

**Reflections on Depo Provera:
Contributions to Improving Drug Regulation in
Canada**

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Controlling reproduction has never been exclusively a private matter between a woman and her partner. Legislation, court decisions, medical practices, cultural norms, and technological innovations have restricted and expanded reproductive options at varying moments in... history.¹

Introduction

In Canada, a drug regulatory system exists to ensure that when new drugs arrive on the market, the intended users can approach them with a high degree of confidence, knowing that the drugs have passed through a drug approval system whose mandate is to protect the health of all Canadians. When it comes to drugs intended for healthy people, as is the case with hormonal contraceptives, this paper takes the position that risks and benefits must favour the highest safety standards.

The regulatory history and safety profile of the injectable hormonal contraceptive Depo Provera has been, and continues to be, controversial. After repeated rejections, Depo Provera was approved for contraceptive use in Canada in April 1997, despite the concerns of women's health groups and community organizations that raised questions about Depo Provera's safety profile.

Opposition to Depo Provera is grounded in a troubling legacy of reproductive pharmacology licensed for women, including drugs such as DES, early high-dose oral contraceptives, the Dalkon Shield, and Hormone Replacement Therapy (HT). A 2005 Health Canada advisory publicizing the negative effects of Depo Provera on bone health adds yet another chapter to the series of problematic stories about approved drugs that pose risks to women's health.

Long before its official approval as a contraceptive, millions of women worldwide were given 'the shot' while questions about clinical trial design, lack of access to research findings, the targeting of vulnerable populations, and related issues of 'informed consent', were not seriously addressed. While Depo's supporters saw it as another 'choice' for women – a great technological advance in fertility and 'population control' – critics saw yet another drug with a questionable safety profile being promoted prematurely to women.

This paper examines the ongoing story of Depo Provera, including: its regulatory history; how it has been and continues to be used, and; what is known about its safety profile. When the full history of reproductive drugs approved for women is considered, the areas of concern highlighted in the Depo Provera saga are not new or unique. From a health policy perspective, this story is both important and instructive in that it shines a light on many of the problems with drug regulatory processes in Canada, including:

- the lack of transparency in the drug regulatory process;
- failure to apply the precautionary principle;
- public dissemination of incomplete and/or misleading information, targeting healthy women;
- application of clinical trial data to untested (or inadequately tested) populations;

¹ Clarke, 1998, p.xv

- failure to apply adequate “informed consent” procedures; and,
- social stereotyping and bias in prescribing practices.

While these issues are of general concern for all prescription drugs, they are particularly germane when the drugs in question are for populations of healthy women. The paper concludes with a series of recommendations designed to address the issues noted above.

Depo Provera: The Basics

Depo Provera® (depot medroxyprogesterone acetate [DMPA]) was developed by the Upjohn Company (now part of Pfizer) in the late 1950’s, and first approved for the treatment of endometriosis, and threatened or habitual miscarriage in 1960 (however, in 1974 it was shown to be ineffective for these purposes).² During the initial testing of Depo Provera in Brazil, researchers noticed that the drug caused women to stop menstruating. In fairly short order this realization led to Depo’s reformulation as a drug for contraceptive use.³

Depo Provera is a long-acting injectable hormonal contraceptive of synthetic progesterone. It is more than 99% effective in preventing pregnancy when given as indicated. A woman who uses Depo Provera must return to a healthcare provider for re-injection once every 12 to 13 weeks. Like other progestin-only contraceptives (containing no estrogen),⁴ Depo Provera prevents pregnancy by inhibiting ovulation and by altering the environment of the cervix and the uterus so that sperm are less mobile, reducing chances for conception and implantation.⁵ Unlike barrier forms of contraception, Depo Provera does not provide any protection against sexually transmitted infections (STIs), or HIV/AIDS. In Canada, Depo Provera costs approximately \$26.00 per injection (\$108.00 per year)⁶ and is covered by provincial formularies and most employer health plans.

It is estimated that among Canadian women users of contraceptives, approximately two per cent use Depo Provera.⁷ An estimated 477,179 prescriptions for the contraceptive use of Depo Provera were filled by Canadian retail pharmacies in 2005.⁸

Why women use Depo Provera

The reasons women use one method of contraception over another varies from one woman to another. For the majority of women, effectiveness and convenience are the primary factors cited for using a particular method.⁹ Women often use Depo Provera because of dissatisfaction with other methods, such as after an unplanned pregnancy. Other reasons

² It was also approved for the palliative treatment of endometrial cancer (1972) and kidney cancer (1974). See Goodman, 1985

³ Goodman, 1985

⁴ Depo Provera is the sole progestin-only contraceptive currently available in Canada.

⁵ Reproductive Health Technologies Project, 2006

⁶ In comparison, oral contraceptives are approximately \$13.00 per pack (\$156.00 per year), and are covered by provincial formularies and employer drug plans.

