

Drug regulatory failure in Canada

The case of Diane-35

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Abstract

If the aim of federal regulation of prescription drugs is to protect public health and to promote safe, effective and informed medicine use, the first five years' experience with Diane-35 (cyproterone acetate and ethinyl estradiol) in Canada is a case study in regulatory failure. An examination of how and why this failure occurred provides an example of why changes are needed to federal drug regulation in Canada.

This paper covers the period from pre-market application to the first five years post-licensing, late 2003. A systematic review of the studies provided to Health Canada to obtain regulatory approval was conducted, as well as a review of subsequent published studies, in order to examine the evidence supporting regulatory decisions both pre- and post-approval.

Regulatory approaches to Diane-35 changed dramatically over time, with initial caution during the pre-marketing stage replaced by a laissez-faire approach during the initial post-market stages, and a renewal of caution following public and media criticism. Health Canada initially refused to approve the product because of safety concerns, and later limited the approved use in the hope of restricting population exposure. The limited criteria for approved use failed to limit population exposure due to a lack of monitoring and enforcement. Health Canada compounded the regulatory failure by failing to adequately enforce restrictions on advertising of Diane-35. Diane-35 has been widely advertised to the Canadian public, despite laws explicitly prohibiting such advertising.

Introduction

The young girl on the ad in *Healthy Woman* magazine looks 15 or 16. She has beautiful, flawless skin and a glowing smile. "Diane-35. Ask your doctor or your dermatologist," says the caption. In the accompanying television ad, young girls prance and preen in front of a mirror, twirling umbrellas to bouncy pop music.

Diane-35 is a combination product consisting of two hormones: cyproterone acetate and ethinyl estradiol. Cyproterone acetate is a progestin with effects that counter the male hormone androgen. Higher doses are used to treat prostate cancer. Ethinyl estradiol is the estrogen component of most birth control pills.

Although prescription drug advertising is illegal in Canada, with the exception of postings of 'name, price and quantity', the manufacturer, Berlex, has promoted Diane-35 widely in television commercials, on bus shelter billboards and posters in women's

washrooms at colleges and universities, and in magazines distributed in doctors' waiting rooms.

A controversial safety record

Diane, a product similar to Diane-35 with a higher dose of estrogen, was first licensed in Europe in 1978. The lower dose form, Diane-35 was licensed for sale in Europe in 1985, and has also been marketed in Asian and Latin American countries both for birth control and as an acne treatment. Diane-35 obtained a federal licence for sale in Canada in 1998. The US FDA has never approved its licensing.

In late 1994, the German drug regulatory agency carried out a safety review of Diane-35 after a woman who had used the drug for birth control for 14 years died of liver cancer.^{1 2} Following this review, Diane-35 was restricted, first in Germany, then in the rest of Europe and Malaysia, to second-line use for severe acne in women with signs of a hormonal imbalance ('androgenization' or excess male hormones). The German authorities had not found definitive evidence that Diane-35 could cause liver cancer, but animal and laboratory studies supported the hypothesis. The progestin in Diane-35, cyproterone, is toxic to the liver in humans, especially at higher doses and with longer duration of use.³ There are safer oral contraceptives available, and relatively safe first line therapies for acne such as benzoyl peroxide, and topical and oral antibiotics.

In Canada, Diane-35 has been approved for use only as a second line treatment for severe acne, accompanied by signs of excess androgen, which has not responded to other acne treatments such as oral antibiotics. This is similar to the restrictions found in European regulations.

Diane-35's approval process in Canada

Health Canada licensed Diane-35 in 1998, 20 years after the first European approval of a combination product containing cyproterone and ethinyl estradiol, called Diane. The only difference between the two products is in the estrogen dose: Diane-35 contains 35 micrograms of ethinyl estradiol per day; Diane contains 50 micrograms per day. The decision by Schering, Berlex's German parent company, to lower the estrogen dose is consistent with a broader trend during the 1970's and early 1980's. Manufacturers had found that lowering the estrogen dose improved the safety and side effect profile of birth control pills without compromising effectiveness.

When the Canadian government approved Diane-35 in 1998, ethinyl estradiol was already present in many birth control pills and cyproterone acetate was available at higher doses as a treatment for prostate cancer. However, Diane 35 was a new combination of existing ingredients, and the patient population for these two types of cyproterone-containing products differs: young women versus older men. Thus a strong rationale existed for a thorough review of Berlex's application for marketing of Diane-35 in Canada.

