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Presentation to the Standing Senate Committee on Social Affairs, Science and Technology on
Post-marketing Trials, Ottawa, November 8, 2012

Thank you for the invitation to speak with you today. My presentation will focus on post-marketing trials involving women, pregnant women and women who are breastfeeding; but first, an important caveat. I agree with Thomas Moore, from the Institute for Safe Medication Practice in the United States, that “[g]etting faster access to newly developed, less thoroughly tested drugs is at best a mixed blessing.”¹ That is to say, I have serious reservations about the move to get drugs to market sooner at the expense of fuller and more robust information about safety and efficacy. I commend to you recent research by Joel Lexchin showing that nearly a third (34.2%) of the drugs that got fast-track “priority review” and approval by Health Canada between 1995 and 2010 got a safety warning (often referred to as a ‘black box’ warning) or had to be withdrawn for safety reasons.²

I am here today to argue for important safeguards for women, pregnant women and women who are breastfeeding. I will conclude with specific recommendations for minimum conditions for moving from Phase III to Phase IV (post-marketing) trials.

Introduction:

Research aims at knowledge production and, more specifically, clinical trials aim to produce reliable evidence in support of evidence based medicine. Clinical trials proceed through four phases: Phases I through IV.

Phase I clinical trials are done to test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g. determine a safe dosage range, and identify side effects).

Phase II clinical trials are done to study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies are done to study the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are done after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.³

In principle, the goal of Phase IV (post-marketing) trials is to “address evidentiary gaps in comparative effectiveness, drug safety and real-world utility” in pursuit of social benefit.⁴ In practice, however, it often appears that these trials are co-opted for private benefit. Common criticisms of current practice surrounding post-marketing trials include: (i) co-optation of the research system to “seed” off-label use of new drugs, devices, or biologics, (ii) production of biased evidence (as a result of statistical under-powering, absence of comparator arms, withholding adverse events, and altering primary endpoints), and (iii) publication bias.⁵

I will now address some of these concerns with reference to sex-based biology understood as “the study of biological and physiological differences between men and women.”⁶ In my view, post-marketing research needs to look for potential sex-related differences in the safety and efficacy of drugs, devices, and biologics (including vaccines) and, more specifically, needs to track and analyze outcomes for women, pregnant women, women who are breastfeeding, and their offspring.

This presentation takes as its starting point the DRAFT Health Canada Guidance Document on *Considerations for inclusion of women in clinical trials and analysis of data by sex* released for public comment in January of this year.⁷

The Health Canada Guidance Document “encourages the generation and consideration of new scientific knowledge about sex differences, and about therapeutic products used in pregnancy and while breastfeeding. It also recognizes the importance of building the evidence base not only throughout the clinical trial process, but also throughout the product lifecycle - *from non-clinical studies through to the post-marketing stage.*”⁸ (italics added)

Therapeutic products used in women:

Adverse event reporting and the conduct of well-designed, post-marketing safety clinical trials are key elements of the lifecycle approach to regulation. Today, I want to persuade you that post-market monitoring and post-market safety trials should be designed in such a way as to make it possible for researchers and regulators to identify potential sex-related differences. This is not routine practice at the present time; it should be.

We know that there are medically relevant biological differences between men and women, girls and boys with respect to both the pharmacokinetics and pharmacodynamics of medications.⁹ Which is to say, that the same medications can and do affect women and men, boys and girls differently. Some of what we know concerns: “the effect of oral contraceptives in increasing or decreasing the speed of clearance of drugs such as aspirin, caffeine, and morphine...; (ii) the effect of bodily rhythms, such as the menstrual cycle, on how drugs are processed...; (iii) differences in response to pain medications... as well as difference in the effects and side effects of antipsychotic and antidepressant medications.”¹⁰ More generally, the FDA estimates that adverse drug reactions “affect women at least one and a half times as often as men.”¹¹ Despite this knowledge, we don’t systematically look for and analyze sex-related differences and we should. Indeed, there is no excuse not to do this in post-marketing trials.

Consider, for example, the October 3 and October 9, 2012 “Health Canada Endorsed Important Safety Information on ZOFRAN®.” ZOFRAN® is a prescription medication for the prevention of nausea and vomiting for patients undergoing chemotherapy and radiation for cancer and for patients who have had surgery. The ‘Safety Information’ released by GSK and Health Canada reports that, when used in high doses, ZOFRAN® can affect the QT interval. The ‘QT interval’ is the time between beats that the heart needs to recharge itself. We know (and have known since the late 1990s) that after puberty the QT interval is fractionally longer in women than in men and that this difference (about 20 milliseconds) makes women more vulnerable than men to medications that prolong the QT interval. The ‘Safety Information’ released by GSK and Health Canada makes mention of several revised dosing instructions including the need to “Avoid ZOFRAN® if you have congenital long QT syndrome,” but does not make mention of the fact that this risk is higher among women than men. ZOFRAN® is widely prescribed in high doses by oncologists for women receiving chemotherapy for breast cancer.