⁷ Black et al, 2006. Note that this figure refers to the general frequency of Depo use among women, and that use varies across groups of women.

⁸ IMS Health Canada, 2006

⁹ Hampton and McWatters, 2002

for using Depo Provera include: it is highly effective and reliable; it is long-acting; it does not produce the sometimes unmanageable side effects that women may experience using contraceptives containing estrogen; it does not require regular supplies or attention, and; it can be used discreetly by women who do not want to disclose their contraceptive use to a family member or partner.¹⁰

Health effects of Depo Provera use

The health effects that women may experience using Depo Provera vary in number and severity. In the controlled environment of clinical trials, the most frequently reported health effects include: menstrual irregularities (irregular bleeding and amenorrhea in 55%-60% of users at 12 months¹¹), abdominal pain or discomfort, weight gain,¹² dizziness, headaches, fatigue, and nervousness. Some women may also experience acne, breast tenderness, depression and decreased libido.¹³ Return of fertility may be delayed for an average of up to nine months from the time of the last injection;¹⁴ however, the delay may persist up to 18 months.¹⁵

In 2004, post-marketing studies revealed that Depo Provera use may result in significant bone mineral density (BMD) loss that increases with duration of use, and that may not be completely reversible. This may lead to an increased risk of osteoporosis and osteoporotic fractures in later life.¹⁶

Other possible health effects

A 2004 study found that women using Depo Provera may be more susceptible to sexually transmitted infections (chlamydia and gonorrhoea) than those who use other birth control methods such as the pill or the patch.¹⁷ The authors were unable to explain this finding and further research is needed on the subject. Recent studies show conflicting evidence about whether Depo Provera directly or indirectly increases the risk of HIV infection.¹⁸ Despite early concerns, there is accumulating evidence suggesting that Depo Provera does not increase women's risk of breast cancer.¹⁹

Why women stop using Depo Provera

Like all hormonal contraceptives, Depo Provera affects a woman's entire system and some users experience more side effects than others. Side effects (mainly irregular menses and weight gain) are the most commonly reported reasons for discontinuation.²⁰

¹⁰ Reproductive Health Technologies Project, 2006

¹¹ Polaneczky et al, 1996; Sangi-Haghpeykar et al, 1996

¹² Westhoff et al, 2007

¹³ Goodman, 1985; Pui, 2006; Tudiver, 1997

¹⁴ Fotherby and Howard, 1986

¹⁵ Tudiver, 1997

¹⁶ Health Canada, 2005

¹⁷ Morrison et al, 2004

¹⁸ Kleinschmidt et al, 2007

¹⁹ Shapiro et al, 2000; Skegg et al, 1995

²⁰ Davidson et al, 1997; Paul, 1997; Polaneczky and LiBlanc, 1998; Tinkle et al, 2001; Westfall et al, 1996

Although some side effects are similar to those experienced by oral contraceptive users, the effects of long-acting hormones like Depo Provera may be more disturbing because a woman cannot alleviate the symptoms simply by no longer taking the drug. Instead, she must wait an extended and unknown amount of time before the drug leaves her system.²¹

The Regulatory History of Depo Provera

Depo Provera has a long and controversial regulatory history in both the United States and Canada. The manufacturer made several applications before the drug was approved for contraceptive use in 1992 in the U.S., and in 1997 in Canada²² (see Table 1).

Depo Provera and the Food and Drug Administration (FDA): the U.S. experience

Depo Provera was initially approved for contraceptive use in the United States in 1974. Relying on the recommendation of its Advisory Committee on Obstetrics and Gynecology (ACOG), the FDA granted limited approval "...for those women who found other methods of contraception unacceptable or difficult and those who were mentally retarded and institutionalized".²³ The FDA concurred with the ACOG that the New Drug Application must: include a physician-based registry of users; provide detailed written information about the drug and its side effects, and; obtain informed consent from patients, or their parents or guardians, prior to the injection.

Opposition to the FDA decision resulted in congressional hearings on the increasing use of advisory committees in new drug approval review. The hearings revealed that the FDA had not provided its initial internal analysis of the drug trial data to the ACOG for consideration. Prior to the ACOG review, FDA medical officers recommended discontinuance of clinical Investigational New Drug use²⁴ because preliminary analysis of Upjohn data suggested possible links between Depo use and cancer. The chair of the hearings concluded that because of the "...many serious and, as yet, unresolved questions concerning [Depo Provera's] safety including the drug's role in causing cancer", approval should not have been granted.²⁵ As a result, the FDA withdrew its approval of the drug pending further advisory review of the scientific evidence.

Four years later, the advisory committee again recommended the same limited approval, despite new evidence of cancers in animal studies. This time the FDA rejected the recommendations for a number of reasons, including: links with cancers in animal studies; risk of foetal exposure; risks of prescribing estrogen to counter Depo-induced menstrual

²¹ The Committee on Women, Population and the Environment is piloting a new project entitled "Depo Diaries" to gather personal testimonies of women's experiences using Depo Provera. See Committee on Women, Population and the Environment, 2007.