In Canada, decisions to approve a drug are made behind closed doors, without public input or access to the information used in decision-making. If someone outside of the

manufacturer or Health Canada would like access to the information, they need to file an official Access to Information request. Health Canada sends these requests to the company, which decides whether or not to release the information. Refusals may then be appealed, a process that can lead to lengthy delays.³

Summary reports of all of the Phase III trials of Diane-35 were obtained through Access to Information requests, as was documentation of the history of Diane-35's approval in Canada. These documents were readily available for Diane-35 because the CBC had obtained them through Access to Information for a television documentary; key sections are posted on the CBC website.⁴

Berlex first applied for market approval in 1993, and was refused. The company applied again in 1996. Health Canada reviewers again raised concerns about potential risks, and refused to approve the product unless the company provided additional information. The main reason that Health Canada reviewers provided for not initially approving Diane-35 was concern about potential increased risks of liver cancer.⁵ Berlex submitted additional information to Health Canada in 1997 and Diane-35 was approved in April 1998.

The additional information Berlex had submitted was the manuscript of a case-control study of liver cancer in women using oral contraceptives. This study did not find that cyproterone exposure increased the rate of liver cancer. However, in the published report of this study, most results for cyproterone were combined with those for medroxyprogesterone, a progestin that had been found to only minimally affect DNA in liver cells, as well as a third progestin.⁶ Only limited results, not adjusted for duration of exposure, were reported for cyproterone alone. The timing and duration of exposure to a cancer-causing chemical can substantially affect risks. Health Canada may have received additional details not provided in the published report; documents obtained through Access to Information contained only a sketchy summary.

Health Canada officials did not dismiss the laboratory evidence of genotoxicity. A July 1997 Health Canada memo notes that cyproterone has been found to affect the DNA of liver cells and that similar genotoxic changes have not been found with other commonly-used progestins. They cautioned that, "until the implications of liver adduct formation are completely resolved, the indication of Diane-35 should be limited to the affected population who will mostly benefit from this drug."⁷ This is the rationale provided for approving the drug only for women severely affected by acne and for whom other treatments had failed.

^a Drug regulatory agencies can function more openly. The US Food and Drug Administration posts evaluation reports on its website, including reports of unpublished studies submitted by the company, and reviewers' comments. Advisory committee hearings are held in public and full transcripts are posted on the web. If information is unavailable on its website, the FDA responds to Freedom of Information requests directly (i.e. without asking the company's permission), usually within two to three weeks.

Studies submitted to Health Canada

The box below provides an overview of the types of studies a company submits to Health Canada when it applies for approval of a new drug. The studies that provide evidence of a product's effectiveness are called 'phase III studies'. These are clinical trials that test the product's effectiveness for its approved use at the dose or doses at which it will be marketed, and in relatively large groups of patients.

What kind of safety and effectiveness studies are needed for market approval?

Companies must provide a range of studies related to a drug's safety and effectiveness in applications for market approval:

- **Laboratory studies** examining the effects of the drug in cells and tissues.
- **Animal studies** that assess short and long-term toxicity, physiological effects, cancer causation, effects on reproduction and on rates of birth defects.
- **Phase I studies in healthy volunteers:** small, short-term studies to discover how the drug acts in the human body, including pharmacokinetics and pharmacology, safety, and effects on a range of physiological functions.
- **Phase II studies:** comparisons of different doses in relatively small groups of patients who have the condition to be treated. These are the first evaluations of effectiveness in humans, and are also used to further evaluate safety.
- **Phase III studies:** studies in larger groups of patients who have the condition the drug is intended to treat. These studies test the drug at approved doses and aim to more closely reproduce normal conditions of clinical care.
- **Phase IV studies:** Sometimes a regulatory agency will also require a company to carry out follow-up studies once a drug is already on the market.

Phase III studies of Diane-35

Berlex submitted five phase III studies to Health Canada considered to be 'pivotal', or of key importance, to the application for market approval for Diane-35. Three of these were double-blind^b randomized^c controlled trials. Two other studies were 'open-label' studies, in which women and their doctors knew what treatment they were taking. One was a randomized controlled trial; the other only included women who were taking Diane-35. It had no comparison group of women taking another treatment or placebo (a 'sugar pill').

'Blinding' of patients and physicians as to treatment allocation is a necessary feature of study design to control bias. For example, it prevents influences such as high hopes for a new treatment and subtle differences in the way doctors treat patients on a new drug compared to those on placebo or an older drug. It also helps to ensure that judgments of treatment outcome are unbiased. Randomization is important to avoid any systematic differences between patients who receive different treatments.

