[81]

IIe. Analysis

Table 4 summarizes how subdermal implants and hormonal and non-hormonal IUDs are classified in Canada, the United States, the United Kingdom, and Australia.

78. Australia, Department of Health, Therapeutic Goods Administration, *Public Summary: Basin Medical Pty Ltd—Mona Lisa Cu375—Intrauterine Device, Metal-Covered* (Symonston, Australia: Therapeutic Goods Administration, March 16, 2018).

79. Australia, Department of Health, Therapeutic Goods Administration, *Australian Product Information: Mirena (Levonorgestrel) Intrauterine Drug Delivery System* (Symonston, Australia: Therapeutic Goods Administration, October 11, 2018): 13.

80. Australia, Department of Health, Therapeutic Goods Administration, *Australian Regulatory Guidelines for Medical Devices,* (Canberra, Australia: Commonwealth of Australia, May 2011): 74.

81. Australia, Department of Health, Therapeutic Goods Administration, *Australian Regulatory Guidelines for Medical Devices*, 98.

Table 4. Contraceptive Device Classification

	Canada	United States	United Kingdom	Australia
Non-hormonal IUD	Class III Medical Device*	Drug	Class III Medical Device**	Class III Medical Device**
Hormonal IUD	Drug	Drug	Drug	Drug
Subdermal Implant	Not approved	Drug	Drug	Drug

* On a scale of I to IV ** On a scale of I to III

Intrauterine devices have the potential to cause severe and long-term damage if designed poorly, as demonstrated by the Dalkon Shield fiasco. Indeed, given the long-term and implantable nature of LARC products, it is imperative that all IUDs and subdermal implants are classified correctly so they can be subject to the appropriate regulations. Most countries agree that hormonal IUDs and subdermal implants primarily function as drug products and should be regulated as such. However, significant differences still remain in the classification of copper-containing non-hormonal IUDs.

Most countries consider copper IUDs to function primarily as medical devices, with the United States as the sole outlier. If the FDA's rationale to regulate all IUDs as drugs was truly to ensure that they were subject to a more stringent approval process, then perhaps the issue was in the FDA's lax medical device regulations, not in the IUD's classification. Classifying all non-hormonal IUDs as drugs may not have been the appropriate solution, especially since the FDA's own guidance document suggests that non-hormonal IUDs should be considered devices. Indeed, the FDA's separate classification could pose a large regulatory burden for manufacturers looking to import copper IUDs to the United States when they have already been approved as medical devices in other jurisdictions.

In 1993, government and industry representatives from Canada, the European Union, the United States, Australia, and Japan founded the Global Harmonization Task Force (GHTF) in an attempt to converge regulatory standards around the world for medical devices. The Task Force saw harmonization as an important way to "decrease the cost of gaining regulatory compliance" for manufacturers and as an essential step to ensuring that patients receive "earlier access to new technologies and treatments."[82] The task force hoped that global harmonization would lead to international recognition of pre-market approvals from other jurisdictions, thus reducing duplicative reviews and alleviating the burden on national regulators and manufacturers.[83] The task force authored several guidance documents outlining suggested principles for regulatory harmonization, including guiding principles for medical device classification. Harmonizing classification schemes was considered an important first step towards regulatory convergence, since classification determines a device's overall approval process.

The GHTF recommended that classification systems should include four risk classes, with the highest class representing the highest risk.[84] The guidance document also suggests that "all devices used for contraception" should be considered the third highest risk class, "unless they are implantable or long-term invasive devices," in which case they should be considered the highest risk class.[85] The document then lists intrauterine contraceptive devices as an example. The European Union's and Australia's guidance documents align with this recommendation. Indeed, the European Union's classification system was explicitly influenced by the classification rules established by the GHTF.[86] In turn, Canada's medical device classification

82. The Global Harmonization Task Force, *Principles of Medical Devices Classification,* (The Global Harmonization Task Force: June 27, 2006): 4.

83. World Health Organization, *Medical Device Regulations: Global Overview and Guiding Principles* (Geneva, Switzerland: World Health Organization, 2003): 2.

84. The Global Harmonization Task Force, *Principles of Medical Devices Classification,* 8.

85. The Global Harmonization Task Force, *Principles of Medical Devices Classification.*

86. European Commission, DG Health and Consumer, *Guidelines Relating to the Application of the Council Directive 93/42/EEC on Medical Devices*, (Brussels, Belgium: European Commission, June 2010): 4.

rules are also influenced by the GHTF because they "borrow significantly" from the EU's system.[87] Yet, Canada continues to classify non-hormonal IUDs as the third highest risk class, not the highest.

Although Canada's classification rules for medical devices is very similar to the rules proposed by the GHTF and the EU, Canada did not adopt the special provision under Rule 16 of the GHTF guidelines (or Rule 14 of the EU guidelines) specifying that implantable or long-term invasive devices should be placed in the highest risk class. Doing so would ensure that LARCs are held to the highest standard of safety and efficacy.

As previously discussed, Class III in the European Union refers to "high risk" devices, while Class III in Canada refers to "moderate-to-high risk." In Canada, Class IV devices are considered "high risk" and therefore are subject to a much more stringent pre-market approval process.[88] Class III devices are only required to submit summaries of safety and efficacy data, while Class IV devices submit more extensive data, including details of all safety and efficacy reports, risk assessments, quality plans, and manufacturing process specifications.[89] A Class IV device application package in Canada is very similar to the European Union's Design Dossier required for Class III devices.

GHTF's guidance document on Principles of Medical Devices Classification was published in 2006. Although the document contained non-binding recommendations, it did encourage regulatory authorities to adopt GHTF guidance "as the opportunity permits."[90] Health Canada is currently reviewing its medical device regulations, so now may be the perfect

87. Canada, Health Products and Food Branch, *Guidance Document: Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices,* 1.

88. Canada, Health Canada, Therapeutic Products Directorate, Medical Devices Bureau, *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications,* (Ottawa, ON: Health Canada, October 23, 1998).

89. Canada, Health Canada, Therapeutic Products Directorate, Medical Devices Bureau*, Preparation of a Premarket Review Document.*

90. The Global Harmonization Task Force, *Principles of Medical Devices Classification,* 4.

opportunity to implement the GHTF's recommendations. Canada already has four risk classes for devices, but in order to comply with the GHTF's guidelines, Health Canada should consider placing intrauterine devices in its highest risk class.

Some Canadians may be concerned that increasing the risk class for non-hormonal IUDs may impose an unnecessary regulatory burden for manufacturers since the approval process for Class IV devices is more strenuous than for Class III. However, the EU's higher risk class for non-hormonal IUDs does not appear to be a deterrent for manufacturers, since there are nearly twice as many non-hormonal IUDs approved for use in the United Kingdom than in Canada. With that said, Canada's market is half the size of the United Kingdom's, so a device manufacturer may not apply for Health Canada approval if the regulatory burden is too large relative to the size of the market. However, since most medical devices seek approval in the European Union prior to applying to Canada, classifying non-hormonal IUDs as Class IV in Canada should not add significantly to the manufacturer's regulatory burden, since the documentation required for Class IV devices in Canada is already very similar to Europe's dossier requirements for Class III devices. Furthermore, increasing the risk class for non-hormonal IUDs would ensure that IUDs are subject to rigorous pre-market review, thus maintaining a high level of safety for all contraceptive devices that apply to Canada, including those who apply without first receiving EU approval.

III. Overview of Regulatory Path

The classification of a LARC product also determines which government agency will review its application, what type of information must be included in its application package, and its overall pathway to regulatory approval.

IIIa. Canada

Because hormonal and non-hormonal IUDs are classified differently in Canada, their applications for pre-market approval are reviewed by different regulatory agencies.

In Canada, Copper IUDs are approved by the Medical Device Bureau of the Therapeutic Products Directorate (TPD), which authorizes all medical device products.[91] The TPD ensures that all medical devices adhere to the *Medical Device Regulations* of the *Food and Drugs Act*.

Upon approval, manufactures of Class II, III, and IV devices receive a Medical Device License, which is required in order for a device to be sold in Canada. A complete list of non-hormonal IUDs approved for use in Canada is available through the Medical Devices Active License Listing Search Tool.[92]

Hormonal IUDs are approved by the Health Products and Food Branch (HPFB) of Health Canada.[93] The HPDB ensures that all new drugs adhere to the *Food and Drug Regulations* of the *Food and Drugs Act.* After reviewing the New Drug Submission filed by the drug sponsor, the product is issued a Notice of Compliance as well as a Drug Identification Number if the HPFB determines that the benefits outweigh the risks of the new drug.[94] The product is then eligible to be marketed in Canada. A complete list of hormonal IUDs approved for use in Canada is available through the Notice of Compliance Database.[95]

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91. Canada, Health Canada, Medical Devices Bureau, Therapeutic Products Directorate, *Safe Medical Devices in Canada*, (Ottawa, ON: Health Canada, November 2007).

92. Canada, Government of Canada, "Medical Devices Active Licenses Search," *Government of Canada*, last modified February 14, 2019, https://health-products.canada.ca/mdall-limh/prepareSearch-preparerRecherche.do?type=active.

93. Canada, Office of Submissions and Intellectual Property (OSIP), "How Drugs are Reviewed in Canada," *Government of Canada,* last modified February 12, 2015, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html.

94. Canada, Office of Submissions and Intellectual Property (OSIP), "How Drugs are Reviewed in Canada."

95. Canada, Government of Canada, "Notice of Compliance (NOC) Database," *Government of Canada*, last modified October 5, 2017, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/database.html.

IIIb. United Kingdom

In the United Kingdom, a drug can obtain approval through one of four routes: the centralized, mutual recognition, national, or decentralized procedures. Regardless of the chosen route, the rules and requirements for drug approval in the EU are consistent across authorization procedures.[96]

The centralized procedure is used if a medicine wants to obtain approval in all EU countries simultaneously through a single marketing-authorization application. The product is then approved and regulated through the European Medicines Agency. Certain medicines are required to go through the centralized procedure, such as medicines containing new active substances and medicines for rare diseases. To date, no LARC has applied through the centralized procedure in Europe.[97]

The national procedure is used when a product only seeks market approval in one EU country. In the case of the UK, the device or medicine would apply through UK's regulatory office for drugs and medical devices, the Medicines and Healthcare products Regulatory Agency (MHRA). Successful drug applications receive a "Marketing Authorization" from the drugs division of the MHRA prior to being placed on the market. If a drug obtains a marketing authorization issued by the MHRA, it is valid in the UK only.

The mutual recognition procedure is used when a medicine is already authorized in at least one EU Member State and wishes to obtain Marketing Authorization (MA) in another state, such as the United Kingdom. The principle is that the UK will recognize the equivalence of the MA already granted in another EU Member State due to the similarities between the authorization processes. The Member State that has already authorized the product submits their

96. European Medicines Agency, *The European Regulatory System for Medicines* (London, UK: European Medicines Agency, 2016): 2.

