Health Canada proposes new regulatory regime for drugs

It seems a simple quid pro quo. Under a new regulatory regime for pharmaceuticals and biologics, Health Canada is proposing to lower the threshold for initial market authorization licenses in exchange for additional safety and efficacy studies as a condition for continuing to sell a drug.

That trade-off is presented in the paper, *The Progressive Licensing Framework Concept Paper for Discussion*, released in February by Health Canada. It outlines a new regulatory regime in which the notion of post-market surveillance is incorporated into Health Canada's oversight of drugs, while also appearing to introduce some variant of conditional or probationary licensing to allow more rapid entry of so-called "extraordinary need" drugs (i.e., small population, early access, breakthrough or compassionate-use drugs) that may be considered too risky for the general population.

Drugs currently undergo extensive testing first in pre-clinical studies that usually investigate mechanisms of action, toxicity and teratogenicity. If pre-clinical studies are acceptable, then approval is granted to proceed to clinical studies. There are 4 incremental phases: phase I studies involve tolerance to medication in healthy volunteers or in patients for toxic drugs such as chemotherapeutic agents; phase 2 studies explore drug dosing, the effect on biological markers of disease as well as some early safety and efficacy in the form of pilot studies; phase 3 trials are the large-scale randomized trials that are designed to demonstrate clinical efficacy and safety; and phase 4 evaluations involve post-marketing surveillance, usually done through the voluntary reporting of adverse events. If concerns arise during phase 3 trials, companies are often requested to un-

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Health Canada is proposing to lower the threshold for initial market approval of drugs.

dertake observational studies to prospectively document safety concerns. The proposed changes will mostly affect phases 3 and 4 of the current regulatory framework.

Health Canada stresses that none of the proposed concepts are written in stone and were advanced to stimulate debate during an 8-month consultations exercise beginning this spring to "modernize" the regulatory regime.

The broad intention is to move to a system of "life cycle management" but the specifics are open for debate, says David Lee, director of the Office of Patented Medicines and liaison and project director of the Progressive Licensing Project. "This is an exploration right now. We're not at a stage where we've concluded any requirements."

Critics, though, say some of the concepts articulated in the paper are so "hazy," "vague" and "convoluted" that it's all but impossible to assess the proposed regime and its potential consequences, let alone determine exactly how much lower Health Canada is proposing to drop the bar for initial drug approval.

At the core of the proposal lies the proposition that drugs should be evalu-

ated over their "full life-cycle" using a flexible and agile "benefit-risk" model, rather than have their safety and efficacy strictly determined during pre-market assessment.

The current regulatory system, with a "threshold set narrowly at considerations of safety and efficacy," fails to adequately assess or weigh a drug's benefits against its risks, the paper argues.

Under the new framework, pharmaceutical firms would still have to demonstrate "efficacy, safety and quality for the proposed conditions of use (e.g., authorized indication, target population, dosing regimen, duration of use) as the baseline requirement for initial market authorization."

But pre-market safety evidence will be "limited to identifying the most commonly occurring adverse drug reactions," while a new "evidence-based, favourable benefit-risk profile for the drug" will be required, the paper adds. "If the profile of the drug is unclear in the sense that the benefit does not clearly outweigh the risk, a further evidence-based determination regarding the impact of market authorization could take into account larger public health, societal and ethical considerations."

The evidence underpinning the benefit-risk profile would “contextualize” the traditional safety, efficacy and quality evidence, and include other information such as “considerations relating to public health and/or individual health, as identified by regulatory and other potential decision-makers,” as well as the level of “risk acceptance.”

“In essence, the standard for initial authorization would require an evidence-based favourable benefit-risk profile for the drug’s use under the proposed conditions.”

Lee says Health Canada is simply proposing to introduce the concept as “another layer” of pre-market licensing. “It sort of grooves more with what we understand prescribers are assessing, and other decision-makers in the system. That’s not adjusting the amount of data that someone would submit. It’s just talking about what we’re actually doing when we’re approving.”