Thus, of the five pivotal phase III trials submitted to Health Canada, the three double-blind randomized controlled trials provide the most reliable information on treatment effectiveness.

^bA study is 'double-blind' if neither the patients nor the clinicians treating and assessing them are told which treatment they have been assigned to take.

^cA study is 'randomized' if each patient who has agreed to participate has an equal chance of being selected for one treatment arm or the other.

Double-blind randomized controlled trials: wrong comparisons, wrong patients

In two studies, Diane-35 was only compared to Diane, a higher estrogen dose product never approved in Canada.^{8 9} This is not a useful comparison in a Canadian context. The third study compared Diane-35 to a contraceptive pill that is approved in Canada, but not as a treatment for acne.¹⁰ Thus this comparison was also inappropriate.

None of the three double-blind randomized controlled trials included a placebo group, although for treatment of acne this is appropriate, since acne is not a life-threatening condition and can improve without drug treatment.

The patient population in these studies was also far from ideal. Diane-35 is only approved in Canada for women with severe acne, accompanied by signs of androgenization, who have failed to respond to previous treatment, for example with oral antibiotics. None of the trials' inclusion criteria specified previous unsuccessful acne treatment. None limited those included to women with severe acne, or to severe acne accompanied by signs of excess male hormones. Most outcomes were combined for all grades of acne severity.

Severe acne that is unresponsive to other treatments may differ from other forms of acne. It is likely to prove harder to treat. If a drug is approved **only** as a treatment for these women, it's important to know how well it works for them.

Additionally, these trials only reported outcomes for women who stayed in the study until the end. In these three trials, between 12% and 33% of the patients withdrew early and the effects of treatment on these women was not reported. It is likely that some women withdrew early because of lack of treatment effectiveness.

In the trial comparing Diane-35 users to women taking a birth control pill, Min-Ovral (150 mcg levonorgestrel-30 mcg estradiol), after six months those on Diane-35 experienced a significantly greater reduction in acne lesions. However, acne clearing differed by an average of around four lesions. Diane-35 users had on average 17.6 fewer acne lesions than when they entered the trial; Min-Ovral users on average had 14 fewer. These included all types of acne lesions: blackheads, pimples with and without pus, and acne cysts. The clinical importance of this degree of difference is questionable. The lack of placebo group in this trial, and in the two trials comparing Diane-35 to Diane, makes it impossible to know how many women would have improved without treatment.

Open-label randomized controlled trial

Berlex also submitted one 'pivotal trial' in which women on Diane-35 were compared to women taking a birth control pill, Marvelon (desogestrel 150mcg-estradiol 30mcg).¹¹ When this trial was first submitted to Health Canada, Marvelon had not yet been approved in Canada. It is now approved for birth control, but not for acne.

Almost all the women had facial acne, but there was no requirement for severe acne, signs of androgenization, or previous unresponsiveness to treatment. All participants and

those treating them knew which drug they were taking. As assessment of acne healing is partly subjective, this may have biased reporting of results.

The authors found that most women in both treatment groups improved. There was greater improvement in facial acne on Diane-35 than on Marvelon. No difference was seen between women taking Marvelon and those taking Diane-35 in healing of chest or back acne. However, the authors only reported outcomes on women who stayed in the trial, and 23% withdrew early. This raises questions about the results as some women may have left early due to poor outcome. The authors should have reported the drugs' effects on all randomized patients.

Uncontrolled open-label trial

The remaining trial that Berlex submitted to Health Canada for market approval had no comparison group, and both patients and doctors knew that the women were getting Diane-35.¹²

Uncontrolled open-label studies provide very limited information about a drug's effectiveness. It is impossible to know if the drug cleared up a woman's acne, if her acne simply got better over time, or if some other change was the true cause of improvement.

Most women in this study had mild acne and therefore were different from the patient population Diane-35 is approved to treat. Those with more severe acne had poorer results than those with milder acne. Many women left the study early, and outcomes are only reported for those who remained. No breakdown is provided in early withdrawals by acne severity, or the proportion leaving because of lack of efficacy. This study combines a flawed design with inadequate reporting.