97. European Medicines Agency Stakeholders and Communication Division, email message to Brooklyn Sutton, June 18, 2019.

evaluation to the MHRA for review. If the applicant is successful, the MHRA will issue an MA for that product, which allows the product to enter the UK market.

If the product has not yet received a Marketing Authorization anywhere in the EU, then the applicant company can submit a single application through the Decentralized Procedure to obtain MAs in multiple EU Member States simultaneously. Under this procedure, the applicant company will ask one of the proposed member states to act as the reference member state (RMS). The other member states are considered Concerned Member States (CMS). If the UK is asked to be the RMS, then the MHRA will be responsible for conducting the initial evaluation of the product. If the concerned member states approve of the MHRA's evaluation, then they will each issue an MA for the contraceptive to be marketed in their country.[98] Conversely, if the UK is assigned as a Concerned Member State, then the MHRA will review the RMS's draft assessment.

Instead of a market authorization, medical devices must receive a CE (conformité européenne) mark to demonstrate that the device complies with the relevant European Council Directives on Medical Devices in order to be marketed in the UK. The marking demonstrates that the product complies with EU health, safety, and legislative requirements.[99] The classification of a medical device determines the process required to obtain a CE mark. For Class III devices, the conformity assessment must be carried out by a "notified body." Notified bodies are independent certification bodies that are accredited by a national Competent Authority (such as the MHRA) to assess whether a product meets the essential requirements laid out in the relevant EU Directives.

98. Heads of Medicines Agencies, "Medicines Approval System," *HMA,* accessed July 11, 2019, https://www.hma.eu/medicinesapprovalsystem.html.

99. United Kingdom, Department for Business, Energy & Industrial Strategy, "Guidance: CE Marking," *Government of the United Kingdom*, accessed July 11, 2019, https://www.gov.uk/guidance/ce-marking#products-that-need-ce-marking.

In the European Union, copper is considered an "ancillary medicinal substance," when used in LARC products, so notified bodies involved in the approval of copper IUDs need to consult with a Competent Authority about the safety and efficacy of the medicinal substance (copper) before granting approval.[100]

Once a medical device receives a Declaration of Conformity from a notified body, it is eligible for a CE marking and can be marketed anywhere in the European Economic Area (EEA). This means that a medical device that receives its CE marking from anywhere within the EU can be sold in the UK without further assessment by a national body. Medical devices that are approved outside the EEA must undergo a conformity assessment and be CE marked before they can be sold within the United Kingdom, or anywhere in the European Union.[101]

New medical device regulations, which will come into force in May 2020, will require integral combination products to provide a conformity assessment by a notified body along with their market authorization application, regardless of the approval procedure they choose.[102] Thus, new hormonal IUDs and subdermal implants will be required to demonstrate that the medical device component meets the relevant safety and performance requirements of Annex I of the Medical Devices Regulation 2017/745. Combination products that were approved prior to May 2020 will be exempt from this new requirement.[103]

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100. World Health Organization and United Nations Population Fund, *TCu380A Intrauterine Contraceptive Device (IUD): WHO/UNFPA Technical Specification and Prequalification Guidance,* (Geneva, Switzerland: World Health Organization, 2016): 24.

101. Jane Summerfield, *Commercialisation of Healthcare in the UK (England and Wales): Overview* (London, UK: Thomson Reuters Practical Law, March 1, 2018): 10-13.

102. European Medicines Agency, "First Guidance on New Rules for Certain Medical Devices," *European Medicines Agency,* February 28, 2019, https://www.ema.europa.eu/en/news/first-guidance-new-rules-certain-medical-devices.

103. European Medicines Agency, *Human Medicines Evaluation Division and Co-ordination Group for Mutual Recognition and Decentralised Procedures—Human, Questions and Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU 2017/745 and (EU) 2017/746)* (London, UK: European Medicines Agency, 27 February 2019): 5-6.

The European Union's new requirements for combination products essentially requires hormonal IUDs and subdermal implants to obtain approval as both a drug (through a market authorization) and as a medical device (through a CE mark). This model is very similar to the process that Canada moved away from in 2006.

IIIc. United States

After a drug completes its clinical testing and is deemed to be safe and efficacious by the manufacturer, the drug sponsor can seek market approval in the United States by submitting a New Drug Application (NDA) to the Federal Drug Administration.[104] The NDA includes all of the data collected from clinical trials conducted in both animals and humans, information about how the drug product works, and how it is manufactured. Since LARC products are all classified as drugs in the United States, the Center for Drug Evaluation and Research (CDER) is the regulatory agency that reviews the NDA. CDER ensures that the drug product complies with *The Federal Food, Drug, and Cosmetic Act* and section 21 of the *Code of Federal Regulations* for New Drug Applications. While reviewing the application package, the review team—which is comprised of chemists, medical doctors, pharmacologists, and other experts—determines if they agree with the drug sponsor's conclusion that the benefits outweigh the risks of the new drug. It is at this point that the CDER may consult with the Center for Drug Evaluation and Research about the device component of the LARC. The review team then submits their conclusions to the CDER division director (who has the ultimate authority to accept or ignore the review team's recommendation). Then, the FDA prepares a complete response letter to the drug sponsor justifying its decision to either approve or reject the drug. If the drug is approved, it can then enter the market.

104. United States, U.S. Food and Drug Administration, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective," *United States Government,* last modified November 24, 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

IIId. Australia

The Medical Devices and Product Quality Division of the Therapeutic Goods Administration approves and monitors medical devices in Australia. One advantage of using the same classification system as the European Union is that drugs and devices that have been approved for sale in the EU will very likely have the same classification and regulatory requirements in Australia.[105] Indeed, most of Australia's guidelines for drug and device approvals are adopted directly from the European Union. The Therapeutic Goods Administration (TGA) in Australia is responsible for reviewing and approving new drug and device applications and ensuring that all new products conform to the standards outlined in the *Therapeutic Goods Act 1989.*

The drug approval process in Australia is very similar to the Centralised Procedure followed in the European Union, with the Medicines Regulation Division of the TGA acting as the central authority. Once an application is approved, hormonal IUDs and subdermal implants receive an AUST R number, which signifies that the drug has been fully assessed for safety, quality, and efficacy.[106] The product is then listed on the Australian Register of Therapeutic Goods.

The requirements for medical device approval in Australia are also very similar to those in the European Union. So similar, in fact, that Australia has a Mutual Recognition Agreement (MRA) with the European Union for medical devices. This means that if a medical device is approved for sale within the EU and it is manufactured within an EU country, then Australia will recognize the European approval of that device, and it can be placed on the Australian market

105. Emergo, "Australia TGA Regulatory Approval Process for Medical Devices," *UL*, last modified May 20, 2019, https://www.emergobyul.com/resources/australia-process-chart.

106. Australia, Department of Health, Therapeutic Goods Administration, "How We Regulate Medicines," *Australian Government,* June 20, 2019, https://www.tga.gov.au/how-we-regulate-medicines.

without further assessment by the Therapeutic Goods Administration.[107] The agreement works the other way too—devices manufactured and approved in Australia can also be marketed in the European Union.

Prior to 2012, the TGA specifically excluded implantable contraceptive devices and intrauterine contraceptive devices from qualifying under the MRA because "confidence-building arrangements [had] not occurred".[108] In 2012, the TGA decided to exclude all Class III devices from the MRA, again citing a lack of "confidence-building arrangements." [109] As a result, all new Class III devices, including non-hormonal IUDs, must go through an independent assessment by the TGA until further notice.

In May 2019, the TGA announced that it will start accepting decisions made by the United States Federal Drug Administration and from Health Canada as evidence to support medical device authorizations.[110] Now, non-hormonal IUDs that have already been through the United States or Canadian regulatory process can benefit from an abridged conformity assessment in Australia. However, since non-hormonal IUDs are regulated as drugs in the United States, they may not benefit from the abridged application because their application will require additional documentation to be classified as a device.[111] Given Australia's previous exclusion of contraceptive devices from their Mutual Recognition Agreement with the European Union, it is

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107. Australia, Department of Health, Therapeutic Goods Administration, *Australian Regulatory Guidelines for Medicial Devices (ARGMD)* (Symonston, Australia: Therapeutic Goods Administration, May 2011): 161.

108. Australia, Department of Health, Therapeutic Goods Administration, *Australian Regulatory Guidelines,* 23, 138.

109. Australia, Department of Health, Therapeutic Goods Administration, "Medical Device Amendments to the EU-Australia MRA on Conformity Assessment to Come into Effect 1 January 2013," *Therapeutic Goods Administration,* 30 November, 2012, https://www.tga.gov.au/medical-device-amendments-eu-australia-mra-conformity-assessment-come-effect-1-january-2013.

110. Australia, Department of Health, Therapeutic Goods Administration, "Use of Market Authorisation Evidence From Comparable Overseas Regulators/Assessment Bodies for Medical Devices (Including IVDs)," *Australian Government,* June 18, 2019, https://www.tga.gov.au/publication/use-market-authorisation-evidence-comparable-overseas-regulators-assessment-bodies-medical-devices-including-ivds.

111. Nick Paul Taylor, "Australia Starts Accepting FDA Reports in Device Filings," *MedTech Dive,* August 22, 2018, https://www.medtechdive.com/news/australia-starts-accepting-fda-reports-in-device-filings/530665/.

also unclear if contraceptive devices from other countries will be eligible for the abridged conformity assessment.

IIIe. Analysis

Some policy advocates believe that Canada should pursue a mutual recognition agreement with other countries as a way to reduce the regulatory burden on Health Canada and to increase patient access to innovative drugs and devices.[112] The most frequently recommended jurisdictions to work with are the United States and the European Union, given their market dominance. However, mutual recognition would be quite difficult without a unified classification system. Furthermore, experience from Australia demonstrates the difficulties of mutual recognition when regulators are unable to trust each other. This example is particularly striking considering how Australia adopted most of their regulations directly from the European Union, so the standards for approval should be similar.

Removing Health Canada's autonomy when it comes to contraceptive approvals would also result in a "brain drain" of skilled and experienced policy professionals. Canadian regulators would move to other jurisdictions where their talents could be better utilized, thus depleting Canada's policy capacity.[113]

Additionally, Canadians might be wary of trusting drug and device approvals from other jurisdictions. The EU's mutual recognition procedure has been criticized for putting the needs of manufacturers over the safety of consumers, since the only regulatory authority to collect user-fees from manufacturers is the one that initially approves the drug or device. This financial reward can incentivize regulators to speed up the approval process and approve almost anything that comes their way. One EU regulator was caught boasting that it only rejected four medical

112. Bacchus Barua and Nadeem Esmail, *The Case for Mutual Recognition of Drug Approvals,* (Vancouver, BC: Fraser Institute, September 2013).

113. Dr. Joel Lexchin, telephone conversation with author, August 7, 2019.

device applications in the past five years.[114] It is also important to note that notified bodies are third party regulators that receive their authority from EU countries but are not government entities themselves.