²² It is important to note that because of a loophole in the US FDA and Health Canada's drug approval process, thousands of women were prescribed Depo-Provera as a contraceptive before it was officially approved for that specific use. This practice is referred to as 'off-label' prescribing, and is legal in both countries.

²³ Green, 1988, p. 423. See Green for a detailed account of the FDA and Depo-Provera story prior to its full approval.

²⁴ One of the main purposes of an Investigational New Drug (IND) application to the regulatory agency is to provide detailed documentation of the (preclinical) data showing that it is 'reasonable' (including reasonably safe for initial use in humans) to proceed with clinical (human) trials. See Center for Drug Evaluation and Research, 2001

²⁵ Green, 1988, p. 424

irregularities, and finally; because the need to justify the drug for a significant population had not been demonstrated.²⁶

Upjohn appealed to a Board of Appeal; however, in 1984 the Board recommended that Depo Provera continue to be denied approval for contraceptive use. Based on the lack of long-term safety data, Depo Provera was ruled “not safe for general marketing”.²⁷ By ruling that existing data were insufficient to prove the drug’s safety, rather than sufficient to prove its danger, the Board of Appeal left open the prospect that new data would eventually render its decision moot.

The FDA finally approved Depo Provera for contraceptive use in 1992. Approval was largely based on the results of the World Health Organization (WHO) studies of women in Kenya, Mexico, and Thailand, that demonstrated that the association between Depo Provera and breast cancer was statistically weak and comparable to the association between breast cancer and other hormonal contraceptives.²⁸

The Canadian experience: regulation and public health concerns

In Canada, women’s health groups and community agencies closely followed the regulatory odyssey of Depo Provera in the United States. Drawing on women’s experiences of harm caused by other reproductive agents, such as DES and the Dalkon Shield, several organizations came together in 1985 to form the Canadian Coalition on Depo Provera. The Coalition consisted of concerned health care providers, consumer, women’s health, and disability groups, and international non-governmental organizations. Many of these groups had attended the 1981 2nd International Conference on Women’s Health in Geneva, where they met with women from India, Bangladesh, Thailand and Latin America who were critical of the drug’s use in clinical trials and its off-label²⁹ use in population control programmes.

The Coalition sought to broaden the limited regulatory debate defined by government and industry by opening up the process. “They wanted to know about funding, about the conduct of research, about which risks are investigated and which are not, about what research was done and why, about the implications (epidemiological and ethical) of using women of the Third World as test subjects, about the acceptability of generalizing from these women to women in Canada.”³⁰ They raised questions about women’s participation in regulatory decisions concerning drugs intended for women. Specific demands included: a registry to monitor Depo use; public hearings on long-term safety issues; more research in Canada and internationally on women’s experiences with Depo Provera, and; that marketing companies’ submissions and practices be made public and open to review.³¹

The actions of the Coalition brought the question of regulatory approval of drugs into both the public and the political domains. In response to pressure by the Coalition, Health and

²⁶ Goodman, 1985

²⁷ Green, 1988, p. 430

²⁸ WHO, 1991

²⁹ Off-label prescribing refers to the practice of prescribing prescription drugs for purposes for which they have not been officially approved.

³⁰ Kaufert, 1991, p. 122

³¹ Tudiver, 1997

Welfare Canada (now Health Canada) held a series of national meetings on fertility control in 1986.³² From the Coalition's perspective however, the process around these meetings was fundamentally flawed. Although the coalition originally demanded national, public hearings, attendance at the meetings was by invitation only, there was a minimum of publicity, and the meeting environment was tightly controlled. Nevertheless, while some hearing participants supported approval of Depo Provera for contraceptive use, most presenters raised concerns about Depo Provera, such as the risk of side effects, long-term safety issues such as loss of bone density, and reported cases of inadequate informed consent, in particular among immigrant and refugee women, Aboriginal women and teens, and women with disabilities in Ontario institutions.³³

In 1988, Health Canada rejected Upjohn's application for approval of Depo Provera for contraceptive use. The company's 1992 appeal was again rejected on the basis of unresolved long-term health risks for Canadian women. Then, in 1997, Depo Provera was officially approved for contraceptive use in Canada.