Conclusion:

Phase III trials failed to establish effectiveness for the use approved in Canada
Health Canada approved Diane-35 although it was not tested in the patient population it was approved to treat. Nor was it tested against placebo or any other acne treatment. Thus the studies submitted to Health Canada did not establish Diane-35's effectiveness for its approved use. How effective Diane-35 is for its approved use remains an open question. The lack of appropriate effectiveness studies also raises questions about the adequacy of the approval process: why didn't Health Canada require Berlex to provide studies showing that Diane-35 was more effective than placebo, and as or more effective than other acne treatments, in women with severe acne who had failed to respond to one or more other acne treatments, and who had signs of androgenization?

Literature review – published effectiveness studies

To test the possibility that Diane-35's effectiveness for its approved use has been established in other studies, a literature search was carried out in four computerized databases.^d Studies were included if they met the following conditions:

- They included women of reproductive age with severe acne, accompanied by signs of androgenization, that had been unresponsive to previous treatment with oral antibiotics or other acne treatments available in Canada;
- They compared Diane-35 to other acne treatments approved in Canada and/or placebo; and
- They assessed Diane-35's effects on acne lesion counts and healing rates during treatment and/or following treatment discontinuation.

No published studies met these three criteria.

Sixteen published randomized controlled trials have examined the effects of cyproterone and estrogen combinations on acne. This group includes three studies in Berlex' application for market approval, discussed above.^{8 10 11} Another seven studies did not include Diane-35; they tested different doses of estrogen and/or cyproterone. The remaining 6 studies included 3 comparisons between Diane-35 and birth control pills not approved in Canada,^{13 14 15} one comparison to other hormones not approved for acne,¹⁶ one comparison to Diane,¹⁷ and one comparison to a cyproterone lotion and a placebo lotion.¹⁸ Daily use of a lotion can affect acne healing, so this type of placebo is inappropriate for Diane-35, a pill. Thus none of these published studies tested Diane-35's effectiveness as compared to either placebo (in a pill form) or acne treatments.

Conclusion – no appropriate effectiveness studies

It is impossible to know, on the basis of all available published and unpublished studies, whether Diane-35 is effective for the specific use and patient population for which it has been approved. No evidence was found from randomized controlled trials establishing the effectiveness of Diane-35 as a second line treatment for severe acne, as compared to placebo or other acne treatments available in Canada.

Safety studies

The main scientific controversy surrounding Diane-35 concerns its safety, especially whether there are greater risks of potentially fatal blood clots (venous thromboembolism), liver toxicity or liver cancer with Diane-35 than with other estrogen-progestin combination products. Recent safety concerns have focussed to a greater extent on venous thromboembolism (VTE) than on liver toxicity or potential cancer risks. VTE consists of blood clots that usually occur in the leg (deep vein thrombosis). They can travel to the lung (pulmonary emboli), where they can cause serious harm and in some cases lead to death. VTE is a rare harmful effect of all combined estrogen-progestin

^d The bibliographic databases were Medline, Embase, Web of Science, and the Cochrane Library of Systematic Reviews. These databases include comprehensive lists of articles published in journals. They can be searched on-line by subject, keyword, author or journal, and are available through university libraries and many public libraries.

products, including those used for birth control. However, several studies found Diane-35 to be riskier in this regard than many birth control pills. Regulatory agencies in the UK, Australia, New Zealand, and Canada have sent out safety advisories about these risks.

In order to find out what is known about risks of VTE with Diane-35, the safety studies submitted to Health Canada were reviewed and computerized databases were searched for any published safety studies in women exposed to Diane-35. This included observational studies following up large groups of women prescribed Diane-35 and individual case reports.

Does Diane-35 lead to higher risks of venous thromboembolism (VTE)?

Eight published case-control studies^c have examined the risks of venous thromboembolism (VTE) with Diane-35.

Two of these studies focus specifically on Diane-35. The first compares the rate of VTE with Diane-35 to the rate on levonorgestrel-containing oral contraceptives.¹⁹ The latter are commonly used birth control pills known to have lower risks of VTE than some other birth control pills. The second study compares the risk of VTE in women with a diagnosis of acne, hirsutism (extra facial or body hair) or polycystic ovary syndrome (also a sign of hormonal imbalance) taking Diane-35 or birth control pills.²⁰ The authors wanted to see whether the extra risk of VTE while taking Diane-35 was due to underlying differences in risk in women with hormonal imbalances.

The six remaining studies examined differences in VTE risk in oral contraceptives containing various types of progestins.^{21 22 23 24 25} These studies include Diane-35 users, but do not specifically focus on Diane-35.