In 2015, an Oxford professor submitted a fake report to a notified body in Austria touting the benefits of implanting parts of a mesh bag used to hold mandarin oranges into people's bodies. The report was riddled with red flags, yet the notified body was ready to grant the mesh bag a CE mark.[115] If that had happened, then the bag could have been sold in every EU country without further scrutiny. Despite harmonized standards, notified bodies have been criticized for a "lack of uniformity" in applying the rules, which encourages manufacturers to seek out notified bodies with the most lax operating standards.[116] Without a system to uphold consistently high regulatory excellence, unsafe drugs and devices may slip through the cracks. Thus, mutual recognition agreements are only as strong as the weakest regulator.

As a result of these controversies, consumers might be concerned that a mutual-recognition procedure would deprive Health Canada of its ability to ensure that all drugs are held up to the same standard, which could open up the possibility for unsafe drugs to enter the market.

Instead of implementing a mutual recognition agreement for drugs or devices, Health Canada should continue to communicate with other jurisdictions where a product has already been approved and seek insight from other professionals when necessary. Currently, drugs and devices are required to give an overview of the product's marketing history in their application package.[117] Canada should seek out the reviewer's notes from jurisdictions and take those into

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114. Claire Newell and Holly Watt, "Faulty Medical Implants Investigation: Patients' Health Put at Risk by Unscrupulous EU Regulators," *The Telegraph*, October 22, 2012.

115. Lois Rogers, "Scandal of Fruit Netting 'Approved As Surgical Implant,'" *The Sunday Times,* January 11, 2015, https://www.thetimes.co.uk/article/scandal-of-fruit-netting-approved-as-surgical-implant-dvcqd2rt9mr.

116. Baylie M. Fry, "A Reasoned Proposition to a Perilous Problem: Creating a Government Agency to Remedy the Emphatic Failure of Notified Bodies in the Medical Device Industry," *Willamette Journal of International Law and Dispute Resolution* 22, no. 1 (2014): 177.

117. Canada, Health Canada, *Therapeutic Products Directorate, Medical Devices Bureau, Preparation of a Premarket Review Document.*

consideration when reviewing a product's application, just like Australia has recently committed to do. Open communication between regulators can reduce approval time while still maintaining Health Canada's independence.

IV. Clinical Trials

Pre-clinical and Clinical Evidence

Drug and medical device approvals in the United Kingdom, Canada, the United States, and Australia are all based on a risk-benefit ratio. Since no drug or device is perfectly safe, a product will only be approved if the regulatory team determines that the product's benefits outweigh its potential risks. Because regulators treat drug and device approvals separately, manufacturers are required to submit different types of evidence of the product's safety and efficacy depending on its classification.

IVa. Drugs

Drug manufacturers provide evidence of their product's safety and efficacy through clinical and pre-clinical trials data. Each country has slightly different criteria for trial methodology, and different thresholds for safety and efficacy. As a result, a product's clinical trial design may be acceptable in one country, but not in another. The way a regulator interprets clinical trial data may also vary depending on national standards and regulatory expertise.

Drug testing occurs in five phases: pre-clinical studies (test tube and animal testing), phase I clinical trials (safety), phase II (efficacy), phase III (efficacy in controlled settings), and phase IV (post-market studies to establish effectiveness in real world settings).[118] In order to approve a new drug, regulators review evidence from pre-clinical studies and phases I to III of clinical trials, with some regulators requiring a commitment to submit Phase IV data at a future date. Phase III trials have larger sample sizes than phases I and II, and human participants are

118. United States, U.S. Food and Drug Administration, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective."

closely monitored for potential side effects. Most regulators require evidence from two separate, well-controlled phase III pivotal trials in order to approve a new drug. However, the definition of a "well-controlled" trial can differ among regulators.

Through pre-clinical and clinical testing, drug trials for hormonal contraceptives specifically test for safety, potential side effects, and effectiveness at preventing pregnancy in both clinical and real-world settings. Across the four jurisdictions included in this study, clinical testing must be done in healthy females, and must last for the duration of the LARC product's intended use.

IVb. Medical Devices

Medical device trials, on the other hand, are not phased in the same way that drugs are. In the United Kingdom, Canada, and Australia, medical devices are not required to be tested in human subjects prior to market approval. In Canada specifically, all Class III and IV medical device license applications must include evidence of "clinical effectiveness," but not clinical efficacy as demonstrated through formal clinical trials. [119] Canadian regulatory requirements allow clinical effectiveness to be demonstrated in a variety of ways, including literature reviews or real-world evidence reviews.[120] Similarities exist in regulations for medical devices in the United Kingdom and Australia, where devices only need to demonstrate that they perform as they are designed, but are not required to demonstrate clinical efficacy.[121] This means that copper IUDs do not have to be tested in humans before they enter the market in Canada, the United Kingdom, or Australia. Furthermore, if a device is similar enough to another device that is already on the market, it may be exempt from submitting any clinical efficacy data to the

119. CBC News, *Health Canada Responses CBC SRC Star* (Toronto, ON: CBC News, November 13, 2018): 3.

120. CBC News, *Health Canada Responses,* 3.

121. Gail A. Van Norman, "Drugs and Devices: Comparison of European and U.S. Approval Processes," *JACC: Basic to Translational Science* 1, no. 5 (August 2016).

regulator.[122] Since most copper IUDs only vary in terms of device size and the amount of copper covering the plastic frame, it is likely that new T-shaped copper IUDs are exempt from undergoing investigational testing altogether.[123]

Since copper IUDs are regulated as drugs in the United States, manufacturers are required to show the FDA that its product is safe and efficacious each time a new copper IUD applies for market approval.[124] This means that copper IUDs that had previously been approved in Canada, the European Union, or Australia without clinical data would have to undergo formal clinical testing in humans in order to apply to the United States. Clinical trials are the longest and most expensive part of drug development, sometimes taking over a decade to complete.[125] The additional clinical testing requirements may be one of the reasons why there are over 20 non-hormonal IUDs available in the UK, 12 in Canada, and only one in the United States.

Given the large cost of conducting clinical trials, drug sponsors will often use data from the same trial to obtain approval in multiple countries. However, it can be difficult to design a clinical trial for an internationally marketed product if the trial requirements differ across jurisdictions.

IVc. Good Clinical Practice

In an effort to harmonize accepted best practices for clinical trials, the United States, Japan, and many European countries met in Brussels in 1990 at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH developed "Good Clinical Practice" (GCP) guidelines, which are an

122. CBC News, *Health Canada Responses.*

123. Even though it is not required, it is possible that non-hormonal IUD manufacturers chose to conduct clinical testing in humans prior to seeking market approval. However, without analyzing the submission packages in each jurisdiction—which are not publicly available—it is not possible to tell.

124. Beaton, "Why Does America Have Fewer Types of IUDs."

125. Gail A. Van Norman, "Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs," *JACC: Basic to Translational Science* 1, no. 3 (April 2016): 171.

international quality standard for conducting clinical trials and investigational testing. Good Clinical Practice attempted to harmonize clinical trial standards to ensure that safety requirements for human participants are consistent across the world, and to ensure that trial data would be internationally recognized.[126]

Regulators in Canada, Australia, the United States and the United Kingdom all look for adherence to GCP guidelines when evaluating clinical trial data from new drug submissions.

Good Clinical Practice guidelines have also been developed for medical device testing. The United States and the United Kingdom require adherence to Good Clinical Practice when investigational testing does occur for new contraceptive devices.[127] Canada, on the other hand, did not require adherence to GCP for medical device testing until 2018, when Canada released a new guidance document on Medical Device Investigational Testing Authorizations. The document states that Health Canada "expects" that manufacturers follow Good Clinical Practice; however, this requirement is not legally binding, since it is not included in the *Medical Device Regulations*.[128] Canada once considered including GCP requirements in the *Regulations*, but decided that "the risks involved did not warrant an increased regulatory burden."[129] By way of comparison, adherence to Good Clinical Practice is required for drug products and is enshrined in the *Food and Drug Regulations.* Without a legally binding requirement, it is not yet clear how strict Health Canada will be in upholding GCP adherence for medical devices.

126. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice* (Brussels, ICH: November 9, 2016).

127. Canada, Health Canada and the Public Health Agency of Canada, *Evaluation of the Medical Devices Program 1999-2000 to 2011-2012*, (Ottawa, ON: Health Canada, February 2014): iii; United Kingdom, National Health Service, "Good Clinical Practice," *NHS,* last modified March 19, 2018, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/.

128. Canada, Health Canada, Guidance Document: Applications for Medical Device Investigational Testing Authorizations (Ottawa, ON: Health Canada, October 2018): 6.

129. Canada, Health Canada and the Public Health Agency of Canada, *Evaluation,* iii.

IVd. Guidance Documents on Contraceptive Clinical Trials

In addition to GCP, Health Canada and the European Medicines Agency have specific guidance documents for the clinical trial design of hormonal contraceptives. Contraceptives are treated differently than other therapeutic drugs because contraceptives are designed to be used for prolonged periods of time by women who are generally healthy, whereas most other therapeutic drugs are used to treat short-term ailments or diseases. Therefore, the threshold for safety under a risk-benefit ratio is higher for contraceptives than that of other drug products.

EMA first published guidance documents for contraceptive trial design in 2000 and updated them in 2005, and Health Canada has used the same guidance document since 2002.[130] The Australian Therapeutic Goods Administration adopted the EU's guidance document in 2001 and continues to reference the EU's updated drafts.[131] The United States is currently collecting stakeholder feedback on their own draft guidance document for contraceptive clinical trials.[132] Because these documents specify that they are meant for hormonal contraceptives, non-hormonal IUDs are not subject to these guidelines.

According to both Canadian and European guidelines, the key studies to determine contraceptive efficacy should be carried out in a "sufficiently representative population," but the Canadian guidelines specify that the demography of the women included in clinical trials should be "comparable to that of Canadian populations."[133] It is unclear what qualifies as the "Canadian

130. Canada, Health Canada, Health Products and Food Branch, *Guidance for Industry: Clinical Development of Steroidal Contraceptives*; European Medicines Agency, Committee for Medicinal Products for Human Use, *Guideline on Clinical Investigation of Steroid Contraceptives in Women* (London, UK: European Medicines Agency, July 27, 2005).

131. Australia, Department of Health, Therapeutic Goods Administration, "Scientific Guidelines: EU Guidelines," *Therapeutic Goods Administration,* accessed July 20, 2019, https://www.tga.gov.au/ws-sg-index?search_api_views_fulltext=contraceptive&items_per_page=10.

132. United States, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy: Guidance for Industry Draft Guidance* (Rockville, MD: Food and Drug Administration, July 2019).