As others have noted elsewhere, the specific reasons for Health Canada's change in position between 1992, when approval for Depo was last denied, and 1997, when approval was granted, are not known.³⁴ In Canada, decisions concerning drug approvals, warnings on drug labels, and other regulatory activities often lack transparency. Depo Provera is a case in point. In 1985, shortly after the U.S. decision not to approve Depo Provera due to long-term safety concerns, the *Globe and Mail* quoted an Upjohn spokesperson as saying that Depo Provera would likely be approved in Canada because, "we do things in a more private way in Canada...Here it is a matter between us and Health and Welfare."³⁵

Canadian regulatory agencies are, in theory, accountable to the public they are mandated to protect. However, the lack of transparency about drug approvals makes it impossible to review or evaluate the data on which decisions are based, and means that accountability is more fictitious than real. One has to question whose interests are being given priority in this system. Clearly health practitioners (who make prescription decisions and provide information and counselling to women), and women themselves (who will consume the drugs and experience any benefits or ill-effects), are not being well served by a system that does not permit full disclosure of available data.

³² Health and Welfare Canada, 1986

³³ Tudiver, 1997; Zarfasm, 1981

³⁴ Parent, 2000; Tudiver, 1997

³⁵ *Globe and Mail* cited in Tudiver, 1997

Depo Provera and the Loss of Bone Mineral Density

*We are also concerned about recent research, which shows a decrease in bone density in Depo-Provera users thereby increasing their risk factor for osteoporosis, a disease which is a significant health problem for Canadian women.*³⁶

*There has never been any question concerning the efficacy of Depo Provera for contraception, although...One [residual safety issue] is the possibility of osteoporosis in women who use the drug. The sponsor will be required to conduct post-marketing studies of this topic.*³⁷ (from approval letter in U.S., 1992)

From women's health groups to regulatory experts, those who have followed the story of Depo Provera have long been aware of the risk of osteoporosis in Depo users. In 1991, the Canadian Coalition on Depo Provera wrote to then federal Health Minister Benoit Bouchard and cautioned against Depo's approval, citing safety concerns, including research that showed decreased bone density in Depo Provera users.³⁸

The 2005 Health Canada advisory is based on studies conducted by Pfizer³⁹ and the National Institutes of Health (NIH), which found that Depo Provera may cause a significant loss of bone mineral density, that the loss increases with duration of use, and that the loss may not be completely reversible. The advisory recommends that "Depo Provera should be used as a birth control method... **only** if other treatments have been considered to be unsuitable or unacceptable, and should be used for the shortest period of time possible."⁴⁰ The advisory also states that there have been cases of osteoporosis and fracture associated with Depo use.

In response to Health Canada's advisory, Lorri Puil of the Therapeutics Initiative (University of British Columbia), conducted a systematic review of the literature for evidence of the association between Depo Provera and BMD loss in adolescents and premenopausal women. Several important findings were reported (see box below).⁴¹ Although the author states that "no conclusions can be drawn ...without the appropriate studies that assess fracture occurrence in [women and adolescents] exposed [to Depo Provera] and unexposed women or adolescents...", she also cautions that a lack of available evidence must not be interpreted as a lack of effect on bone health.⁴²

³⁶ Canadian Coalition on Depo Provera, 1991

³⁷ FDA Depo Provera approval letter, 1992, cited in Puil, 2006

³⁸ Canadian Coalition on Depo Provera, 1991

³⁹ Upjohn merged with the Swedish based company Pharmacia in 1985 to become Pharmacia & Upjohn which Pfizer purchased in 2003.

⁴⁰ Health Canada, 2005.

⁴¹ It is important to note that BMD testing is an intermediate endpoint that has never been validated as an appropriate measure for fracture risk in adults or adolescents, and there is no evidence that BMD testing is useful in Depo Provera users. See Puil, 2006

⁴² Puil, 2006, p.68

**Key findings from a systematic literature review
of the association between Depo Provera and bone mineral density loss⁴³**

- BMD loss may be especially important for adolescents who are usually acquiring bone mass during this period of their lives; there are no data addressing whether they accrue normal bone mass while taking Depo.
- In adolescents, there is insufficient evidence to determine whether BMD losses will be fully recovered after stopping use of Depo Provera.
- The effect of Depo Provera on bones may vary in relationship to user's age, or "hormonal milieu".
- Women aged 18 to 25 were not included in the studies that led to the Health Canada advisory. This may be a critical age group since peak bone mass will not have occurred at all bone sites by this age.
- There is no evidence to define optimal length of use in different age groups in relation to effect on BMD loss. Although bone loss is greatest in the first two years of Depo use, it continues throughout use.
- There is no evidence that modification of other risk lifestyle factors, such as quitting smoking or increasing weight bearing activity, can alter the impact of Depo Provera on bones.
- There is no evidence that supplementing with Vitamin D, calcium, estrogen, or other marketed drugs for the treatment of osteoporosis, will help offset Depo Provera's negative effect.