Based on these eight studies, there is convincing evidence that Diane-35 increases the risk of VTE to a greater extent than commonly used birth control pills. Five studies compared risks with Diane-35 to levonorgestrel-containing birth control pills: in three, Diane-35 users were 4 to 5 times as likely to experience VTE;^{19 22 23} another study found a doubling of risk.²⁴ Only one of the five studies, carried out in the UK Medi-Plus database, failed to find a statistically significant difference.²⁴ However, the latter's methods were weaker than the other studies that used administrative data,^{19 20 22 24} as researchers knew what drug women were taking when they judged health outcomes. This could have led to a bias in situations where the VTE diagnosis was unclear, especially since it is sometimes difficult to make a definitive diagnosis of VTE.

Women with acne or polycystic ovary disease had double the risk of VTE with Diane-35 as with birth control pills (all types).²⁰ Thus Diane-35 was found to have an effect that was independent of underlying hormonal imbalances that may be associated with an acne diagnosis.

^c In a case-control study, people with an identified disease or health condition (cases) are compared to otherwise similar people without the disease or condition (controls), in order to find out whether differences in exposure exist, for example, to substances thought to cause the health problem.

In the studies that compared VTE rates in Diane-35 users and non-users of birth control pills, women on Diane-35 had between 3 and 29 times the risk of VTE as women not taking birth control pills,^{20 22 23 25} and 18 times the risk of non-users of dying from pulmonary embolism.²¹

VTE is rare among healthy young women. The increase in relative risk with Diane-35 translates to between 3 and 10 extra women experiencing blood clots each year per 10,000 users, as compared to women taking low-risk birth control pills. For women using Diane-35 for birth control, this is entirely preventable harm.

A review of studies of VTE risks with Diane-35 funded by Berlex, Diane-35's manufacturer, argues that Diane-35 is no riskier than oral contraceptives.²⁶ A Danish study, which did not include any direct comparisons between Diane-35 and birth control pill users,²⁵ is put forward as a 'gold standard'. However, without any direct comparisons, it is impossible to know whether risks were higher or lower with Diane-35 in this study than, for example, with levonorgestrel-containing pills. Given that other studies directly compare the risks experienced by women using Diane-35 with those using low-risk oral contraceptives, the Danish study is an odd choice of gold standard.

This review includes inaccurate data from one of the comparative studies.²² In a letter to the editor, Mario Pini, the study's first author, states that the number of cases of VTE among Diane-35 users reported in the review is lower than the number observed in his study, and the number of cases of VTE among oral contraceptive users higher.²⁷ Additionally, a World Health Organization study that had found approximately five times the risk of VTE with Diane-35 as with levonorgestrel-containing oral contraceptives²³ is reported in the review as showing a lower risk of VTE with Diane-35 than with oral contraceptives. The review's author, Walter Spitzer, may have carried out different analyses. However, he fails to mention that the study's authors had found the opposite effect, nor to explain the reasons for this difference. The impression left is that Diane-35 was found to be safer than birth control pills in this study, whereas it was found to be less safe than the only type of pill to which it was compared.

These arguments about scientific evidence are anything but academic. They directly affect not only product sales, but also women's lives. It is always possible to dismiss a body of evidence as being imperfect. The more important question, however, is what we know from the research published to date, giving the greatest weight to studies that use sound, unbiased research methods. On balance, there is good evidence that the risk of VTE with Diane-35 is higher than with low-risk low-dose birth control pills.

Liver toxicity

One case-control study measured the risk of a range of liver disorders in women with acne, hirsutism, or polycystic ovary disease.²⁸ The authors found a trend towards more liver toxicity with Diane-35 that was not statistically significant. However they note that their study may not have been large enough to detect a difference.

Laboratory and animal studies and liver cancer

One of Diane-35's ingredients, cyproterone, affects the DNA of liver cells, sometimes causing permanent changes. This is a genotoxic effect, a possible sign of a chemical's ability to cause cancer by affecting the genetic material governing cell division and function. A dose-dependent effect was found in the liver cells of rats. In laboratory studies on human liver tissue, similar effects were found when tissue was exposed to cyproterone at concentrations that were lower than those found in users of Diane-35.²⁹

Studies on monkeys, rats and mice, submitted in Berlex's application for market approval, also showed abnormal liver cell growth (hyperplasia) in animals exposed to cyproterone, lending support to the hypothesis that Diane-35 increases cancer risks.³⁰ It is not possible to directly extrapolate from animal studies to humans, thus these results are suggestive rather than being definitive.