133. Canada, Health Canada, Health Products and Food Branch, *Guidance for Industry: Clinical Development of Steroidal Contraceptives,* 4-5; European Medicines Agency, Committee for Medicinal Products for Human Use, *Guideline on Clinical Investigation of Steroid Contraceptives,* 4.

population" given that Canada's ethnic makeup is so diverse, but it is possible that Health Canada could reject contraceptive data based on this parameter, as they have done in the past for other drugs intended for female use.[134]

For LARC products specifically, Canadian and European guidelines specify that trials to determine efficacy should last as long as the product's intended use. For example, an IUD that is intended to be used for up to five years at a time should be tested for at least five years. The EU guidelines specify that at least 200 women should participate in LARC efficacy trials, but the Canadian document does not offer an exact number.[135] The draft document of the FDA's guidelines specifies that at least 400 women should be enrolled in studies involving a new molecular entity, or at least 200 if the product does not involve a new molecular entity.[136]

The guidelines also differ in terms of the amount of safety information required. The EMA guidelines specify that the minimum amount of safety information should include studies that follow women over one year of treatment, whereas the Health Canada guidelines state that the minimum amount of safety information should come from two years.[137]

The Health Canada guidelines have been criticized for having excess requirements beyond what is asked for in similar countries such as the United States, the United Kingdom, France, and Sweden. Specifically, Health Canada's requirement that all study participants receive an endometrial biopsy was listed as a particular burden that is not required anywhere

134. Amir Attaran, Twitter Post, July 16, 2019, 8:14, https://twitter.com/profamirattaran/status/1151132924923666433.

135. European Medicines Agency, Committee for Medicinal Products for Human Use, *Guideline on Clinical Investigation of Steroid Contraceptives,* 5; Canada, Health Canada, Health Products and Food Branch, *Guidance for Industry: Clinical Development of Steroidal Contraceptives,* 5.

136. United States, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Establishing Effectiveness,* 3.

137. European Medicines Agency, Committee for Medicinal Products for Human Use, *Guideline on Clinical Investigation of Steroid Contraceptives,* 5; Canada, Health Canada, Health Products and Food Branch, *Guidance for Industry: Clinical Development of Steroidal Contraceptives,* 6.

else.[138] Some researchers postulate that Health Canada's stringent guidance document is largely responsible for the decline in the number of contraceptive applications to Health Canada.[139]

IVe. Analysis

Despite international efforts to harmonize clinical trial requirements, significant differences still exist for trials involving hormonal contraceptives. Guidance documents do not contain legally binding requirements, but they do outline common traits that regulators are trained to look for. However, these guidance documents were developed when hormone-containing LARC products were just entering the market. LARC development has progressed substantially since both of these guidance documents were initially released. The first-ever hormonal IUD entered the Canadian market in 2001, and several more LARC products have been developed since then, including smaller IUDs, frameless IUDs, subdermal implants, and long-acting vaginal contraceptive rings. Health Canada's guidance document should be updated to reflect the most recent scientific advancements. Health Canada should also aim to collaborate with the FDA and the EMA to eliminate unnecessary requirements and harmonize clinical trial guidelines for contraceptives. Harmonization can be especially helpful for LARC manufacturers since clinical trials are expected to last as long as the product's intended use, which can be up to 10 years for some IUDs. It may not be feasible for a manufacturer to redo a clinical trial in order to obtain approval in a particular country due to the large expense and time commitment required.

When seeking harmonization, it is important for regulators to ensure that standards are not set according to the least stringent safety standards. Like the ICH and GCP guidelines, clinical trial requirements for hormonal contraceptives should be developed with input from medical professionals and researchers to ensure that requirements are harmonized to a high

138. Azzarello and Collins, "Canadian Access."
139. Azzarello and Collins, "Canadian Access."

standard of safety and efficacy. Industry input should be considered so that policy makers can re-evaluate proposed guidelines that are identified as unreasonably onerous. However, input from industry should be minimal throughout the process in order to prevent rent-seeking behaviour, since manufacturers benefit when regulatory standards are low.

Harmonizing clinical trial requirements would reduce the regulatory burden for manufacturers by allowing the manufacturer to use data from the same trial in several market approval applications. Thus, harmonized standards for contraceptive trials would encourage LARC products to seek approval in new markets, while still ensuring a consistently high threshold for safety.

Regarding copper IUDs, class III and IV devices should be required to perform trials in healthy human subjects prior to market approval. Contraceptive devices can cause significant harm if developed poorly and can pose a significant health risk if pregnancy occurs while using the device. Therefore, non-hormonal IUDs should be held to a similar standard for safety and efficacy testing as hormonal LARC products. An amendment should be made to the *Medical Device Regulations* to require manufacturers of high-risk contraceptive devices to adhere to Good Clinical Practice when conducting investigational testing.

V. Post-Market Surveillance

After a drug receives marketing approval, it may be subject to further post-market surveillance, or "Phase IV" clinical trials. While Phase III trials aim to determine a product's *efficacy*, that is, how the product performs under controlled settings in healthy human subjects, Phase IV trials measure a product's *effectiveness,* that is, how the product performs in real-life situations.[140] Phase IV data is important because clinical trials for contraceptives are often not conducted in women who smoke, are taking other medication, or have other pre-existing

140. Peter G. Smith, Richard H. Morrow, and David A. Ross, *Field Trials of Health Interventions: A Toolbox, 3rd Edition,* (Oxford, United Kingdom: Oxford University Press, 2015): 396.

conditions. Moreover, Phase III trials may not be large enough to detect important, but relatively uncommon side effects.[141] For example, a post-marketing study of the Mirena hormonal IUD found that lactating women using the device were at an increased risk of uterine perforation.[142] This new information resulted in an update to the prescribing guidelines. Other post-market studies observed that hormonal IUDs are a safe and effective form of birth control for women with fibroids and for nulliparous women, which again impacted prescribing practice.[143]

Some drug products are only approved on the condition of additional post-market studies. When this happens in Canada, a new drug product is issued a "Notice of Compliance with Conditions." Whether or not the studies are required by the regulator, Phase IV trials provide important insight into a product's suitability for the wider population. Additionally, if the newly reported risks discovered in phase IV trials are determined to outweigh the benefits for certain populations, then the regulator may decide to impose prescribing restrictions or require additional labelling for the product outlining the newly discovered contraindication.

Although medical device investigational testing is not phased in the same way as drug trials, post-market studies for medical devices also provide valuable information for regulators and medical professionals, especially in the absence of pre-market trials.

Va. Pharmacovigilance

An important aspect of post-market surveillance is pharmacovigilance, or adverse event reporting. An adverse event is an unexpected or serious side effect that occurs while using a pharmaceutical product. In Canada, drug manufacturers are required by law to tell Health

141. Smith, Morrow, and Ross, *Field Trials,* 395.

142. K. Van Houdenhoven, K.J.A.F. van Kaam, A.C. van Grootheest, T.H.B. Salemans, and G.A.J. Dunselman, "Uterine Perforation in Women Using a Levonorgestrel-Releasing Intrauterine System," *Contraception* 73 (2006).

143. Andrew M. Kaunitz, "Progestin-Releasing Intrauterine Systems and Leiomyoma," *Contraception* 75, no. 6 (June 2007); Sarah Prager and Philip D. Darney, "The Levonorgestrel Intrauterine System in Nulliparous Women," *Contraception* 75, no. 6 (June 2007).

Canada about all serious adverse reactions that occur both inside and outside of Canada within 15 days of becoming aware of the issue.[144] For medical device adverse reactions, manufacturers are required to inform Health Canada within 10 days of becoming aware of an incident that led to the "death or a serious deterioration in the state of health" of the user.[145] For incidents that did not lead to death or serious health issues, but "could do so were it to recur," the manufacturer is required to inform health Canada within 30 days of becoming aware of the event.[146] Manufacturers are only required to report foreign adverse reactions to Health Canada if the manufacturer intends to take corrective action, or if the foreign regulatory agency requires the manufacturer to take corrective action.[147]

Canada also recently extended mandatory reporting requirements for adverse events that occur within hospitals. Canada's mandatory requirements are enforceable since they are set out in legislation; however, the definition of a "serious" adverse event is still somewhat vague, especially in relation to birth control products.

For example, in 2013, a faulty batch of birth control pills by Apotex Inc. contained an extra week of placebo pills, which exposed users to an increased risk of unplanned pregnancy. When the manufacturer reported the issue to Health Canada, the department did not issue an urgent recall because an unintended pregnancy was not considered a serious enough adverse event. [148] A spokesperson from Health Canada explained that a recall was not issued sooner because the department considered unplanned pregnancies as a "lifestyle impact" rather than a

144. Canada, Health Canada, *Reporting Adverse Reactions to Marketed Health Products: Guidance Document for Industry,* (Ottawa, ON: Health Canada, May 23, 2018).
145. *Medical Device Regulations*, SOR/98-282, s.60(1)(a)(i).
146. *Medical Device Regulations*, SOR/98-282, s.60(1)(a)(ii).
147. *Medical Device Regulations*, SOR/98-282, s.60(1)(b).
148. Carly Weeks, "Birth-Control Recall: Experts Still Unsatisfied With Health Canada Despite Investigation Into Delays," *The Globe and Mail,* April 12, 2013, www.theglobeandmail.com/life/health-and-fitness/health/birth-control-recall-experts-still-unsatisfied-with-health-canada-despite-investigation-into-delays/article11163040/.

"health impact."[149] In a report reviewing Health Canada's actions throughout the recall, unintended pregnancies are continuously referred to as a "social concern" rather than a health concern.[150]

While it is true that unintended pregnancies have serious social implications, pregnancy in general can come with significant health risks for some women, such as blood clots, high blood pressure, and diabetes.[151] Women with certain pre-existing conditions are at an even higher risk of incurring serious health complications during pregnancy. Life-threatening complications are more likely to occur in poorer countries, but severe complications still happen in Canada, the United States, the United Kingdom, and Australia, especially among marginalized populations.[152] Pregnancy can also adversely affect a woman's mental health; this risk is accelerated when the pregnancy is unintended.[153]

Even though manufacturers and other groups are required to report serious adverse events, efficacy issues resulting in unplanned pregnancies, issues with fertility returning back to normal after discontinuation, and other adverse events related to contraceptives may not be considered "serious" enough to be reported to Health Canada. Thus, adverse events for contraceptive products may be underreported. No contraceptive is 100 per cent effective at preventing pregnancy, but if pregnancies are occurring at a rate unexpected by the manufacturer after market approval, then this could reveal an underlying issue with the product's efficacy and safety, thus highlighting a need for further investigation.

149. Weeks, "Birth-Control Recall."

150. Risk Sciences International, *Review of Health Canada's Actions in the Recall of Alysena 28*, (Ottawa, ON: Risk Sciences International, September 13, 2013).

151. A.L. Nelson and A. Rezvan, "A Pilot Study of Women's Knowledge of Pregnancy Health Risks: Implications for Contraception," *Contraception* 85, no. 1 (January 2012).

152. Emily E. Petersen, et al., "Vital Signs: Pregnancy-Related Deaths, United States, 2011-2015, and Strategies for Prevention, 13 States, 2013-2017," *Morbidity and Mortality Weekly Report* 68, no. 18 (May 10, 2019).