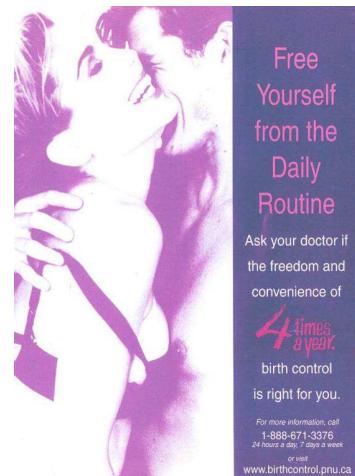
Given the available evidence, it is impossible to know at this time whether or not Depo Provera use will put women at greater risk for fractures in later life. However, because of the evidence of significant bone mineral density loss and the seriousness of certain fractures, especially hip fractures, a precautionary approach by healthcare providers and women is warranted. In this case, precaution dictates that until there is clear evidence to the contrary, we should proceed on the assumption that Depo Provera use may be associated with serious fractures and should therefore be used with extreme caution. Adolescent users of Depo Provera in particular, may be at greater risk for osteoporotic fractures in later life given that Depo-induced BMD loss may compound BMD loss that occurs naturally during menopause.

The lessons learned from repeated failures to exercise caution towards reproductive drugs and devices are clear. The experiences with DES, early high-dose oral contraceptives, and the Dalkon Shield demonstrate that when approvals are granted for broad-based use before long-term safety data are available, women's health is not protected; indeed, it may be seriously harmed. The Depo story is yet another example of unnecessary harm, particularly when considering bone health issues.

⁴³ Puil, 2006

Promotion of Depo Provera

Although prescription drug advertising is illegal in Canada, Depo Provera has been advertised directly to women and teens across the country. Canadian women are also exposed to American ads through television and print media that cross the border unrestricted.⁴⁴ Advertising campaigns by the manufacturer typically portray Depo as a convenient, hassle-free method of birth control. For example, a print ad campaign in the Canadian magazine *Healthy Woman* that ran repeatedly from 2000 to 2003 read, “Free yourself from the daily routine. Ask your doctor if the freedom and convenience of 4 times a year birth control is right for you.” Prescription drug ads in Canada do not mention side effects or health risks. Although they do mention side effects in the U.S., the overall tenor of drug ads remains misleading.



Given Depo’s questionable safety profile, ads like these are misleading, and are likely to lead to unwarranted and inappropriate use. This is not the only example of healthy women in Canada being the targets of incomplete and/or misleading information about products that can be harmful to their health. The advertising campaign for Diane 35, a hormonal acne medication promoted for and used off-label for birth control, provides another striking example of this phenomenon.⁴⁵

Depo Provera Use in Vulnerable Populations

International use as a population control measure

Historically, family planning programmes typically limited contraceptive choice to those methods that resulted in either: 1) permanent sterilization, or; 2) temporary sterilization as in the case of Depo Provera.⁴⁶ Even before its approval as a contraceptive, Depo Provera was promoted by family planning programmes and population control agencies, predominantly in the so-called “developing” countries, because it was identified as a highly effective, provider-controlled technology that promised to drive down birth rates among poor women.⁴⁷ Many women’s groups have opposed the use of injectable contraceptives like Depo Provera in developing countries because Depo Provera poses particular health concerns for poor women, who may have low bone density due to poor nutritional status.⁴⁸ These women are already vulnerable because access to local health care facilities is often inadequate or non-existent, and the right to informed consent is often overlooked.

⁴⁴ Direct-to-Consumer Advertising of prescription drugs is illegal in Canada, with the exception of posting of name, price and quantity. See Mintzes and Baraldi, 2001

⁴⁵ Mintzes, 2004

⁴⁶ Quinacrine sterilization is a non-surgical, permanent method of sterilization by the synthetic anti-malarial chemical quinacrine that dissolves and forms scar tissue when inserted into the uterus, blocking the fallopian tube to prevent fertilization. See Dasgupta, 2005

⁴⁷ Given that conflicts of interest in regulatory agencies can influence decision-making, it is interesting to note that many members of the ACOG were also involved in population control policy. See Goodman, 1985.

⁴⁸ Canadian Women’s Health Network, 2004; Sarojini and Laxmi, 2005

In more developed countries, Depo Provera is disproportionately prescribed to society's most marginalized and disadvantaged groups. And recipients are often not fully informed of the side effects and potential health risks of the drug. These groups include: Aboriginal women; women with disabilities; incarcerated women; girls and women in long-term care facilities; women with drug and alcohol addiction problems; poor women; women of colour, and; teenagers.⁴⁹ The patterns are telling; in the United Kingdom Depo is used most often by Asian and West Indian women, in Australia by Aboriginal women, and in New Zealand by Maori and Pacific Island women.⁵⁰ Access to adequate health care services and facilities is an issue for women living in poor communities all over the world, including within more affluent countries such as Canada.