There have been eight cases of liver cancer reported in cyproterone users, five in children and adolescents treated with high doses for precocious puberty, two in men treated for prostate cancer and one in a Diane-35 user.²⁹

The experience in Canada:

What happened following Diane-35's approval?

Rapid increase in sales

In the one-year period from September 1999 to September 2000, sales of Diane-35 increased by 45%.³¹ Promotional campaigns aimed at health professionals and the public are likely to have contributed to this rapid increase. Such rapid increases in sales are unlikely to reflect a sudden surge in the number of women with severe, untreatable acne. A much more likely explanation is promotion of use among larger population groups.

Berlex, the manufacturer, cannot legally advertise Diane-35 for contraceptive purposes to physicians in Canada, as it not approved for this use. However, Berlex provided an "unrestricted educational grant" to authors of a report distributed to Canadian doctors.³² This report, "Diane-35 – is it an oral contraceptive?", affirms that Diane-35 is as effective for birth control as other estrogen-progestin combination pills available in Canada. The other key message in this report is reassurance on safety: a statement that Diane-35 has "no significant teratogenic effect" [i.e. does not cause birth defects], that it may have beneficial effects on the liver, and that there is no evidence it causes liver cancer, even following longer-term use. The report clearly conveys the idea that this product may be used for birth control.

Once a drug is licensed for sale in Canada, physicians may prescribe it for uses other than those officially receiving federal regulatory approval, a practice called 'off-label' prescribing. The article described above promotes use of Diane-35 for birth control and was funded by Berlex, the manufacturer. This is an 'off-label' use. It is illegal for a manufacturer to promote off-label use of a medicine. However, Health Canada does not monitor promotion to physicians. Most activities are delegated to industry self-regulation. A key part of the regulatory failure with Diane-35 was the failure to prevent promotion of

off-label use following market approval. The only promotion to physicians that should have been allowed is for use for severe acne, unresponsive to other agents and accompanied by signs of hormonal imbalance.

Although acne is a common condition, affecting an estimated 85% of people aged 15-24 to some degree, in most cases the condition is mild and does not require prescription drug treatment. The subgroup of acne patients for which Diane-35 is licensed, women with severe and difficult-to-treat acne, is much smaller.

Health Canada's rationale for approving this drug for a restricted indication – second-line use in a subset of women with severe acne – was to limit population exposure to a drug with potential serious risks to those most likely to benefit.⁷ If Health Canada then failed to prevent the drug from being promoted for off-label uses for much larger population groups, women needing birth control or with mild acne, this regulatory strategy, arguably, was unsuccessful.

Health Canada is the federal agency responsible for enforcement of the Food & Drugs Act. It is responsible both for deciding if a drug is safe and effective enough to be marketed and for post-market surveillance, or monitoring after a drug has been approved. The regulation of advertising is one part of post-market surveillance. Very few resources – less than one full-time staff position – are devoted to this activity by Health Canada; most activities are delegated to industry self-regulation.^f Health Canada's failure to follow up to make sure that Diane-35 was used only by a small, restricted population of women with severe acne is part of a more general inability to follow up the thousands of drugs on the market in Canada.

In addition to failing to prevent promotion of Diane-35 to physicians for off-label use, Health Canada failed to prevent widespread direct-to-consumer advertising. Diane-35 was advertised to the public on billboards, in magazines, on television and in cinemas. These ads show beautiful young women with clear, flawless skin. Someone with severe acne that has failed to respond to previous acne treatments does not have this kind of skin. These ads mention the product's name and suggested young women 'ask your doctor or your dermatologist'. The aim is clearly to stimulate sales. Health Canada failed to take regulatory action to prevent this advertising even in response to complaints. As is described below, only after a television exposé did the regulator begin, to a limited extent, to regulate.

^f Although Health Canada is ultimately responsible for regulation of pharmaceutical advertising, it delegates regulation of most promotional activities concerning prescription drugs to the brand-name industry association, Rx&D, regulation of over-the-counter drug ads to Advertising Standards Canada, and regulation of ads aimed at health professionals to the Pharmaceutical Advertising Advisory Board, a 'multi-stakeholder' association.

Media and public attention

In January 2003, a CBC television documentary raised concerns about the safety of Diane-35, Berlex's promotional campaign, and the widespread use of the product for birth control, an unapproved use. This documentary sparked considerable controversy, including charges of media alarmism.