153. Jinwook Bahk, Sung-Cheol Yun, Yu-mi Kim, and Young-Ho Khang, "Impact of Unintended Pregnancy on Maternal Mental Health: A Casual Analysis Using Follow Up Data of the Panel Study on Korean Children (PSKC)," *BMC Pregnancy and Childbirth* 15, no. 85 (April 3, 2015).

In light of the Apotex Inc. recall controversy, some Canadian scholars have suggested that the definition of an adverse reaction should be clarified to prevent "restrictive interpretations" of what constitutes "injury" and "harm" caused by an ineffective drug product.[154]

Vb. Mandatory Periodic Reporting

In addition to immediate reporting of serious adverse events, drug manufacturers are required to prepare an annual report for Health Canada summarizing all adverse drug reactions (including non-serious reports) that the manufacturer became aware of over the past year.[155] The manufacturer is also expected to summarize post-market studies conducted for its product, whether published by the manufacturer or an outside source.[156] However, the manufacturer is only required to submit that report to Health Canada if the new information changes the risk-benefit assessment, or if the Minister specifically requests the report.[157]

In Australia, drug sponsors are required to submit Periodic Safety Update Reports (PSUR) to the Therapeutic Goods Administration for at least three years after a drug is approved.[158] In the European Union, all drugs, whether they were approved nationally or centrally, are required to prepare and submit PSURs through a central repository.[159] Unlike Canada, the EMA and national competent authorities require manufacturers to submit all PSURs.

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154. Matthew Herder, Elaine Gibson, Janice Graham, Joel Lexchin, and Barbara Mintzes, "Regulation Prescription Drugs for Patient Safety: Does Bill C-17 Go Far Enough?" *Canadian Medical Association Journal* 186, no. 8 (May 13, 2014): E290.

155. *Food and Drug Regulations,* CRC c 870, sections c.01.018-c.01.020.

156. Canada, Health Canada, Health Products and Food Branch, *Guidance Document Periodic Benefit-Risk Evaluation Report (PBRER) International Conference on Harmonisation (ICH) Topic E2C(R2),* (Ottawa, ON: Health Canada, February 21, 2013): 21.

157. Canada, Health Canada, "Questions and Answers Regarding the Adoption of Periodic Benefit Risk Evaluation Report (PBER) Review at Health Canada," *Government of Canada,* last modified March 10, 2013.

158. Australia, Department of Health, Therapeutic Goods Administration, *Medicines and Vaccines Post-Market Vigilance: Statistics for 2017*, (Symonston, Australia: Therapeutic Goods Administration, August 2018): 9.

159. European Medicines Agency, "Periodic Safety Update Reports (PSURs)," *European Medicines Agency*, accessed August 10, 2019, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs#submission-requirements-and-eu-reference-dates:-the-eurd-list-section.

Rather than relying on the manufacturer's assessment, the agencies independently assess the PSURs and determine for themselves if the risk-benefit balance has changed. Drugs are required to submit PSURs at different intervals, depending on the conditions included in their marketing authorization. In the United States, drug manufacturers are required to submit a Periodic Benefit-Risk Evaluation (which serves the same purpose as a PSUR) to the FDA at varying frequencies, depending on the product.[160]

Post-market reporting requirements can be time-consuming for internationally marketed LARC products when each regulator has varying reporting intervals and requirements. In 2004, the ICH developed guidelines for Harmonised Pharmacovigilance Planning to try to reduce this duplicative effort.[161] The European Union, the United States, and Canada have all formally adopted the ICH guidelines, so the type of information contained in post-market reports is fairly consistent across jurisdictions.[162] To reduce the administrative burden for manufacturers, Canada accepts periodic summary reports that were prepared according to ICH guidelines for other jurisdictions so long as the manufacturer prepares a Canadian-specific section discussing post-marketing experience in the Canadian context.[163] Despite harmonized content requirements, reporting intervals and procedures still vary among regulators.[164]

160. United States, Department of Health and Human Services, Food and Drug Administration, *Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research, E2C(R2) Periodic Benefit-Risk Evaluation Report (PBER) Guidance for Industry,* (Silver Spring, MD: Food and Drug Administration, July 2016).

161. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline: Pharmacovigilance Planning E2E,* (ICH: November 18, 2004).

162. ICH, "Efficacy Single," *ICH,* accessed August 10, 2019, https://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html.

163. Canada, Health Canada, *Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products: Guidance Document for Industry,* (Ottawa, ON: Health Canada, May 2018): 8.

164. Mohit Hans and Suresh Kumar Gupta, "Comparative Evaluation of Pharmacovigilance Regulation of the United States, United Kingdom, Canada, India and the Need for Global Harmonized Practices," *Perspectives in Clinical Research* 9, no. 4 (2018).

Historically, post-market surveillance requirements have been significantly lighter for medical devices than for pharmaceuticals. Post-market reporting was often voluntary and unregulated.

In 2017, the EU passed a new regulation requiring manufacturers of Class III devices to also prepare Periodic Safety Update Reports and submit them through an online portal to be reviewed by the notified body that was involved in the device's initial approval.[165] The new regulation is expected to come into force in May 2020. PSURs will be required to be updated annually. Similarly in Australia, Class III device sponsors are currently required to submit annual reports to the TGA for the first three years after approval, although these guidelines are under review.[166] In 2018, Health Canada announced that it will follow the lead of the European Union and start requiring medical device manufacturers to prepare annual reports just like pharmaceutical manufacturers.[167] The reporting requirement would apply to Class II, III, and IV devices, although the legislation has not yet been finalized. Again, these reports need to be prepared annually, but will only need to be submitted to Health Canada if the manufacturer determines that there is a change in the risk-benefit balance.

Vc. Spontaneous Voluntary Reporting

Periodic post-market reporting and mandatory serious event reporting are important tools to help regulators monitor side effects and contraindications that were not discovered during pre-

165. European Union, "Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices (article 86)" *Publications Office of the European Union,* 2017, https://publications.europa.eu/en/publication-detail/-/publication/83bdc18f-315d-11e7-9412-01aa75ed71a1/language-en/format-PDF/source-58036705.

166. Australia, Department of Health, Therapeutic Goods Administration, *Australian Regulatory Guidelines for Medical Devices*, 291.

167. Canada, Health Canada, "Notice of Intent: Strengthening the Post-Market Surveillance and Risk Management of Medical Devices in Canada," *Health Canada*, last modified March 10, 2018, https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/medical-devices/noi-strengthening-post-market-surveillance-risk-management-medical-devices.html.

market investigational testing. However, these post-market reports depend on the manufacturer becoming aware of adverse events.

Canadian consumers and medical professionals can voluntarily report adverse reactions to the manufacturer or directly to Health Canada. The United Kingdom, the United States, and Australia all have voluntary adverse event reporting mechanisms for the public to aid in post-market surveillance.

Studies show that adverse reactions are grossly underreported, which can lead to delays in discovering patterns and changing prescribing practices.[168] Mandatory reporting for certain groups, such as nurses, doctors, or pharmacists, can help increase adverse event reporting, but as previously discussed, some birth control side effects may not be considered serious enough to file a report. Additionally, women report that their doctors are often dismissive about birth control's side effects, so non-serious adverse LARC events may still go unreported if left to medical professionals.[169] A literature review examining the quality of consumer adverse reaction reports found that patient reports often described reactions in more detail than reports from health care practitioners, and provided more information on the impact of the event on patients' lives.[170] Another report found that patients appreciate the opportunity to file adverse event reports themselves, especially when they feel their doctor dismissed their concerns.[171] Therefore, voluntary patient reports provide important information that may not otherwise be reported if left to medical professionals. Unfortunately, adverse drug reports are rarely voluntarily submitted.

168. L. Hazell and S.A. Shakir, "Under-Reporting of Adverse Drug Reactions: A Systematic Review," *Drug Safety* 29, no. 5 (2006).

169. Elisa Wells, *Countering Myths and Misperceptions About Contraceptives* (Seattle, WA: PATH, June 2015): 3.

170. Tony Avery, et al., "Evaluation of Patient Reporting of Adverse Drug Reactions to the UK 'Yellow Card Scheme': Literature Review, Descriptive and Qualitative Analyses, and Questionnaire Surveys," *Health Technology Assessment* 15, no. 20 (May 2011).

171. Claire Anderson, Janet Krska, Elizabeth Murphy and Anthony Avery, "The Importance of Direct Patient Reporting of Suspected Adverse Drug Reactions: A Patient Perspective," *British Journal of Clinical Pharmacology* 72, no. 5 (November 2011).

A prime example of the dangers of underreporting is the case of Essure, a permanent contraceptive device. Essure comprised of two metal coils inserted into the fallopian tubes by a doctor. The body naturally created scar tissue around the coils, which prevented sperm from reaching an egg. The procedure could be done in a doctor's office without anesthesia, did not require any incisions, and patients could return to normal activities the same day.[172] Essure entered the Canadian market in 2002 as a Class III medical device and was marketed as a safer alternative to tubal litigation. However, tens of thousands of women around the world have experienced serious complications with Essure. Many Canadian patients experienced pain, back aches, rashes, and constant bleeding after having the device inserted, but when they reported these complications to their doctors, they were either told that the effects were normal and would subside with time, or that the complications were unrelated to the implant.[173] As a result, Health Canada received only one adverse event report within the first 12 years that Essure was sold on the Canadian market.[174] Indeed, the widespread nature of these complications were not publicly acknowledged until 2013, when women around the world started sharing their stories through a Facebook support group. Since the device is intended to remain in the body permanently, some women have opted for a hysterectomy in order to remove the device from their bodies. As of October 2018 in the United States, over 18,000 women have filed lawsuits against Essure's manufacturer, Bayer.[175]

In response to the increasing number of health complaints, the notified body in Ireland suspended Essure's CE marking in 2017, which halted all new sales of the device within the

172. Laura Clemenston, Lisa Ellenwood, and Gillian Findlay, "Feeling 'Sliced Up Inside': Birth Control Implant Essure Led to Pain, Serious Problems for Some Women," *CBC News,* December 2, 2018, https://www.cbc.ca/news/health/fifth-estate-essure-implant-files-1.4925978.

173. Clemenston, Ellenwood, and Findlay, "Feeling 'Sliced Up Inside'."

174. Clemenston et al., "Feeling 'Sliced Up Inside'."

175. Clemenston et al., "Feeling 'Sliced Up Inside'."

European Union.[176] The manufacturer subsequently withdrew the product from the market in a few select countries, including Canada and the United Kingdom, and is now no longer marketed anywhere in the world.