All Safety Information letters should include a comment on sex-related differences either confirming that there are none or explaining what they are. Instead, too frequently, there is silence on the matter.

Therapeutic products used in pregnancy

Most therapeutic products are not tested in pregnant women and therefore are not labeled for use in pregnancy. For this reason, almost all drugs and vaccines used in pregnant women are ‘off-label’. Off-label prescribing occurs when a physician prescribes a drug for an unapproved indication, or prescribes a drug for an approved indication but (i) in an unapproved patient population, (ii) at an unapproved dose, or (iii) in an unapproved form of administration. It is legal for physicians to practice off-label prescribing. It is not legal for manufacturers to promote off-label prescribing.¹²

As Anne Lyerly and colleagues argue convincingly, there is a moral obligation to involve pregnant women in research. Only in this way can we hope to provide women with effective treatment during pregnancy, promote fetal safety, reduce the harms of suboptimal care, and provide pregnant women and their fetuses access to the benefits of research participation.¹³

Notwithstanding this obligation, drug use in pregnancy is complicated because of potential harm to the developing fetus and the newborn. Post-marketing safety for this patient population requires long-term safety studies and patient registries for both women and children. Untoward side effects of therapeutic products may not show up for years. Consider, for example, our experience with DES (diethylstilbestrol) prescribed to pregnant women between 1940 and 1971 (in the US), 1978 (in Europe) for the prevention of miscarriage, premature birth and other pregnancy problems. We now know that this drug is a carcinogen in humans. *In utero* exposure to DES causes clear cell adenocarcinoma of the vagina and cervix and breast cancer in female children and increases the risk of testicular abnormalities in male children.

But lest you think this is old history, let me tell you about a current potentially risky use of progesterone supplementation in early pregnancy. In North America, progesterone is routinely used in high doses in *in vitro* fertilization (IVF), usually for the first 12 weeks of pregnancy, to

prevent pre-term fetal loss. What evidence supports this practice? One randomized controlled trial reported in 1992 that involved 120 women.¹⁴ Since then, there is some evidence of harm to male children if the progesterone used is not micronized. Because progesterone is a sex hormone it stands to reason that reproductive organs could be affected. Male children have been born with penile abnormalities (feminization). But what about possible the long-term harms?

Responsible post-marketing research involving pregnant women has to include mandatory long-term follow-up, especially of children.

Therapeutic products use while breastfeeding

My third and final point concerns post-marketing research involving women who are breastfeeding.

Consider the March 2 and March 7, 2012, “Health Canada Endorsed Important Safety Information on domperidone maleate.” This prescription medication is for the treatment of stomach and intestine problems (such as gastritis). It is also used off-label for breast milk supplementation to help with breast milk production in women experiencing insufficient lactation. Earlier this year the Motherisk program reported (on the basis of a meta analysis of relevant trials) that domperidone increases breast milk supply.¹⁵

The ‘Safety Information’ issued by Health Canada and manufacturers of domperidone products reports an association between use of the drug and increased risk of serious abnormal heart rhythms or sudden death from cardiac arrest in patients taking more than 30mg a day or in patients who are more than 60 years of age. As a direct result of the black box warning, lactation consultants are reluctant to recommend the use of this medication to women despite the fact that the dosage does not exceed 30mg a day and the patients are not more than 60 years of age. This could be seen as problematic given the many benefits of breast feeding. The ‘Safety Information’ letter should address this issue and provide direction specific to the patient population of breast feeding women given its well documented use in this population.

Conclusion

It is imperative that post-marketing research pay particular attention to the use of therapeutic products by women, pregnant women and women who are breastfeeding.

1. When serious safety issues are identified and a ‘Safety Information’ letter is issued by Health Canada and drug manufacturers, there should be explicit information relevant to: Therapeutic use in women; Therapeutic use in pregnancy; and Therapeutic use while breastfeeding. That information should either confirm that there are no additional unique concerns for one or more of these populations or provide details about additional unique concerns for one or more of these populations.
2. The importance of controlled prospective long-term studies (especially with off-label use of therapeutic products) cannot be overstated. Here it is important to remember the

tragedy of DES. These long-term studies should include strategies to minimize loss to follow-up.

