Evaluative Sciences. "It's not infrequent to admit people [to hospital] for heart failure after they've taken NSAIDs."

At low doses for a week or so, traditional NSAIDs are "not worth fussing about," he added. "But if people are using chronically, it might be a decent thing to know [about potential adverse events]."

Although the evidence of potential adverse events wasn't deemed sufficient to move ibuprofen behind-the counter, safety concerns were sufficient to persuade Health Canada to include new warnings in all traditional NSAIDs, including ibuprofen.

"We found an increase in relative risk [of cardiovascular events with prolonged use and high dosage] of NSAIDs compared to placebo and this wasn't known before and needed to be integrated into the labels," says Berthiaume. High dosage is defined as the highest approved dosage; the time period was not defined, but all the studies reviewed ran for more than 3 months.

Berthiaume couldn't say when the new labels will appear, adding that it depends on financial resources and "competing priorities" at Health Canada. "There's a relatively good level of awareness [of the risk of serious cardiovascular events] among health care professionals, and hopefully among the public," he added.

The US Food and Drug Administration told drug manufacturers to beef up warnings on nonprescription NSAIDs by Dec. 15, 2005.

The evidence of potential vascular and cardiovascular risks arose from some COX-2 inhibitor studies that used NSAIDs as comparators, thus generating data on those drugs' risks.

Health Canada launched a review of the cardiovascular risks associated with COX-2-selective NSAIDs, including rofecoxib, valdecoxib (Bextra), celecoxib (Celebrex) and meloxicam (Mobicox and other generics), after Merck & Co. withdrew rofecoxib from the world market on Sept. 30, 2004 due to new findings regarding its cardiac risk (see story on page 234). — Barbara Sibbald, *CMAJ*

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Vioxx should be allowed back on the market advises expert panel

Rofecoxib (Vioxx) ought to be allowed back on the market, concludes Health Canada's Expert Advisory Panel on the Safety of COX-2 Selective Non-steroidal Anti-Inflammatory Drugs (NSAIDs).

After Merck & Co. withdrew rofecoxib from the world marketplace on Sept. 30, 2004 (*CMAJ* 2004;171[9]: 1027-8), Health Canada launched a review of the cardiovascular (CV) risks associated with COX-2-selective NSAIDs, including rofecoxib, valdecoxib (Bextra), celecoxib (Celebrex) and meloxicam (Mobicox and other generics). The 400-page review includes pre-clinical and clinical trials, adverse drug reaction reports and other data.

In its comments on that review, released in June 2006, Health Canada decided that both rofecoxib and valdecoxib (which was withdrawn in December 2005 following evidence of increase CV events and severe cutaneous adverse reactions) will remain off the market unless a new drug submission is received and approved by Health Canada.

"At this time, we have not made a decision about whether to resubmit," says Merck Frosst spokesperson Marlene Gauthier.

The 13 members of the Expert Advisory Panel, who met for 2 days in Ottawa in June 2005, included people with backgrounds in rheumatology, cardiology, gastroenterology, internal medicine, family medicine, clinical trial methodology and epidemiology, plus 2 patients with rheumatoid arthritis. The report was released in July 2005.

The panel voted 12 to 1 in favour of potential future sales for rofecoxib, noting that most NSAIDs carry cardiovascular risk and that rofecoxib has a decreased frequency of both gastrointestinal intolerance and peptic ulcer diseases compared with traditional non-selective NSAIDs, and that "patients benefit from having a variety of drugs to choose from." The panel did not recommend that valdeocoxib go back on the market due to the rare but severe skin reactions.

"There's no question [rofecoxib] increases cardiovascular risk compared to placebo," says Dr. Andreas Laupacis, who headed Health Canada's Expert Advisory Panel. "But the absolute increase is very small."

Given that the risk is comparable to that of traditional NSAIDs, such as ibuprofen (see article on page 233), but that it has a lower incidence of gastrointestinal problems, "What's the rationale for not making it available?" asked Laupacis the president and CEO of the Institute for Clinical Evaluative Sciences.

> "Patients benefit from having a variety of drugs to choose from."

