Pandemic Vaccine Fast-Tracking System Years In The Planning

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TORONTO — As pharmaceutical companies rush to make swine flu vaccine, regulators in Canada, the U.S. and Europe are flipping into gear plans they have honed over several years on fast-tracking flu vaccine for a pandemic.

The approaches are not identical, but are variations on a theme. Flu vaccines have been used safely for decades and this pandemic version is just one more flu vaccine, they say.

"Really, the same manufacturer will be making the same vaccine and it's just considered as a (strain) switch," explains Dr. Elwyn Griffiths, director general of the biologics and genetic therapies directorate, the section of Health Canada that regulates vaccines.

Though they work within the frameworks of different laws, Health Canada, the U.S. Food and Drug Administration and the European Medicines Agency (EMEA) all intend to treat the pandemic vaccine as a supplement or amendment to existing flu vaccines licences, either for seasonal or pandemic vaccine.

The goal is to try to speed approval of the vaccine so that it can be used before the pandemic is over — if and when political or public health authorities decide vaccinating all or parts of the population is the right way to go.

"Remember, these are two separate decisions," says Dr. Norman Baylor, director of the FDA's office of vaccines research and review. Baylor uses his hands during a recent meeting in Gaithersburg, Md., to explain the demarcation between approving pandemic vaccine and ordering mass vaccination.

"The decision to deploy the vaccine, that's over here. The decision to license the vaccine, that's over here," he says, holding his hands out to opposite sides of his body.

The second "over here" is the realm of the regulatory agencies, which have been working with the World Health Organization and each other for years striking plans for how to respond to the special demands of a pandemic. The impetus was the dangerous H5N1 virus, which kills about 60 per cent of people infected. Obviously rapid action would be needed if it started a pandemic.

"The idea was 'How can we do it? How can we move forward?'" Griffiths explains.

The work led to "Regulatory Preparedness for Human Pandemic Influenza Vaccines," a set of guidelines crafted by the WHO's expert panel on biological standardization.

Governments and their vaccine regulators realized that if pandemic vaccines were treated like a brand new vaccine — recently introduced products to protect against HPV or rotaviruses, for instance — clinical trials involving tens of thousands of people would be needed.

The pandemic would be over before the pandemic flu shots would be injected into anyone but the volunteers in the clinical trials.

That approach is obviously impractical. And regulators believe it is also unnecessary for flu vaccines, which have been reformulated countless times to target new virus strains in the half century or so they've been in use.

Over that time, billions of flu shots have been administered. While people often complain of soreness at the site of the injection, serious side-effects from flu shots are extremely rare.

Unfortunately for those making decisions about this vaccine, the most famous side-effect incident linked to flu vaccine arose the last time there was a mass campaign to vaccinate against a swine flu virus.

An outbreak of swine influenza in the U.S. in early 1976 led to fears a pandemic was emerging. More than 40 million people in the U.S. were vaccinated. The pandemic never materialized, but roughly 500 people developed Guillain-Barre Syndrome, a normally temporary paralytic condition. About 25 deaths were attributed to the vaccination program.

Science can't always explain why GBS occurs and it still can't answer why the 1976 vaccination program led to a spike in cases. Experts hope the modernization of flu vaccine manufacturing since 1976 will eliminate the risk of a repeat performance.

But they also know that even if this vaccine were to elevate the risk of developing GBS, clinical trials are unlikely to detect it. Millions of doses of the 1976 vaccine were administered before U.S. authorities could see that there was a problem and that the problem was likely related to the vaccine.

So how will regulators proceed now?

To understand Canada's approach, it's helpful to first look at what the EMEA has done.

It offered all flu vaccine manufacturers the chance to go through a special advance licensing process, producing a "core dossier" of safety and immunogenicity data on their manufacturing processes and their pandemic vaccines.

Three companies — Baxter International, GlaxoSmithKline and Novartis — went through the process, using H5N1 vaccines as their surrogate pandemic vaccines.

These "mock-up dossiers," as they are called, serve as the regulatory proof of safety and immunogenicity of any pandemic vaccine these manufacturers make. Manufacturers then apply for a "pandemic variation" to switch the subtype covered by the vaccine from H5 to the pandemic virus, in this case an H1N1.

"The whole concept of the mock-up vaccine relies on the fact that you can extrapolate to some extent the clinical efficacy data," explains Monika Benstetter, a press officer for the EMEA.

The agency says it can process a pandemic variation application in five working days, though it will still be up to national governments as to whether they want to use the fast-tracked vaccines.

Canada went through a similar process with this country's pandemic vaccine contractor, GSK, says Griffiths. But whereas the EMEA actually licensed the pandemic vaccines, Canadian authorities held the approval in abeyance.

"They (Europe) have licensed 'the mock' if you like . . . and then all that was needed was a strain change," he explains. "We have come to the starting line, if I can put it that way, with the mock H5N1 and we did not license."

He insists the difference is a "nuance" that won't gum up the works in Canada. "We can use all those (mock up dossier) data, switch in the new strain and away you go."

But Griffith says Health Canada wants GSK to do a small trial — involving 100 to 200 people, probably — to generate some safety and immunogenicity data for the H1N1 vaccine before the pandemic vaccine can get approval. Like the EMEA, Health Canada can turn that application around in five days, he says.

As for the U.S., Baylor told the meeting of an FDA advisory committee on vaccines last week that the FDA intends to treat swine flu vaccine as a so-called strain change. No one on the expert advisory panel objected to the plan.

Strain change is the regulatory tool the FDA uses to allow manufacturers to make the frequent adjustments needed for seasonal flu vaccine.

Flu shots have to be tweaked almost annually to keep up with the rapidly mutating influenza viruses. The strain change system lets manufacturers pull out virus strains no longer needed and slot in vaccine against newer viruses more likely to cause disease.

In the U.S when seasonal flu vaccine is updated in this manner, no new studies are required; a strain change is considered a supplement to the original vaccine licence. (Canada uses a similar approach for seasonal flu vaccine, though it requires a small study each time.)

In this case, though, FDA officials have said they want manufacturers to do trials on

the pandemic vaccine to validate that it's safe and ensure it is effective at the dose size that will be used. The data from those studies aren't expected to be available when swine flu vaccination programs start, however.

In fact, given the timing of when pandemic vaccines are likely to be approved and when dosing studies undertaken by companies and governments are likely to be completed, it is quite possible that dosing regimens — the amount of vaccine per shot and number of shots needed — could change midstream in countries that will have the first access to pandemic vaccine.

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