If patients had been encouraged to file adverse event reports for Essure, then regulatory bodies may have noticed an emerging pattern sooner. Adverse reactions such as back aches and migraines may seem minor and even unrelated to the device, but a pattern emerges when reported in large numbers. Eventually it was discovered that some of these side effects were actually a sign that the device had migrated and perforated internal organs. If women had not started sharing their experiences online, then some of these linkages may never have been discovered. Adverse event reporting is essential to limit the number of complications experienced by patients; if reports are not filed, then regulators and researchers are unable to develop strategies to prevent the complication from recurring.

Canada has faced issues with underreporting for years. In 2002, the United Kingdom and the United States received more than five times as many adverse event reports per capita for medical devices than Health Canada.[177] At the time, Health Canada acknowledged that its lower levels of reporting were due, "in part, to its limited activities in the area of post-market surveillance."[178]

In 2009, Canada followed the United Kingdom's example and established an online adverse event reporting database to make it easier for consumers and health care professionals to

176. Natasha Hinde and Rachel Moss, "Essure Sterilisation Implant: Growing Health Concerns Over the Permanent Contraception," *Huffpost,* August 29, 2017, https://www.huffingtonpost.co.uk/entry/what-is-the-essure-sterilisation-implant-and-why-is-it-causing-women-to-need-hysterectomies_uk_59a521bde4b0446b3b862624?ec_carp=1483728053529348031.

177. Canada, Office of the Auditor General of Canada, *Report of the Auditor General of Canada to the House of Commons: Chapter 2 Health Canada—Regulation of Medical Devices,* (Ottawa, ON: Office of the Auditor General of Canada, March 2004): 22.

178. Canada, Office of the Auditor General of Canada, *Report of the Auditor General,* 22.

file a report. Currently, medical devices and drugs have separate online portals for consumers to file adverse event reports.[179]

The United Kingdom's Yellow Card reporting scheme was one of the first spontaneous adverse event reporting mechanisms for drugs and devices in the world. Over time, reporting eligibility has been expanded to the general public, although doctors and nurses continue to file the most reports.[180] The system has identified important risks associated with many health products, with the help of its high reporting rate compared to other reporting schemes in the European Union.[181] For example, the MHRA identified risk factors associated with the Nexplanon implant migrating to the lungs after receiving three adverse event reports.[182] The MHRA subsequently advised health care professionals to teach patients how to check that the implant was properly in place. The MHRA also advised doctors to perform a chest x-ray as soon as possible if the implant could not be located by touch. These updated recommendations should increase the odds of catching this rare complication sooner, thus preventing further adverse health effects.

In 2015, the MHRA launched a Yellow Card app to further ease online reporting.[183] The United States FDA has a similar app to report adverse medical device reactions, although the app cannot currently be used for drug reports.[184]

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179. Canada, Government of Canada, "Report an Adverse Reaction or Medical Device Problem," *Government of Canada,* last modified July 24, 2019, https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

180. United Kingdom, Medicines and Healthcare Products Regulatory Agency, *Trends in UK Spontaneous Adverse Drug Reaction (ADR) Reporting Between 2008-2012,* (London, UK: MHRA, 2013): 20.

181. Steve Chaplin, "The Yellow Card Scheme—Why are GPs Under-Reporting?" *Prescriber* 17, no. 15 (August 5, 2006): 18.

182. United Kingdom, Medicines and Healthcare Products Regulatory Agency, *Contribution of Yellow Cards to Identifying Safety Issues,* (London, UK: MHRA, accessed August 10, 2019): 9.

183. United Kingdom, Medicines and Healthcare Products Regulatory Agency, "Digital Evolution for Ground-Breaking Yellow Card Scheme," *MHRA*, July 14, 2015, https://www.gov.uk/government/news/digital-evolution-for-ground-breaking-yellow-card-scheme.

184. United States, Food and Drug Administration, "MedWatcher Mobile App," *Food and Drug Administration,* September 25, 2018, https://www.fda.gov/medical-devices/medical-device-reporting-mdr-how-report-medical-device-problems/medwatcher-mobile-app.

Improving the ease of patient adverse event reporting may increase the number of adverse events received by Health Canada. Of course, receiving the reports is only half the battle. Health Canada also needs to ensure that it has a sufficient system in place to assess emerging patterns and update product information when necessary to reflect new information.

Even with a vigorous pre-market approval processes, regulators cannot foresee all of the potential risks that may accompany a new contraceptive. Post-market surveillance can give Canadians peace of mind knowing that a new contraceptive—whether it is considered a drug or device—will continuously be monitored. Since women's complaints are frequently dismissed by medical professionals, online reporting ensures their concerns will be heard.

Vd. Analysis

Post-market surveillance data can also be informative for regulators who are considering approving a drug product that has a long market history in another jurisdiction. For example, a new drug submission for Nexplanon, a subdermal implant, was rejected by Health Canada even though the product had already been approved in the European Union, Australia, and the United States. Additionally, the implant had already been marketed in over 80 countries for decades, but the manufacturer's clinical trial data was not recent enough to meet Health Canada's standards.[185] The manufacturer decided that it was not financially feasible to conduct new trials given the small size of Canada's market.[186] This is an example where increased communication between international regulators could prove beneficial. If a device has been on the market in a comparable jurisdiction for several years prior to applying to Health Canada, the Canadian regulators could discuss the application with the initial authority that approved the device. In addition to discussing trial design, Canada could collect and analyze information from studies conducted after the device entered the market, such as adverse event reports, academic papers, or

185. Barton, "Stringent Health Canada Requirements."
186. Barton, "Stringent Health Canada Requirements."

the manufacturer's PSUR. Utilizing other countries' post-market surveillance data could potentially be more insightful than original clinical trial data, since post-market data is collected in real world settings with larger sample sizes.

This option is already within Health Canada's purview for many medicinal products, since Health Canada has confidentiality arrangements with a number of international regulators, including the EMA, MHRA, FDA, and TGA.[187] The arrangement allows Health Canada to share and receive pharmacovigilance data that may otherwise be considered confidential business information. [188] Regulators can also share safety concerns that arise from periodic safety update reports and adverse drug reactions.

Since many LARC brands are internationally marketed, manufacturers should continue to periodically report on their global marketing history once they are approved, as outlined in the ICH guidelines. Manufacturers should also continue to report on global adverse events, not just those that take place within Canada. To enforce this, Canada should amend the *Medical Device Regulations* to require high-risk device manufacturers to report foreign adverse events to Health Canada, regardless of whether or not the foreign regulator required the company to take corrective action. International communication is especially important for a small market like Canada, where adverse event data may be underestimated if limited to domestic reports.

Health Canada is making important progress towards proactive post-market surveillance by extending the annual reporting requirement to medical device manufacturers. However, unlike in the United Kingdom, the United States, and Australia, Health Canada does not independently assess each periodic safety update report. Canada only requires the manufacturer

187. Canada, Health Canada, "Health Products and Food Branch International Collaborative Arrangements," *Government of Canada,* last modified March 8, 2019, https://www.canada.ca/en/health-canada/services/drugs-health-products/international-activities/international-collaborative-arrangements.html.

188. European Medicines Agency, "Partners & Networks: Canada," *European Medicines Agency,* accessed August 12, 2019, https://www.ema.europa.eu/en/partners-networks/international-activities/bilateral-interactions-non-eu-regulators/canada.

to submit its annual report if the manufacturer determines that the risk-benefit ratio has changed. This approach is risky because manufacturers have an incentive to keep their risk-benefit assessment consistent to increase sales and prevent lawsuits. This approach is especially risky for LARC products in particular given their higher threshold for safety in a risk-benefit assessment. For example, despite international scrutiny, Essure's manufacturer still maintains that the device has an acceptable risk-benefit ratio and cited a "decline in sales" as the reason for taking the device off the market.[189] In order to mitigate manufacturer bias, Health Canada should require LARC manufacturers to submit PSURs at a predetermined interval. Health Canada should assess each report to independently determine if the risk-benefit ratio has changed. To reduce the regulatory burden for internationally marketed LARC products, Health Canada could aim to align its report schedule with the European Union when possible. In order to ensure that the product is rigorously reviewed, Health Canada should conduct an assessment of the report independent of foreign regulators.

To encourage Canadians to file domestic adverse event reports, Health Canada should launch an educational campaign on the benefits of adverse event reporting in tandem with developing a single online portal for drug and device reports, similar to the United Kingdom's Yellow Card website. Having a unified website for all adverse reactions can help consumers navigate the system, especially when patients may not be aware if their LARC product is regulated as a drug or device. To further ease adverse event reporting, Health Canada should also consider developing an app to file drug and device reports.

189. Susan Scutti, "Bayer to Stop Selling Essure Birth Control Device in US," *CNN,* Friday 20, 2018, https://www.cnn.com/2018/07/20/health/essure-bayer-sales-stop-bn/index.html.

VI. Transparency

VIa. Canada

Once a regulatory body finishes reviewing a drug or device submission, some jurisdictions publish a public document summarizing the regulatory body's decision to approve or reject the product. In Canada, these documents are known as Regulatory Decision Summaries (RDS) and Summary Basis of Decision documents (SBD). Starting in 2015, Health Canada began posting RDSs and SBDs on its website to help Canadians understand Health Canada's rationale for approving certain drugs and medical devices.[190] These summary documents are written by technical writers hired by Health Canada. They are designed to build public trust in the approvals system and ensure that doctors and patients have accurate information about a product's safety and efficacy. Summary Basis of Decision documents come with Readers' Guides and are written with a general audience in mind, although the language becomes progressively technical towards the end of the document.[191] SBDs are only published for drugs approved after 2012 that contain new active substances, and Class III and IV devices that contain "novel" technology.[192] Due to this restriction, an SBD has not been written for any LARC product in Canada to date.

Regulatory Decision Summaries, on the other hand, are published for new prescription pharmaceuticals and devices approved after April 2015, including those that contain previously approved active substances.[193] RDSs are similar to SBDs, but are much shorter, and are also published for all approved Class III and IV medical devices. Additionally, RDSs provide the

190. Canada, Government of Canada, "Regulatory Decision Summaries," *Government of Canada,* January 31, 2019, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/regulatory-decision-summary.html.

191. Canada, Health Canada, *Frequently Asked Questions: Summary Basis of Decision (SBD) Project: Phase II* (Ottawa, ON: Government of Canada, June 29, 2012): 1.

192. Canada, Health Canada, *Frequently Asked Questions: Summary Basis of Decision,* 1.

193. Canada, Government of Canada, "Regulatory Decision Summaries."

rationale for applications that were rejected by Health Canada. Positive decision summaries for drugs and Class IV medical devices have been posted to the Health Canada website since 2015, and Class III positive decisions are currently being added for devices approved on or after January 31, 2019. Negative decision summaries, however, will only be posted for rejected pharmaceuticals and Class IV devices.[194] This means that negative decisions for new copper IUDs will not be posted, but negative decisions for hormonal IUDs or subdermal implants will be. Additionally, regulatory decision summaries for previously approved contraceptives will not be retroactively posted. As a result, RDSs are currently only available for two hormonal IUDs, and no non-hormonal IUDs.