In late December 2002, a few days after the CBC had interviewed Health Canada staff for the documentary, the agency posted the first safety advisory on Diane-35.⁵ In April 2003, Health Canada required Berlex to send out a 'dear health professional' letter to all physicians in Canada, warning them of risks of VTE.³³ In addition, a consumer advisory was posted on Health Canada's website. The timing of the documentary in relation to these safety advisories suggests that media attention contributed to the decision to take regulatory action.

Women's health groups had previously raised similar concerns to Health Canada, with much less success. In late 1999, when Berlex began to promote Diane-35 on billboards in Montreal, DES Action Canada made a complaint to Health Canada and the Pharmaceutical Advertising Advisory Board. It led to an investigation, some meetings and correspondence, and changes to Berlex's website. However, in spite of receiving a letter from Health Canada saying that the problem had been solved, DES Action staff noted that the Diane-35 billboards continued to be displayed at Montreal bus shelters. In early 2000, DES Action held a press conference at a bus shelter. Soon after the billboards were removed from Montreal bus shelters, although they continued to run in other cities.

Women and Health Protection sent a second letter of complaint to the Deputy Minister of Health in March 2001, following Berlex's launch of a new national billboard, television and cinema ad campaign for Diane-35.³⁴ This complaint led to no perceptible regulatory action and the Diane-35 ad campaign continued. Print ads continued to run in *Healthy Woman*, a Canadian magazine funded by Rogers Media Inc, found in family physicians' and gynaecologists' waiting rooms with ads appearing in every issue until September 2003. *Healthy Woman* ceased publication in January 2004.

Thus, Canadian laws prohibiting direct-to-consumer advertising and complaints from women's groups proved largely ineffective in preventing or limiting advertising campaigns that targeted adolescent girls and young women and promoted sales of a potentially hazardous product.

Canadian voluntary adverse drug reaction reports

The main function of voluntary adverse drug reaction reporting is to allow for early recognition of previously unknown harmful drug effects. An adverse drug reaction report is a report of a harmful effect for which a drug is the suspected cause. In some cases this suspicion may be wrong. However, many harmful drug effects are first discovered through voluntary reporting. In Canada, few resources are devoted to encouraging or educating physicians and the public about the need to report harmful drug effects, and the reporting rate is low.

From April 1998 to December 2002, during nearly five years, there were only 25 reports of adverse drug reactions in which Diane-35 was the suspected cause, including one death. About three-quarters of these reports were of serious adverse events according to the World Health Organization definition: life-threatening, leading to hospitalization or prolonged hospital stay, or resulting in ongoing disability, cancer or birth defects.

Health Canada posted a first safety advisory about Diane-35 on December 23, 2002, the CBC documentary was aired on January 14, 2003, and a 'dear health professional' letter was sent to physicians on April 10, 2003. The primary focus of both media attention and the advisories was the increased risk of VTE with Diane-35. In the ten months from January to October 2003, the rate of voluntary adverse drug reaction reports increased more than ten-fold, from an average of 0.4 to 4.6 reports per month. The additional 46 reports over this time period were almost all serious according to the World Health Organization definition and included 33 reports of VTE and 5 additional deaths. It is unlikely that the rate of death and serious adverse events rose dramatically following press and regulatory attention; a much more likely explanation of this difference is that physicians and patients became more aware of Diane-35's potential risks, and were more likely to suspect the drug as a possible cause and to report the events that occurred.

How many deaths, serious adverse events and harmful effects in total have occurred in Canada? What proportion have occurred in women using the product for mild acne or birth control, or in women who have asked for Diane-35 after seeing ads for the product? This figure remains unknown. The ten-fold increase in reporting rate in such a short period, however, is dramatic testimony to the large degree of under-reporting of suspected adverse events, including deaths.

Conclusion

Diane-35 was approved in Canada on the basis of studies that failed to test its effectiveness in comparison to placebo or other acne treatments. It was not tested in the specific population for whom it was approved, women who are likely to be hard to treat as they have failed to respond to other treatments. It was approved in spite of safety concerns, but only for a limited use. Once approved, however, Health Canada did not monitor use to ensure that it was indeed restricted. The agency lacks the resources for effective monitoring, and those recommending restricted use would have known about the lack of monitoring capacity.

The experience with Diane-35 in Canada is a potent example of why drug regulation should be open and accountable. These decisions were made in secret, without public scrutiny. Would the same decisions have been made if there had been full public access to information and public participation in the regulatory process?

