FOR THE RECORD

FDA sketches parameters for tamper-resistant opioids

The United States Food and Drug Administration (FDA) has issued draft guidance to industry to help develop tamper-resistant formulations of generic opioids that are more difficult to crush and thus less likely to be abused by addicts.

"The FDA is extremely concerned about the inappropriate use of prescription opioids, which is a major public health challenge for our nation," FDA Commissioner Dr. Margaret A. Hamburg stated in a press release (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm?source=govdelivery). "This draft guidance is an important part of a larger effort by FDA aimed at preventing prescription drug abuse and misuse."

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling sketches the FDA's "thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf).

Existing formulations of opioids that have been designed to deter abuse "have not yet proven successful at deterring the most common form of abuse — swallowing a number of intact pills or tablets to achieve a feeling of euphoria. Because opioid analgesics must be able to deliver the opioid to patients for the management of pain, the extent to which an abuse-deterrent product is able to reduce abuse will never be absolute. Therefore, the extent of abuse deterrence can only be understood when studied relative to a comparator."

"Opioid analgesics can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent formulations should target known or expected routes of abuse for the opioid drug substance for that formulation. As a general framework, abuse-deterrent formulations can be categorized as follows:

1. Physical/Chemical barriers — Physical barriers can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse.
2. Agonist/Antagonist combinations — An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product may be formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed but becomes active if the product is crushed and injected or snorted.
3. Aversion — Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used.
4. Delivery System (including depot injectable formulations and implants) — Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, a sustained-release depot injectable formulation that is administered intramuscularly or a subcutaneous implant can be more difficult to manipulate.
5. Prodrug — A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for intravenous injection or intranasal routes of abuse.
6. Combination — Two or more of the above methods can be combined to deter abuse."

The guidance sketches the methodologies and requirements of studies that should be submitted in support of a licensing application for tamper-resistant opioids, including clinical abuse potential studies, as well as proposals for labelling requirements.

"Including information about a product's demonstrated abuse-deterrent properties in labeling is important to inform health care providers, the patient community, and the public about the product's predicted or actual abuse potential. Accordingly, FDA encourages sponsors to seek approval of proposed product labeling that sets forth the results of physicochemical, physiologic, pharmacodynamic, pharmacokinetic, and/or formal postmarketing studies and appropriately characterizes the abuse-deterrent properties of a product."

The combined effect of approvals based on targeted data and a "flexibility, adaptive approach to labeling" will be a beneficial effect on public health, the guidance added.

The proposal will ultimately allow for "four general tiers of claims available to describe the potential abuse-deterrent properties of a product." To wit:

"Tier 1: The Product is Formulated with Physicochemical Barriers to Abuse

Tier 2: The Product is Expected to Reduce or Block Effect of the Opioid When the Product is Manipulated

Tier 3: The Product is Expected to Result in a Meaningful Reduction in Abuse

Tier 4: The Product has Demonstrated Reduced Abuse in the Community."

"An example of a Tier 1 claim could be: These data demonstrate that, when the intact formulation is ground in a coffee grinder, the resulting particle

size makes insufflation extremely difficult; and when those particles are heated they form a gelatinous substance that cannot be drawn up into a syringe or insufflated. Therefore, it appears that injection or snorting of the manipulated drug product would be difficult. However, abuse of this product is still possible by the oral route. This statement would be followed by an appropriate acknowledgment that data from laboratory studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and that this information may be modified based on the results of such studies."

All that said, the FDA also indicated it plans to be "flexible" in its approval process. "The science of abuse deterrence," it noted, "is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. This means that FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products." — Wayne Kondro, *CMAJ*

Number of nurses continues to rise

The number of regulated nurses working in Canada increased by roughly 8% between 2007 and 2011 to a total of about 360 000, according to the Canadian Institute for Health Information (CIHI).

"More than 92% of those eligible to practise in 2011 were employed, meaning approximately 8% were outside of the workforce (whether by choice or unable to find employment). Of those employed, more than 56% were employed full time," states CIHI's new report, *Regulated Nurses: Canadian Trends, 2007 to 2011* (https://secure.cihi.ca/free_products/Regulated_Nurses_EN.pdf).

The regulated nursing professions in Canada are registered nurses (including nurse practitioners), licensed practical nurses and registered psychiatric nurses.

The number of nurses per 100 000 of the population also rose, from 1011 to 1046, though this figure remains below the peak seen in the early 1990s.

In 2011, the average age of a regulated nurse was 44.8 years, but the nursing profession appears to be replenishing it ranks with younger members, as the portion of nurses under age 35 increased from 20.9% to 23.7%. Most new graduates tend to head for British Columbia, Alberta and Ontario. International graduates make up less than 8% of the nursing workforce.

Also increasing was the number of nurse practitioners, from 1344 to 2777, a substantial bump attributed to an increased investment by provinces and territories into the nurse practitioner profession. — Roger Collier, *CMAJ*

Psychological health and safety standard unveiled

Billing the standard as the "first of its kind in the world," the Mental Health Commission of Canada, the Canadian Standards Association and the Bureau de normalisation du Québec (BNQ) have unveiled a voluntary, national boilerplate for promoting psychological health and safety in the workplace.

The standard sketches "requirements for a documented and systematic approach to develop and sustain a psychologically healthy and safe workplace," the trio assert in *Psychological health and safety in the workplace — Prevention, promotion, and guidance to staged implementation* (http://shop.csa.ca/en/canada/occupational-health-and-safety-management/cancsa-z1003-13bnq-9700-8032013/invt/z10032013/?utm_source=redirect&utm_medium=vanity&utm_content=folder&utm_campaign=z1003).