Information on rejected applications can be especially important for Canadian women who are awaiting the arrival of innovative contraceptive devices that are approved elsewhere. The Gynefix, for example, is a frameless non-hormonal IUD that has been prescribed by doctors in Europe for over a decade.[195] All non-hormonal IUDs currently approved in Canada are T-shaped, but the frameless structure of the Gynefix fits all uterus shapes, has fewer menstrual side-effects, and has a lower probability of getting dislodged in the body than a T-shaped device.[196] Given Health Canada's current classification scheme, it is likely that the GyneFix would be considered a Class III medical device. Since Health Canada does not release data on Class III medical device applications unless they have been approved, it is uncertain if the Gynefix has ever applied to Canada. However, the Gynefix was available in a Vancouver clinic for a test trial until 2014.[197] No information is publicly available about the results of the trial, but

194. Canada, Health Canada, "Notice: Health Canada's Action Plan on Medical Devices: Continuously Improving Safety, Effectiveness and Quality—Informing Canadians About Medical Device Treatment Options," *Government of Canada,* January 31, 2019, https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/activities/announcements/notice-pre-market-transparency-initiative-medical-devices.html.

195. Beaton, "Why Does America Have Fewer Types of IUDs?"

196. Wildemeersch, "New Intrauterine Technologies," 226-229.

197. Cheerful Deathling, "I Took Too Long, Now the IUD's Gone. Bagow! (Gynefix No Longer Available in North America. I Am SO FRUSTRATED.)" *Reddit*, 2015,

Canadian women who participated have taken to the internet to discuss their positive experiences with the Gynefix, and to express their confusion about why the device is still not available here.[198] Since the trial has now ended, some Canadian women have travelled to Europe to receive the device, as the Gynefix is not available anywhere in North America.[199] Canadian women should be able to find out if contraceptive devices had applied for Health Canada approval and were subsequently rejected. If the Gynefix was rejected for safety or efficacy reasons, then perhaps Canadian women would reconsider going through such great lengths to receive it.

Open access to regulatory summary documents ensures that women and doctors can be accurately informed about the safety and efficacy of approved (and rejected) LARC products. Due to advertising restrictions, Canadian women learn about approved contraceptives from doctors, word of mouth, and the internet. Some schools may also provide information about contraceptives in their provincial sexual health curricula. In Canada, hormonal IUDs are only allowed to advertise to the general public if the ad "does not exceed name, price and quantity" of the device.[200] Since non-hormonal IUDs are classified as medical devices, they are completely prohibited from advertising to the general public.[201] Reliable, evidence-based, and unbiased information on contraceptive products is an especially valuable resource for women, especially when considering the large amount of unreliable information available on the internet. [202]

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https://www.reddit.com/r/TrollXChromosomes/comments/2p3rmj/i_took_too_long_now_the_iuds_gone_bagow_gynefix/.

198. Ellen Weibe, "GyneFix-Viz: A Study of Serosal-Anchor Distance," *U.S. National Library of Medicine,* accessed November 27, 2018, https://clinicaltrials.gov/ct2/show/study/NCT01979835; Cheerful Deathling, "I Took Too Long."

199. Michele Claire, "Scheduled to Get a Gynefix Mini at Willow Women's Clinic in Canada!" *IUD Divas,* January 31, 2012, https://iud-divas.livejournal.com/3029238.html.

200. Musende, *Health Canada's Regulatory Oversight*, 31.

201. Musende, *Health Canada's Regulatory Oversight*, 31.

202. Peter Papathanasiou, Laurent Brassart, Paul Blake, Anna Hart, Lel Whitbread, Richard Pembrey and Jill Kieffer, "Transparency in Drug Regulation: Public Assessment Reports in Europe and Australia," *Drug Discovery Today* 21, no. 11 (November 2016): 1812.

A 2015 Canadian survey found that misconceptions about the safety of IUDs were quite common, with 18 per cent of women mistakenly believing that an IUD can cause infertility.[203] Studies show that LARC use increases dramatically when women have access to reliable information about their contraceptive options.[204] Additionally, when women are presented with information about the effectiveness of different contraceptive methods, they are far more likely to choose an IUD.[205] Having easy access to reliable information enables women to come prepared to consult with their doctors about which contraceptive method will work best for their bodies. Unfortunately, there is still little public information available about approved LARC products in Canada.

One source of information that Canadians do have access to are product monographs, which contain scientific, consumer, and prescribing information. Drug manufacturers prepare product monographs as part of the drug approval process. Once approved by Health Canada, manufacturers send the monograph to health care professionals to inform them about the appropriate use of the drug.[206] Up until 2014, the general public could only read full product monographs after completing an Access to Information Request.[207] Now, product monographs are publicly posted on the Health Canada website. The monograph contains more technical information regarding potential risks and side effects of the drug, contraindications, a summary

203. Brian Hauck and Dustin Costescu, "Barriers and Misperceptions Limiting Widespread Use of Intrauterine Contraception Among Canadian Women," *Journal of Obstetrics and Gynaecology Canada* 37, no. 7 (July 2015): 611.

204. Angela Dempsey et al., "Predictors of Long-Acting Reversible Contraception Use Among Unmarried Young Adults," *Contraception* 84, no. 3 (September 1, 2011): 317.

205. Jennifer J. Frost, Laura Duberstein Lindberg, and Lawrence B. Finer, "Young Adults' Contraceptive Knowledge, Norms and Attitudes: Associations with Risk of Unintended Pregnancy," *Perspectives on Sexual and Reproductive Health* 44, no. 2 (2012): 112; David L. Eisenberg, et al. "Knowledge of Contraceptive Effectiveness," *American Journal of Obstetrics and Gynecology* 206, no. 6 (June 2012): 479.e6.

206. Canada, Health Canada, *Frequently Asked Questions: Product Monographs Posted to the Health Canada Website*, (Ottawa, ON: Government of Canada, July 11, 2014): 1.

207. Canada, Health Canada, *Frequently Asked Questions: Product Monographs*, 2.

of the clinical trials, adverse drug reactions that occurred during clinical trials, post-market adverse reactions, and information about how the drug achieves its primary purpose.

Product monographs can be a useful source for women who want to know more about a LARC product's technical safety and efficacy information. However, since product monographs can be quite long and are intended for pharmacists and physicians, they can be difficult to understand for someone without a medical background. Additionally, product monographs are not available for medical devices.

With an increasing amount of scientific information reviewed as part of the drug/device approval process, regulators are tasked with preparing summary documents that meet a variety of stakeholder needs. [208] For example, RDSs and SBDs may not provide satisfactory information for doctors and researchers, since they are only summaries of relevant documents submitted during the approval process. These summaries may not provide enough information to uncover latent safety concerns or to reveal potential bias in trials.[209] When Health Canada held stakeholder consultations regarding SBDs, a number of consumer groups expressed that SBD documents would only be useful if there were an additional online-portal with access to complementary information, such as details of clinical trials and reviewers' notes. [210] Instead of summary documents, many medical professionals and researchers want access to the full regulatory file, including raw data so that they can conduct their own independent analyses.

Up until recently, it was extremely difficult for Canadians to access information from Health Canada when they wanted to learn more about an approved drug product. For example, one Canadian doctor spent seven years trying to access clinical efficacy data from Health Canada

208. Papathanasiou, et al., "Transparency in Drug Regulation," 1812.

209. Joel Lexchin and Barbara Mintzes, "Transparency in Drug Regulation: Mirage or Oasis?" *Canadian Medical Association Journal* 171, no. 11 (November 23, 2004): 1364.

210. Ann Silversides, *Transparency and the Drug Approval Process at Health Canada* (Toronto, ON: Women and Health Protection, Fall 2005): 19.

for a controversial morning sickness pill.[211] The delay was largely caused by the fact that information contained in a drug/device application package was considered confidential business information by Health Canada. This meant that the public—including medical professionals—could only review the data through an Access to Information request, and only after the government received permission from the product sponsor to release the information. Even then, the data received may be heavily redacted, and the recipient could have to sign a confidentiality agreement before receiving the information.

After years of consultations and stakeholder feedback, Health Canada announced that it would start releasing anonymized clinical data through the new Clinical Information Portal starting March 13th, 2019. Health Canada will update the portal with the clinical information of new drugs as they are approved; however, clinical data for drugs approved prior to March 2019 will only be added upon request. [212] Clinical information for medical devices will start to be uploaded to the portal starting in 2021. This new push towards greater transparency in clinical trials data has the potential to increase the quality of contraceptive products and improve public health. Researchers will be able to scrutinize the data and publish independent assessments that may spur a continual conversation about the suitability of LARCs for certain populations, thus assisting with post-market surveillance. [213]

Health Canada's move towards greater clinical trials transparency is another effort to bring Canada more in line with the European Union.[214] The EU's 2014 policy document states

211. Kelly Crowe, "Morning Sickness Drug Diclectin Doesn't Work, Confidential Industry Documents Reviewed By Doctor Show," *CBC News,* January 17, 2018, https://www.cbc.ca/news/health/diclectin-pregnancy-nausea-vomiting-persaud-duchesnay-confidential-industry-documents-health-canada-1.4491300.

212. Health Canada, "Health Canada Finalizes Regulations to Provide Public Access to Clinical Information on Drugs and Medical Devices," *Health Canada,* March 13, 2019, https://www.newswire.ca/news-releases/health-canada-finalizes-regulations-to-provide-public-access-to-clinical-information-on-drugs-and-medical-devices-801820018.html.

213. Peter C Gøtzsche, "Why We Need Easy Access to All Data from All Clinical Trials and How to Accomplish It," *Trials* 12, no. 249 (November 23, 2011).

214. Canada, Department of Health, "Regulations Amending the Food and Drug Regulations (Public Release of Clinical Information)," *Canada Gazette* 151, no. 49 (December 9, 2017).

that clinical trial data should not be considered commercially confidential information, because the interests of public health outweigh the interests of the manufacturer.[215]

VIb. United Kingdom

In 2015, the European Medicines Agency started to post clinical study reports to its website for all new drug approvals. The reports contain information about the design and results of clinical trials. Clinical study reports are expected to contain anonymized individual patient data once the second phase of the policy is implemented.[216]

For drugs that are approved through the centralised procedure in the European Union, detailed product information is compiled into a European Public Assessment Report (EPAR), which is then published on the European Medicines Agency website. The report is similar in purpose to a Summary Basis of Decision in Canada, in that it justifies to the public the EMA's decision to approve or reject a marketing authorization request. Unlike Canada, an EPAR is not a single document, but a portfolio of documents containing scientific assessments and summaries of clinical trials data that supports the EMA's decision to approve or reject a drug.[217] Each approved drug has its own EPAR webpage, which includes a "question and answer" style summary for the general public, followed by attachments to more technical documents for doctors and researchers. However, as previously mentioned, no LARCs have applied for market authorization through the centralised procedure.