The experience with Diane-35 is also an example of the hazards of direct-to-consumer advertising of prescription drugs. The decision to advertise a drug is based on expected effects on sales. It is not based on a drug being especially safe, especially effective or superior to alternatives. The Diane-35 advertising campaigns make a mockery of claims that direct-to-consumer advertising educates the public about health treatments. These

ads omit the key information young women need to know about this product: that safer alternatives are available, both for birth control and mild to moderate acne, and that even for the restricted use for which Diane-35 has been approved, there is inadequate evidence to know whether or not Diane-35 is effective.

All medicines can cause harm as well as benefit. Without systematic scientific evidence of benefit, no harmful effect, however rare, is worth the risk. This message is hardly revolutionary; it is one of the key principles of drug regulation. The case of Diane-35 in Canada is an illustration of the gap that can form between principles and practice, to the detriment of public health, when regulatory decisions are made behind closed doors. That gap needs to be closed.

Recommendations

1. Transparency in the pre-market approval processes

The level of public access to information and public participation in the drug approval process should, at a minimum, be consistent with the standard in place at the U.S. Food and Drug Administration. Pre-market studies should not be considered confidential; full study reports should be made public. The basis for regulatory decisions should be published on the web, and advisory committees considering approval should meet in public, with the possibility for presentations from groups other than the manufacturer.

2. Regular (3 or 5-year) reviews for product license renewal

Drugs should not be approved for an unlimited period. They should be re-licensed 3 years after first market approval and should continue to be subjected to regular licensing reviews afterwards. These reviews should be done in a public environment. The burden of proof should continue to be on manufacturers to provide evidence of sufficient safety and effectiveness.

3. Open, accountable and responsible regulation of drug promotion

Messages to the public and to health professionals about approved products should not be inaccurate, deceptive or misleading. Neither current industry self-regulatory procedures nor Health Canada's approach to regulation are working to prevent the public from receiving misleading advertising messages. Health Canada needs to actively monitor companies' advertising and promotional activities. It should use meaningful sanctions to effectively enforce existing regulations on promotion in order to deter future infractions, and ensure that inaccurate or misleading information, intended for either the public or health professionals, is corrected.

Health Canada should also pay specific attention to preventing promotion of off-label use of medicines. This should be done by active monitoring of the information that sales representatives provide to physicians, the activities of paid 'opinion leaders', the content of sponsored scientific symposia and journal supplements, and press information provided by companies or public relations firms acting on their behalf. Off-label promotion is illegal for good reason: the company has not provided Health Canada with systematic evidence of a product's effectiveness and safety for the off-label uses.

4. Enforcement of Canada's law prohibiting direct-to-consumer advertisements

There is no public health rationale for allowing direct-to-consumer broadcast or print reminder advertisements for prescription drugs, such as the Diane-35 ads. Health Canada has allowed these ads since 2000, based on a 1978 price-advertising clause in the Food & Drugs Act. This clause should be eliminated, as it is no longer used to advertise prices, or amended to explicitly prevent reminder advertisements. (Reminder ads generally include the name of the drug with an accompanying lifestyle image. Price is rarely, if ever, mentioned.) Similarly, there is a need for better enforcement of the law prohibiting direct-to-consumer advertising when a company runs disease-oriented television or print ads that do not mention brand names in advertising copy, but are linked to a broader advertising campaign, aimed both at the public and at prescribing physicians, for a specific prescription drug.

5. Active post-market surveillance

Health Canada needs active programmes to follow up new drugs, drugs for which there are identified safety concerns and drugs that will be used by high risk populations such as children, pregnant women and the elderly. The current system of voluntary adverse drug reaction reporting is inadequate. Much more education, public awareness raising and better systems for safety reporting are needed. We also need active follow-up of users of new drugs, through existing administrative databases (such as those run in certain provinces and which hold prescribing information) and through cohort studies (where the drug-taking group is compared to another group in a critical way) of large numbers of new users. These activities should be adequately funded through general tax revenues or an earmarked tax on companies' sales.

6. A recourse mechanism for complaints

Well-publicized, accessible complaint procedures should be available to the public if, for example, a company is suspected of carrying out illegal activities or a federal agency of failing in its administrative duties. This should include the possibility to initiate an investigation into problematic drug approvals. These should take place in public, with procedures that allow for meaningful public involvement. As a start, we recommend an investigation into the approval of Diane-35.

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