Law professor and American author Dorothy Roberts argues it is oppressive to distribute injectable contraceptives like Depo Provera to women of colour in poor communities where women are told "this is what you should use". Roberts argues that in the United States there is widespread belief that the 'problems' that black people face are caused by becoming pregnant and having children. Misguided attitudes like these have prompted many reproductive rights advocates to challenge the general philosophy behind population control programmes and practices. As Betsy Hartmann, Director of the Population and Development Program at Hampshire College, has argued, "The root causes of poverty, environmental degradation and political instability lie in unjust and inequitable social and economic systems – not in women's fertility."⁵¹

Women and girls on the margins of Canadian society

Prior to its approval, Canadian anthropologist Patricia Kaufert cautioned that Depo Provera would not generally be prescribed to "... the Canadian women of the white middle class. The women at risk live in the Third World, or are Canadian women who are poor, Native, immigrant, the mentally, physically or morally disadvantaged in the eyes of the community."⁵²

Unfortunately, there are no data on Depo utilization in Canada by region or sub-population, such as Aboriginal girls and women, women with disabilities, or those living in long-term care facilities. However, it is known that Depo Provera was administered to women with disabilities long before it was officially approved for contraception use. According to DAWN Ontario (DisAbled Women's Network Ontario), "Physicians and institutional staff have administered Depo Provera to women with mental or physical disabilities, rarely informing them of the drug's side effects. Some disabled girls as young as 12 have been given the drug without being informed of its side effects."⁵³ For the convenience of caregivers, girls and women in some long-term care institutions are given Depo to stop periods for 'hygienic reasons' (whether or not they are sexually active), and to prevent pregnancies. Although healthcare providers may believe they are helping these

⁴⁹ Bunkle, 1993; DisAbled Women's Network Ontario, n.d.; Littlecrow-Russell, 2000; Roberts, 1997; Smith, 2003; Tait, 2000; Women's Health Interaction & Inter Pares, 1995

⁵⁰ Women's Health Action, 2005

⁵¹ Hartmann, 2006

⁵² Kaufert, 1997, p.137

⁵³ DisAbled Women's Network Ontario, n.d.; Zarfasm et al, 1981

girls, such practices raise ethical issues about informed consent and the use of Depo Provera as a form of (temporary) sterilization.

A recent Canadian study of young women with developmental delay in an outpatient clinic found that Depo Provera was the most commonly prescribed drug in response to caregiver and family concerns about menstrual hygiene and unwanted pregnancies. The authors stressed that given the proper support, many young women with developmental delay can learn menstrual hygiene, which may help families avoid further 'medical management' in individuals who are often already taking several drugs.⁵⁴

Depo Provera and Aboriginal women in Canada

Although detailed documentation is not available, there is growing evidence that Depo Provera is prescribed disproportionately to Aboriginal women and teenagers. In November 2005, Maclean's magazine ran a story on the over-prescribing of Depo-Provera as birth control to native women⁵⁵. A survey of 25 Aboriginal women and teenagers on Vancouver Island found that 50% were using Depo Provera. Many of the users reported that they had not been informed of the health risks associated with the drug. Compared to the 2% of Canadian contraceptive users on Depo Provera, it is estimated that 10 to 20% of Aboriginal women using contraceptives use Depo Provera.⁵⁶

The higher rate of Depo use among Aboriginal women has been explained, in part, by the advantages that the method offers to women who appreciate the privacy and easy access.⁵⁷ However, according to Canadian anthropologist Caroline Tait, higher rates of use may be better explained by a history of colonization and racism, and the negative stereotypes that permeate non-Aboriginals' views towards Aboriginal people in general, and Aboriginal women's capacity to be good mothers, in particular.⁵⁸ While researching foetal alcohol syndrome, Tait found that social workers too readily label Aboriginal children with the syndrome, and health professionals too readily turn to Depo Provera in an effort to control Aboriginal fertility.⁵⁹ In this context, it is arguable that reproductive technologies like Depo Provera are more about social regulation through fertility control, than about reproductive rights and freedom. Furthermore, this 'quick fix' approach ignores the need to address the socio-political and economic power imbalances underlying the complex realities of Aboriginal women's lives.

The health advisory on Depo Provera and bone health may be of particular importance to Aboriginal users. In Manitoba, statistics indicate that Aboriginal females and males have more than twice the rate of hip fractures compared with non-Aboriginal Manitobans. Preliminary data from the First Nations Bone Health Study suggests that there may be a high incidence of osteoporosis in Aboriginal women.⁶⁰

⁵⁴ Dizon et al, 2005

⁵⁵ This section of the paper draws heavily from Hawaleshka, 2005.

⁵⁶ Hawaleshka, 2005

⁵⁷ DisAbled Women's Network Ontario, n.d.; Hawaleshka, 2005; Zarfasm et al, 1981

⁵⁸ C. Tait, personal communication, September 8, 2006.

⁵⁹ Hawaleshka, 2005

⁶⁰ Leslie et al, 2002

Conclusion

The history of Depo Provera provides an example of what can happen when a drug is approved with a high degree of secrecy in the absence of long-term safety data. It illustrates the potential risks when regulatory agencies ignore the critical voices and experiences of the intended users – in this case, *healthy* women and teenagers.