Health Canada's comments on that review and own scientific review of certain COX-2s, recommend shorter and lower doses of all COX-2s and traditional NSAIDs.

"That's clear in the report," says Dr. Marc Berthiaume, director of Marketing Pharmaceuticals and Medical Devices Bureau.

During public consultations, Berthiaume says people indicated they wanted to know the risk, but they also wanted to be able to "make that choice."

Health Canada's review concludes that the "benefit–risk balance favours" the continued sale of celecoxib and meloxicam. In accordance with the panel's recommendations, the labels were revised in September 2005 to warn of the increased risk of CV adverse events and to suggest using these drugs at the "lowest effective dose for the shortest possible duration of treatment."

Since the COX-2 withdrawals in 2003, the estimated number of filled prescriptions in Canada has plummeted from 7.3 million (worth about $476 million) to 3.5 million (valued at about $199 million) in 2005. — Barbara Sibbald, *CMAJ*

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Cervical cancer vaccine may come soon to Canada

Canapress

The vaccine is most effective when given before a person is sexually active. In the US, it's approved for females age 9 to 26.

A new vaccine against cervical cancer that could save hundreds of thousands of lives worldwide each year may soon be available in Canada.

Gardasil (quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine) was approved in the US in June and could be offered there as early as September. Although Health Canada would not say if it will approve the vaccine, the drug's manufacturer, Merck Frosst, is confident Canadians will join other North Americans in having the world's first vaccine that protects against a risk factor for a cancer. Mexico approved the drug 1 week before the US.

In anticipation of Health Canada's approval, the National Advisory Committee on Immunization (NACI) has already started ironing out recommendations on who should get the vaccine, how it can best be delivered and other immunization practices.

"This is a great advancement for women's health," said Dr. Shelley Deeks, a medical epidemiologist and executive secretary of NACI. "We'll look at things like school leaving, like sexual debut data. All of those things will be taken into account when we make a recommendation."

Gardsil prevents infection from 2 genotypes of HPV — 16 and 18 — that cause 70% of cervical cancer. It also prevents infection from HPV 6 and 11, 2 genotypes that are the cause 90% of genital warts.

HPV is an extremely common sexually transmitted infection. In Canada, about 75% of sexually active people will have at least 1 HPV infection in their lifetime. However, most people never know they are infected and most infections resolve on their own. Yet virtually all cases of cervical cancer are linked to HPV. While relatively rare in Canada, due to widespread availability of Pap tests, cervical cancer kills about 370 Canadian women annually; another 1350 or so are diagnosed with it each year.

This pales in comparison to the death toll in developing countries where cervical cancer kills about 240 000 women a year. The World Health Organization predicts that mortality rates could rise by almost 25% over the next 10 years and views the HPV vaccine as a major public health advance.

"WHO is very interested in this development and has an active collaboration with PATH [Program for Appropriate Technology in Health] to accelerate introduction of HPV vaccine in the developing world," said Dr. Marie-Paule Kieny, WHO's Director, Initiative for Vaccine Research, in an e-interview from Geneva, Switzerland.

Right now, several obstacles prevent WHO from including the HPV vaccine in its essential medicines list, added Kieny, including the vaccine's short supply and high cost.

The vaccine costs US$370 for a full 3-shot course given over 6 months. US sales could top $1 billion; Canadian sales could total $100 million a year.

Ironically, what is being heralded as a medical triumph by many is also rife with controversy infused in the politics of teen sex. Gardasil prevents HPV but does not treat it, so the vaccine is most effective when given before a person has sex. For the vast majority of women the vaccine's debut comes too late and regular Pap tests remain essential. The FDA has approved it for use in girls and women age 9 to 26. Some conservative groups in the US have opposed making the vaccine mandatory, arguing that parents should decide whether their children get vaccinated. Another concern is that the vaccine could give girls the wrong message that sex is safe. The more sex partners a person has, the greater the risk of an HPV infection.

A further complication could arise from Gardasil's limited demonstrated efficacy. Long term studies now underway should indicate whether booster shots will be required. — Alicia Priest, Victoria

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