3. It is imperative that there be treatment registries with independent data collection and analysis. With research involving pregnant women, a special challenge for regulators will be in determining the time frame for mandatory follow-up. Ideally, the children born to women using new drugs should be followed to middle age. As this is unlikely to be the case, careful attention must be given to the time frame for mandatory follow-up.
4. All ‘Safety Information’ letters should include references to original sources so that prescribers can access this information and exercise clinical judgment. Here it is worth remembering that evidence-based medicine successfully integrates “individual *clinical expertise* with the best available external *clinical evidence* from systematic research”¹⁶ (italics added).
5. As recommended by Moore “For the first three years after approval, new drugs should carry a special warning akin to the black triangle used in Britain. It should be prominent and mean to every physician, New Drug: Caution Indicated.”

In closing, I draw to your attention the fact that my presentation has focused narrowly on the issue of safety (the collection, analysis and management of information about adverse effects associated with widespread use) and emphasized the need for robust research in the post-marketing phase. I worry about the absence of incentives for manufacturers to look for and report on additional data about effectiveness.

¹ Moore, T. (2012). New Drug: Caution Indicated. *Arch Intern Med*. Published Online: October 8, 2012 doi: 10.1001/2013.jamainterm.610

² Lexchin J. (2012). New Drugs and Safety: What happened to new active substances approved in Canada between 1995 and 2010? *Arch Intern. Med*. Published Online: October 8, 2012. doi: 10.1001/archintermed.2012.4444

³ United States. Office of Extramural Research (OER) Web Site. Glossary. <http://grants.nih.gov/grants/policy/hs/glossary.htm?print=yes&>

⁴ London, A.J. Kimmelman, J, Carlisle, B. (2012). Rethinking research ethics: The case of postmarketing trials” *Science*. 336: 544-545.

⁵ Ibid.

⁶ Society for Women’s Health Research. *What is Sex-based biology?* Available online: http://www.womenshealthresearch.org/site/PageServer?pagename=hs_sbb

⁷ Some version of this document presumably will replace the *Therapeutic Products Programme Guidelines: Inclusion of Women in Clinical Trials*, 1997. Available online: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/womct_femec-eng.pdf

⁸ Health Canada. *Guidance Document Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex* DRAFT – January 9, 2012

⁹ Pharmacokinetics (how a drug is metabolized, absorbed, and cleared from the body); pharmacodynamics (how a drug affects bodily organs and processes)

¹⁰ Epstein S. (2007) *Inclusion: The politics of difference in medical research*. Chicago: University of Chicago Press, 237.

¹¹ Ibid., 238.

¹² Section 9(1) of the Food and Drugs Act deals with false, misleading or deceptive advertising and Section C.08.002. of the regulations stipulates that: “(1) No person shall sell or advertise a new drug unless (a) the

manufacturer of the new drug has filed with the Minister a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission or an abbreviated extraordinary use new drug submission relating to the new drug that is satisfactory to the Minister; (b) the Minister has issued, under section C.08.004 or C.08.004.01, a notice of compliance to the manufacturer of the new drug in respect of the submission; (c) the notice of compliance in respect of the submission has not been suspended pursuant to section C.08.006; and (d) the manufacturer of the new drug has submitted to the Minister specimens of the final version of any labels, including package inserts, product brochures and file cards, intended for use in connection with that new drug, and a statement setting out the proposed date on which those labels will first be used. Available online: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/page-293.html#docCont

¹³ Lyerly, AD, Little M, Faden R. (2008).The second wave: toward ethical inclusion of pregnant women in clinical research. *Int. J. Fem Approaches Bioeth.* 1(2), 5-22.

¹⁴ Prietl G, Diedrich K, Van der Ven, H. et al. (1992). The effect of 17 α -hydroxyprogesterone caproate/oestradiol valerate on the development and outcome of early pregnancies following in vitro fertilization and embryo transfer: a prospective and randomized controlled trial. *Hum Reprod*; 7 (Suppl1): 1-5.

¹⁵ Osadchy A, Moretti, ME, and Koren G. (2012) Effect of domperidone on insufficient lactation in puerperal women: A systematic review and metaanalysis of randomized controlled trials. *Obstetrics and Gynecology International*. Doi:10.1155/2012/642893.

¹⁶ Sackett DL, Rosenberg WMC, Gray JAM et al. (1996) Evidence based medicine: What it is and what it isn't. *BMJ* 312, 71-72.