From the time Depo Provera was first used as a contraceptive, it was controversial; thirty-five years later, the controversy continues. For example, while the Health Canada advisory on BMD loss recommends limiting use “to the shortest period of time possible”⁶¹, guidelines from the WHO⁶² and the Society of Obstetricians and Gynaecologists of Canada (SOGC)⁶³ do not suggest any time limit. Although critics identify BMD loss as a major public health concern, others including Andrew Kaunitz, author of one of the key studies⁶⁴ that prompted the FDA and Health Canada advisories, see the potential decline in Depo use as the public health concern.

In response to the FDA’s black box warning⁶⁵, Kaunitz wrote, “The FDA should consider revising or rescinding the black box warning to reflect current science regarding DMPA use and skeletal health. Otherwise, the women we serve will be unnecessarily deprived of an important contraceptive option, and the health of individuals as well as the entire public health will suffer”.⁶⁶

In our need to control our own fertility, women are faced with the reality of having to choose from contraceptive methods that provide varying degrees of effectiveness and safety. There is no doubt that situations exist where Depo Provera may be an appropriate contraceptive choice for a woman. For example, a woman may choose Depo if she is dissatisfied with or incapable of using other methods (either drug or barrier based), where pregnancy is contra-indicated for health, and for other self-identified reasons. Nevertheless, given the uncertainty of the drug’s effect on long-term health, the risks and benefits of Depo Provera must be carefully re-evaluated with users on a regular basis, as recommended in the Health Canada advisory.

The impact of the advisory on Depo Provera use is uncertain, since safety warnings do not appear to affect prescribing practices.⁶⁷ This point is highly relevant to the approval of potentially risky drugs like Depo Provera. It underscores the argument that once a drug is released onto the market, a demand for that drug is created. It is not certain whether physician practices and/or consumer demand will change once that demand is firmly established.

⁶¹ Health Canada, 2005

⁶² WHO, 2005

⁶³ Black et al, 2006

⁶⁴ Kaunitz et al, 2006

⁶⁵ A black box warning is the strongest warning that the FDA issues about drugs and is designed to inform healthcare providers and consumers about serious problems associated with use of a drug. It is interesting to note that some reproductive rights groups have raised questions about possible political reasons behind the FDA’s application of this level of warning to Depo Provera. See National Women’s Health Network, 2005

⁶⁶ Kaunitz, 2005, p. 166

⁶⁷ Lexchin, 2005

Issues of informed consent and bias in prescribing are particularly highlighted with Depo Provera because it is a provider-controlled technology. Some providers may too readily assume that women will be non-compliant, and teenagers simply too forgetful to consider alternate and safer forms of birth control. Immigrant, refugee and Aboriginal women have complained about providers offering them Depo Provera as a first choice contraceptive without exploring other options.⁶⁸ By not entering into a full discussion of the range of available options, including barrier methods, well-intentioned healthcare providers can deny women their right to fully informed consent.

The evidence currently available has not established that Depo Provera is a safe drug. Rather, as this paper illustrates, it may pose serious harm to women's health.⁶⁹ The new evidence demonstrating Depo Provera's effect on bone density makes it even more important that women receive comprehensive, unbiased information about all methods of contraception, including barrier methods, in combination with non-judgmental, non-coercive, supportive care.⁷⁰ It is only within this context of care that teenagers and women can make truly informed decisions about which contraceptive method best meets their needs.

⁶⁸ Tudiver, 1997

⁶⁹ Known class action lawsuits have been filed against Pfizer in Canada and the United Kingdom by users of the drug who developed osteoporosis.

⁷⁰ Shulman, 2006

Recommendations⁷¹

1. Greater transparency in the drug regulatory process

In Canada, public access to information and public involvement in the drug approval process should meet, at a minimum, the standards of the U.S. Food and Drug Administration. Pre-market studies should be available to the public, rather than considered confidential. The basis of approval should be available to the public, advisory meetings should be open to the public, with input from stakeholders other than the manufacturers. The controversial approval history of Depo Provera exemplifies the need for a more transparent drug approval process.

2. Regular reviews of drugs once they are on the market

Mandatory re-evaluation of the safety of new drugs within five years of their approval for use would increase drug safety, and increase the public's confidence in Health Canada's ability to protect public health. Review priority should be given to those drugs with controversial approval histories, where potential for harm has been flagged since pre-approval, as in the case of Depo Provera, bone mineral density, and the risk of osteoporosis.

3. Improved post market surveillance programmes

Health Canada needs active programmes in place to follow up new drugs – particularly for those drugs with identified safety risks pre-approval. Active follow-up of users of new drugs, through existing administrative databases (such as those run in certain provinces and which hold prescribing information) is also needed to obtain information on who is prescribed the drug in the real world, beyond clinical trials. This information would be particularly informative for provider-controlled drugs like Depo-Provera where there are concerns that the drug is disproportionately used in Canada's most disadvantaged groups, and where this data is lacking.