"The strategic pillars of a psychological health and safety system are prevention of harm (the psychological safety of employees), promotion of health (maintaining and promoting psychological health), and resolution of incidents or concerns," the standard states. "Human needs when unmet or thwarted can become risk factors for psychological distress; when satisfied can lead to psychological and organizational health. These human needs include security and physiological safety, belonging, social justice, self-worth, self-esteem, self-efficacy, accomplishment, or autonomy."

"One in five Canadians experience a mental health problem or mental illness in any given year and many of the most at risk individuals are in their early working years. Canadians spend more waking hours at work than anywhere else," Louise Bradley, commission president and CEO stated in a press release (www.mentalhealthcommission.ca/SiteCollectionDocuments/January_2013/MHCC_Standard_MediaRelease_ENG.pdf). "It's time to start thinking about mental well-being in the same way as we consider physical well-being, and the Standard offers the framework needed to help make this happen in the workplace."

"Workplaces with a positive approach to psychological health and safety have improved employee engagement, enhanced productivity, and a better financial outlook," added Bonnie Rose, president, standards, for the nonprofit CSA [Canadian Standards Association] Group.

"Mental health problems and illnesses are estimated to account for nearly 30% of short- and long-term disability claims in Canada. In some major employment sectors, the number is closer to 50%. More than 80% of Canadian employers rate mental health problems and illnesses among the top three drivers of both short- and long-term disability claims made by their employees," according to a background document distributed to the media.

The standard outlines the principles that the groups believe should guide psychological health and safety strategies, while specifying, in considerable detail, the elements that should be included in each component of such strategies.

A risk mitigation process, for example, should include a documented procedure for: "a) hazard identification; b) elimination of those hazards that can be eliminated; c) assessment for level of risk for hazards that cannot be eliminated; d) preventive and protective measures used to eliminate identified hazards and control risks; and e) a priority process reflecting the size, nature, and complexity of the hazard and risk, and, where possible, respecting the traditional hierarchy of risk control."

"Factors to assess should include, but are not limited to, the following: a) psychological support; b) organizational culture; c) clear leadership and expectations; d) civility and respect; e) psychological job demands; f) growth and development; g) recognition and reward; h) involvement and influence; i) workload management; j) engagement; k) work/life balance; l) psychological protection from violence, bullying, and harassment; m) protection of physical safety; and n) other chronic stressors as identified by workers." — Wayne Kondro, *CMAJ*

Progress against neglected diseases

While substantial progress has been made over the past three years in reducing the toll taken by 17 so-called neglected tropical diseases, there remain gaps to fill in the global strategy to reduce their impact and only a handful of new therapies have actually been developed to treat several of those diseases, the World Health Organization (WHO) says.

While unveiling a "new phase" in the strategy to reduce the incidence and toll of the diseases, WHO also argued that there is a need to improve treatment delivery mechanisms in many endemic countries.

"With this new phase in the control of these diseases, we are moving ahead towards achieving universal health coverage with essential interventions," Dr. Margaret Chan, director general of WHO stated in a press release (www.who.int/neglected_diseases/2012report/en/index.html). "The challenge now is to strengthen capacity of national disease programmes in endemic countries and streamline supply chains to get the drugs to the people who need them, when they need them."

Eradication targets established in the agency's 2010 report on neglected tropical diseases and WHO's 2012 roadmap for tackling the diseases have resulted in substantial progress, Chan states in the foreword to *Sustaining the drive to overcome the global impact of neglected tropical diseases* (www.who.int/iris/bitstream/10665/77950/1/9789241564540_eng.pdf). "Unprecedented recent progress has revealed unprecedented needs for refinements in control strategies, and new technical tools and protocols. The roadmap identified preventive chemotherapy as a key strategy for tackling, often jointly, a number of these diseases. In 2010, more than 700 million preventive treatments were delivered. Since some of these treatments confer protection against three or more diseases, the impact on the total burden of disease is even greater than suggested by this number."

"The substantial increases in donations of medicines made since the previous report call for innovations that simplify and refine delivery strategies — from forecasting and costing, to the monitoring of drug efficacy and impact, to testing for signs that pathogens are developing resistance under the pressure of mass drug administration. While the prospects for expanding coverage are now vastly improved, endemic countries absorb these donations through large-scale mobilizations of their own, often limited, health resources, further underscoring the need for streamlining and simplification," she added.

The report states that among the greatest achievements has been a substantial scale-up in the use of preventive chemotherapy. "As of 2012, 700 million tablets of albendazole or mebendazole have been delivered annually to treat school-aged children. Programmes in countries where soil-transmitted helminthiases are endemic have already requested an additional 150 million tablets — a figure indicative of the significant increase in treatment coverage. For schisotosomiais, it is expected that improved access to praziquantel will enable an estimated 235 million people to be treated by 2018."

The strategy is on track to eradicate dracunculiasis by 2015, although "operational challenges remain in Chad, Ethiopia, Mali and South Sudan," and to eradicate yaws by 2020, largely as a consequence of a decision to focus more treatment on a single dose of oral azithromycin, the report states.

The report cautions, though, that future progress will depend on such factors as the strength and efficiencies of health delivery systems in endemic countries; access to affordable medicines; trained health care workers; national policies in such areas as public health, water and sanitation; and life's inevitable vicissitudes. "The transmission and persistence of pathogens responsible for neglected tropical diseases depend on vectors or intermediate hosts. Thus, there is the risk that sufficient access to medicine alone will not enable targets to be achieved if measures to control vectors or their intermediate hosts and species are inadequate," it states, noting that dengue fever ranked as the fastest spreading vector-borne viral disease in 2012, indicating a need for the world to "change its reactive approach and instead implement sustainable preventive measures that are guided by entomological and epidemiological surveillance." — Wayne Kondro, *CMAJ*

***CMAJ* 2013. DOI:10.1503/cmaj.109-4399**