But York University Associate Professor and Chair of the School of Health Policy and Management Dr. Mary Wiktorowicz can’t fathom the rationale for proposing to lower the threshold for initial market approval. “They’re very vague about all of this,” she says, adding that the paper fails to even articulate a clear notion of the benefit-risk model that might be used. “If the approval requirements are to be lessened, I want to see what conditions are being put in place and this document doesn’t allow me to get any assurance.”

Others argue the rationale for any of the changes hasn’t been established.

“I don’t see the point,” says Dr. Jim Wright, director of the High Blood Pressure Clinic at Vancouver Hospital, Professor of Pharmacology and Therapeutics, Medicine at the University of British Columbia and managing director of UBC’s Therapeutics Initiative. “They should be making sure that the drugs are safer. At this point, I’m not convinced that they’re doing it, so I don’t think this is the right approach to be taking at all.”

Wright surmises the changes are actually a response to the controversies that erupted over rofecoxib (Vioxx), which Health Canada pulled from the market in 2004 when studies showed long-term use increased the risk of

heart attack (*CMAJ* 2004;171:1027-8). “This seems like exactly the wrong thing to do in response to that. It’s not something where you want to open things up more, where you’ve had a major screw-up.”

Still others, though, believe there is a definite need for more formal post-market surveillance.

“There should be more systematic post-marketing studies done across the country to look at both harm and effectiveness,” says Li Ka Shing Knowledge Institute Director, and drug regulation expert, Dr. Andreas Laupacis. “It would be useful to both Health Canada and provincial and territorial drug formularies.

But Wright counters that there’s no guarantee a move to post-market surveillance would improve safety. As the rofecoxib controversy demonstrated, it’s often extremely difficult “to pick up a post-market effect, like heart attacks, with post-market surveillance.”

The experts say Health Canada’s paper also fails to clearly articulate the structure of the monitoring system it would use; the legal authority under which it would do so; the kinds of requirements that might be placed on manufacturers; or the stick the agency might wield in the event of non-compliance.

Resolution of those issues will be particularly critical in dealing with so-called “extraordinary-need” drugs. Under the proposal, manufacturers would seek approval for these using a “flexible departure” approach, in which they could apply to use a diminished standard of evidence with respect to a new drug’s efficacy and safety if they feel there’s a compelling reason because of “important evidence concerning contextual benefit-risk considerations.”

“The flexible departure route would address the issue of emerging techniques and strategies to target disease identification, drug development (including the use of surrogate markers as study end-points) and data collection and analysis (e.g., adaptive trial design).”

Laupacis and Wiktorowicz both note that the US experience with such an approach has had disappointing results. Studies indicate that manufacturers fail to produce the promised post-marketing studies about 50% of the time.

Yet, the US Food and Drug Administration can do nothing about it because it doesn’t have the legal authority to compel compliance, Wiktorowicz says.

Laupacis says more details are needed around this issue. “If one is going to decide to make drugs available more quickly, if it turns out that the drug isn’t as effective as one thought, or has more harm than one thought, what are the mechanisms, to either withdraw the drug or have it used more selectively? That is not really addressed in the document.”

Wiktorowicz says implementation of progressive licensing will also require “a more sophisticated monitoring system, and better international co-operation. There are several areas in which we’d have to do some more work, put some more funding [into, so as to set] up an actual system in order for this kind of approach to actually protect Canadians.”

University of Toronto Institute for Clinical Evaluative Sciences epidemiologist Dr. Mike Patterson surmises a more fruitful approach might be to create and fund an independent, third-party (possibly academic) network to conduct post-market safety assessments.

Lee says Health Canada will study both the American and European experiences to ascertain the best structure for a post-market surveillance system as well as the specific reporting requirements that might be asked of industry.

Yet, until such issues are ironed out, it’s virtually impossible to assess the pros and cons of the proposed regime, Patterson says. “The discussion paper is to test the water a little bit and to get stakeholders’ reaction to it. I think the general principle is reasonable. But the conditions under which it would be employed needs to be worked out.”

Canada’s Research-Based Pharmaceutical Companies spokesperson Jacques Lefebvre said the proposed changes are being reviewed by Rx&D’s regulatory affairs committee. “We look forward to participating in public consultations on regulatory renewal proposals put forward by Health Canada.” — Wayne Kondro, *CMAJ*

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