Data for drugs approved through mutual or decentralised procedures may be published on the Reference Member State's website or database. This can make it difficult to find product

215. European Medicines Agency, *Publication and Access to Clinical-Trial Data*, (London, UK: European Medicines Agency, June 24, 2013): 2.

216. European Medicines Agency, *European Medicines Agency Policy On Publication of Clinical Data For Medicinal Products for Human Use,* (London, UK: European Medicines Agency, March 21, 2019): 7.

217. European Medicines Agency, "European Public Assessment Reports: Background and Context," *European Medicines Agency,* July 15, 2019, https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context.

information on LARC products, since it requires knowing which country served as the reference member state. Furthermore, the type of data contained in the report can vary depending on which country drafted the report. The EMA has a public list of each country where a drug is approved, but it does not include which country served as the Reference Member State.[218] Several countries have served as reference member states for hormonal IUDs in the European Union: Finland was the first country to approve the Mirena in 1990, Sweden served as the reference member state for the Jaydess and Kyleena, and the United Kingdom took the lead on a number of lesser-known IUDs, including the Levosert and Benilexa.[219]

Information on medical devices is stored in the European Databank on Medical Devices (Eudamed). Eudamed contains information on clinical trial investigations, justifications for device classifications, and other regulatory documents. The databank was established in 2011 but is only accessible to national competent authorities. It is expected that Eudamed content will be partially available to the public starting in 2020.[220]

VIc. United States

In the United States, clinical trial information, along with letters of correspondence between regulators and drug sponsors, labels, patient package inserts, and other relevant data that accompanies a drug submission, is available through the Drugs@FDA database.[221] The database

218. European Medicines Agency, *List of Nationally Authorised Medicinal Products, Active Substance: Levonorgestrel* (London, UK: European Medicines Agency, September 10, 2015).

219. United Kingdom, Medicines and Healthcare Products Regulatory Agency, *Public Assessment Report: Decentralised Procedure Levosert* (London, UK: Medicines and Healthcare Products Regulatory Agency, December 14, 2018); United Kingdom, Medicines and Healthcare Products Regulatory Agency, *Public Assessment Report: Decentralised Procedure Benilexa* (London, UK: Medicines and Healthcare Products Regulatory Agency, February 20, 2015); Sweden, Lakemedelsverket Medical Products Agency, *Public Assessment Report Scientific Discussion: Jaydess (Levonorgestrel)* (Uppsala, Sweden: Lakemedelsverket Medical Products Agency, December 4, 2012); Sweden, Lakemedelsverket Medical Products Agency, *Public Assessment Report Scientific Discussion: Kyleena (Levonorgestrel)* (Uppsala, Sweden: Lakemedelsverket Medical Products Agency, October 3, 2016).

220. European Commission, "European Database on Medical Devices," *European Commission,* accessed July 24, 2019, https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/eudamed_en.

221. United States, Food and Drug Administration, "Drugs@FDA Frequently Asked Questions," *U.S. Food and Drug Administration*, accessed July 24, 2019, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=faq.page#purpose.

contains information for almost all LARCs that were ever approved in the United States, even those that have been discontinued or otherwise removed from the market.[222]

Up until 1994, the FDA published Summary Basis of Approvals (SBA) that were very similar to Canada's new Summary Basis of Decision documents. In 1994, the FDA instead started to publish the redacted documents used in the drug approval process to alleviate the burden on review staff. The redacted reviews provide much more information than the SBAs, but critics have raised concerns that the posted documents are far too technical for the general public.[223] Additionally, some drug products have so many review documents attached to them that it can be difficult to find a specific piece of information.

The United States recently launched a Clinical Data Summary Pilot Program, which will test the feasibility of posting regulatory document summaries in a more user-friendly way. The FDA is also collecting stakeholder feedback on new ways to inform the public about the FDA's decision-making process for individual drug products.[224]

VId. Australia

In Australia, the TGA releases a Public Assessment Report (AusPAR) for approved and rejected prescription medicines. An AusPAR provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve an application.[225] AusPARs are modelled after European Public Assessment Reports, except all the information—including public-friendly summaries and technical review forms—is contained in

222. United States, Food and Drug Administration, "Drugs@FDA Frequently Asked Questions."
223. Silversides, *Transparency,* 17.
224. United States, Food and Drug Administration, "Clinical Data Summary Pilot Program," *U.S. Food and Drug Administration*, June 26, 2019, https://www.fda.gov/drugs/development-approval-process-drugs/clinical-data-summary-pilot-program.
225. Australia, Department of Health, Therapeutic Goods Administration, "Australian Public Assessment Reports for Prescription Medicines (AusPARs)," *Australian Government,* July 8, 2019, https://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars.

one comprehensive document. AusPARs are publicly accessible on the TGA's website. Only prescription medicines that entered the ARTG after November 2009 have an AusPAR. [226]

Australia also releases Product Information documents designed for healthcare professionals and Consumer Medicines Information for consumers; which if combined, would be similar to Canada's Product Monograph.[227] The Product Information document is provided as an attachment to an AusPAR.[228]

There are no similar public documents for medical devices in Australia. The TGA is currently collecting feedback on policy options that will make it easier for consumers to find information in an easily accessible and user-friendly way.[229] Australia does not currently have any plans to release clinical trials information.

VIe. Analysis

Health Canada has made significant efforts in the past five years to increase regulatory transparency for drug and medical device approvals; however, there is still room for improvement. Learning from the United States' experience, it is important for Health Canada to continue to post summary documents in addition to more detailed data so that the general public, medical professionals and researchers can all have access to the type of data they need to aid in post-market surveillance. Summary documents of regulatory decisions are intended to improve public trust in the regulatory system; however, without summaries of all previously approved LARC products, this objective may not be met. Additionally, Health Canada should post

226. Australia, Department of Health, Therapeutic Goods Administration, "AusPARs."

227. Australia, Department of Health, Therapeutic Goods Administration, "Consumer Medicines information (CMI)," *Australian Government,* January 3, 2019, https://www.tga.gov.au/consumer-medicines-information-cmi; Australia, Therapeutic Goods Administration, "Product Information," *Australian Government,* November 20, 2017, https://www.tga.gov.au/product-information-0.

228. Australia, Department of Health, Therapeutic Goods Administration, "Australian Public Assessment Reports for Prescription Medicines (AusPARs)," *Australian Government*, July 25, 2019, https://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars.

229. Australia, Department of Health, Therapeutic Goods Administration, *An Action Plan for Medical Devices,* (Symonston, Australia: Therapeutic Goods Administration, April 2019).

negative decision summaries for Class III medical devices so that women can be informed about why certain non-hormonal IUDs are not available on the Canadian market. The benefits of improving Canada's regulatory system for LARC products may not be fully realized if consumers and medical professionals are not sufficiently informed about the efficacy and safety of contraceptive products.

VII. Conclusion

Health Canada has made many changes over the years to its pharmaceutical and medical device regulations and has announced several more in the wake of the global implant scandal. However, more changes are necessary in order to ensure that Canadian women have access to a variety of safe and effective long-acting reversible contraceptives. The global nature of the implant scandal highlighted the need for national regulators to communicate with each other and for data to be more publicly accessible in order to protect consumers from unsafe products.

Before applying to Canada, most contraceptive drugs and devices first seek market approval in larger markets, such as the United Kingdom and the United States. As a relatively small market, it can be advantageous for Canada to harmonize its regulatory approach as closely as possible with the United Kingdom and the United States in order to reduce the regulatory and administrative burden for LARCs seeking market approval in Canada. At the same time, Canada should not rely too heavily on foreign regulators so as to reduce its domestic regulatory capacity. Canada should maintain its autonomy as an independent regulator in order to prevent a "brain drain" of industry experts and to maintain responsibility for consumer protection. Nevertheless, Canada should continue to work with major regulators to share information through confidentiality arrangements. Regulators can come to different conclusions when interpreting drug and device data, which can spark conversation and encourage further studies. The more

people that assess a product's safety and efficacy, the more information doctors and consumers will have about a product's viability.

Additionally, Canada needs to do more in terms of post-market surveillance and transparency. Post-market data may be more insightful than original clinical trial data, since post-market data is collected in real world settings with larger sample sizes. Improving adverse event reporting will also serve to alert regulators and manufacturers when previously unknown side effects arise. It is especially important to flag potential side effects as early as possible for contraceptive products, since contraceptives are typically used by healthy females for prolonged periods of time, meaning that the acceptable amount of risk under a risk-benefit ratio is lower than for other medical products.

Given the wealth of misinformation available on the internet, it is imperative that women have access to reliable information about the regulatory process for LARCs. Both positive and negative decision summaries need to be publicly available from Health Canada for all LARCs. More detailed clinical data also needs to be made available for independent researchers and medical professionals. Doing so will allow women to make informed choices about their bodies and foster trust in the Canadian regulatory system.

If Canada adapts its regulatory procedures to better align with international regulators and takes measures to improve transparency, then Health Canada will be better equipped to grant market approval to safe and effective long-acting, reversible contraceptives. The regulatory burden for LARC sponsors will be smaller relative to the size of Canada's market, thus prompting new LARC products from other countries to seek out Health Canada approval.

Increasing LARC variety in the Canadian market is the first step to ensuring that women are able to choose a birth control method that works best for her body. Further research should be conducted to ensure that women have unrestricted access to all commercially available products.

Potential study topics include lowering the out-of-pocket cost of contraceptives, ensuring that health insurance plans cover all types of birth control, improving access to pharmacies, and reducing prescribing bias. Ensuring unrestricted access to safe and effective contraceptives is an important step towards increasing women's ability to exercise full bodily autonomy in Canada.

VIII. Summary of Recommendations

1. Reclassify non-hormonal IUDs as Class IV medical devices.
2. Maintain Health Canada's independence as a national drug and medical device regulator.
3. Update Health Canada's guidance document on clinical trial requirements for hormonal contraceptives. Remove unnecessary requirements and harmonize guidelines with the EMA and FDA.
4. Require manufacturers of Class III and IV contraceptive devices to test their products in healthy human subjects prior to market approval.
5. Amend the *Medical Device Regulations* to require manufacturers of high-risk contraceptive devices to adhere to Good Clinical Practice when conducting investigational testing.
6. Analyze post-market data when approving a drug or device that has a long market history in another comparable jurisdiction.
7. Amend the *Medical Device Regulations* to require high-risk contraceptive device manufacturers to report foreign adverse events to Health Canada, regardless of whether or not the foreign regulator required the company to take corrective action.
8. Require LARC manufacturers to submit periodic safety update reports to Health Canada at a predetermined interval. Independently assess each report, regardless of if the manufacturer believes the risk-benefit ratio has changed.
9. Develop a user-friendly online portal for drug and device adverse event reporting. Launch an educational campaign in tandem to encourage spontaneous voluntary reporting.
10. Release Summary Basis of Decision and Regulatory Decision Summary documents for all previously approved LARC products.
11. Post negative decision summaries for all Class III medical devices so that women can know why certain non-hormonal IUDs are not available on the Canadian market.

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