4. Establishment of a national Depo Provera registry

Health Canada should implement a Depo Provera registry that protects women's privacy, yet enables the research needed to make sound, informed safety decisions and provide appropriate prescribing information for healthcare providers. A registry would provide a means of alerting women quickly to any health threats that develop. This is a public health issue and, therefore, a federal government responsibility.

5. Qualitative research to capture women's experiences with Depo Provera

Research using qualitative methodologies is needed to capture the experiences of women within and across cultural communities, and within and across different socio-economic groups. An independent community-based research program should be established. Researching the experiences of Aboriginal teenagers and women with Depo Provera should be prioritized. Furthermore, the researchers should be chosen in consultation with the community that is to be studied (that is, a participatory approach to the research should be taken).

⁷¹ The story of Depo Provera raises some of the same drug regulatory and safety issues highlighted in other work by Women and Health Protection. See, for example, Mintzes, 2004, "Regulatory failure in Canada: the case of Diane 35".

6. Enforce and strengthen ban on direct-to-consumer advertisements of prescription drugs
Direct-to-consumer advertisements of prescription drugs should not be allowed given the lack of evidence of health benefits and the serious potential for harm. The Government of Canada should, at a minimum, enforce the existing law that prohibits the advertising of prescription drugs directly to consumers

7. Appropriate unbiased written materials made accessible
Since knowledge and information dissemination is critical to public health, provincial and federal governments should fund the development of unbiased educational materials on contraception, with the involvement of intended users. These materials should be made available in primary care health centres, in secondary schools and in appropriate community centres so all teenaged girls and women, including those living in rural and remote geographical areas, can access these materials. These materials should be culturally sensitive and written in culturally appropriate, accessible language.

8. Product label to include specific information for new drugs
When new medications, formulations, and delivery systems are introduced to the market, their package labels should alert patients and health care providers that the products are new and that there may be uncertainties about their risks and benefits. This would help to clarify the widely held misperception that Health Canada approval of a new drug denotes a guarantee of safety and certainty about its risk-benefit profile. Also, labels should clearly indicate whether a drug is approved as a first or second line treatment.

9. Accountable public processes to review drugs with longstanding controversial histories in the advent of new health alerts
When health advisories are issued for drugs with controversial regulatory histories, such as Depo Provera, Health Canada should hold hearings to review the history of the use, approval, and post-marketing surveillance of such drugs. At the very least, an inquiry by the Standing Committee on Health should be held.

Pfizer Canada should establish an independently managed compensation fund. Profits from the sale of Depo-Provera should be used to cover the costs to individual women and to Canada's health care system when women's health and well-being have been harmed by the drug. The fund should also cover the costs for women involved in the class action suits.

Table 1: Key Events in Regulatory History of Depo-Provera – 1960-2005 ⁷²

	Federal Drug Administration (FDA/USA)	Health Canada (HC)
1960	DMPA approved for habitual or threatened miscarriage and endometriosis on the basis of safety, not effectiveness	
1965	Manufacturer submits Notice of Claimed Investigational Exemption for a New Drug (IND) to conduct human clinical trials on safety and efficacy of DMPA as a contraceptive	
1967	Initial new drug application* (NDA) filed	
1972	DMPA approved for palliative treatment of endometrial cancer	
1974	'Limited approval' granted to Depo Provera for contraceptive use Approval for miscarriage and endometriosis withdrawn due to inadequate data on effectiveness	
1978	FDA rescinds approval for limited marketing of DMPA for contraceptive use FDA approves DMPA as a palliative treatment for kidney cancer	
1984		Application to HC by Upjohn for approval of DMPA for contraceptive use
1985	Board of Inquiry recommends against approval of DMPA for contraceptive use based on the lack of long-term safety data. Depo-Provera deemed "not safe for general marketing"	
1986	Application for use as a contraceptive withdrawn by manufacturer	Health Canada holds closed hearings on contraception in five Canadian cities
1988		Upjohn's application is rejected
1992	April: A new NDA filed for DMPA as a contraceptive June: FDA's Fertility and Maternal Health Drugs Advisory Committee holds public hearings October: Depo Provera approved for contraceptive use	Upjohn appeals the rejection following approval in the U.S. The appeal is rejected by HC
1997		Depo Provera is approved for contraceptive use
2004	FDA and Pfizer issue a "black box warning"	
2005		Health Canada issues a health advisory regarding use of DMPA

*Approval of a new drug application (NDA) is a licence granted by the regulatory agency to a pharmaceutical company to market a drug.

⁷² Regulatory information in the table draws from the work of Green, 1988; Goodman, 1985; Puil, 2006; Tudiver, 1997

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