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FOLLOW THE SCRIPT™

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FROM THE LAB TO THE PHARMACY: THE DRUG DEVELOPMENT PROCESS

Previous issues of *Follow the Script*™ have touched on the drug approval process in Canada, but let's take a step back and take a look at the research and development that's involved before a drug is approved by Health Canada to enter the market.

Pharmaceutical research is a large and growing business internationally, and drug manufacturers must follow a lengthy and complex process to study and test new drugs. Most drugs that start the development process drop off at various stages and never make it to the market.

Sponsoring the research

All research to develop new drugs is funded by a sponsor – usually a brand-name pharmaceutical company but not always; sponsors can also be researchers from universities, hospitals, or research organizations.

Since clinical trials in Canada must be led by a physician, trials are typically done through hospitals or universities in partnership with the pharmaceutical company.

Regardless of who is doing the actual research, a brand-name pharmaceutical company will eventually manufacture and market the drug.

Drug discovery

A new drug starts out with scientists developing a substance – either chemical or biological – that could be used to treat a specific disease or condition. Sounds simple, but scientists look at thousands of compounds before finding one that looks promising. This substance is tested in tissue cultures and a variety of small animals to determine its effects.

If the substance, or drug, is doing what the scientists expect and want it to, additional studies are undertaken. This stage is called pre-clinical development and includes additional animal testing as the drug is given in different amounts over different periods of time to determine its effects – expected and unexpected – and the dosage responsible. If the drug isn't causing any serious harm and is producing the desired effect, it can proceed to the next stage: clinical trials.[1]

Clinical trials

The purpose of clinical trials is to study the dosage, effectiveness, and safety of the drug in humans with the participants and the results closely monitored. Clinical trials are conducted by physicians along with a research team. All clinical trials are done in phases under controlled conditions with each phase designed to study a specific aspect of the drug.

Phase one

In this phase, researchers are trying to find out whether the drug is safe and whether people can tolerate it. This can be the phase with the highest level of risk as the drug has never been administered to humans before. A small number of healthy participants is divided into groups taking different dosages of the drug at different times. The researchers are determining a safe dose of the drug to bring about the desired result, as well, they are collecting information on the side-effects the participants experience.

Phase two

In phase two the effectiveness of the drug for a particular disease or condition is studied based on the dosage and schedule determined in phase one. This phase usually involves a larger group of people who have the condition but are otherwise healthy. The researchers are continuing to gather information on the effects of the drug at different dosages and to identify common side-effects.

Phase three

Phase three trials generally involve a much larger number of participants than the other phases, sometimes at many different locations. Sometimes the drug is assessed against other drugs or treatments currently in use. If this phase shows that the new drug is safe and effective, and its value outweighs any risks, a new drug submission can be made to Health Canada for approval to market the drug.

Phase four

Sometimes a drug goes on to a phase four clinical trial after it's approved and on the market. In this phase researchers are gathering additional information on possible risks and benefits of the drug over the long term.[2]

What is a "randomized, controlled double-blind study"?

Phase three trials are frequently randomized, controlled, double-blind studies. Randomized means the participants are divided into at least two groups – one group receives the drug (the experimental group) while the other group (the control group) receives the current treatment or no treatment. Double-blind means neither the participant nor the researcher knows to which group a participant has been assigned while the trial is in progress. This type of trial is considered the "gold-standard" of medical research.[3]

The role of Health Canada

To protect the public, all prescription and non-prescription drugs for sale in Canada have to be approved by Health Canada before they can go on the market. Health Canada's role is to regulate, evaluate, and monitor the safety, efficacy, and quality of drugs (and other products). This includes both biologic and chemical-based drugs.[4]

For new drugs in development, Health Canada reviews:

- Applications to conduct clinical trials. The applications include details about the research and pre-clinical studies, the dosage of the drug, and information about the researchers conducting the trial. Permission to conduct a clinical trial is granted once Health Canada is satisfied the drug is being used appropriately, any risks are minimized, and the objectives of the trial are likely to be met. Health Canada maintains a clinical trials database which provides an overview of many clinical trials taking place in Canada.[5]

- New drug submissions from pharmaceutical manufacturers. These submissions include the results of the pre-clinical studies and clinical trials as well as other details about the drug's packaging, labelling, side-effects and therapeutic claims. Even after approval is granted, Health Canada continues to monitor the drug. Manufacturers are required to provide updated information on adverse effects (i.e., side-effects), safety concerns, etc., that arise as the drug becomes more widely used.[6]

After the drug is approved…

Getting the new drug approved by Health Canada isn't the last step. After receiving the approval, the pharmaceutical manufacturer conducts an educational and marketing campaign to doctors so they'll prescribe the new drug. For example, if this drug treats a condition that has other options available, the manufacturer has to persuade doctors that this new treatment is better than existing treatments. As well, the pharmaceutical manufacturer promotes the drug to plan providers, like GSC and provincial drug plans, who will evaluate the drug for inclusion on their formularies for reimbursement.

There's also the continued reporting to Health Canada about adverse effects and what that can mean for a drug, even when it's been on the market for a while. Read on as we discuss Health Canada's drug approval process in "Behind the Counter."

Sources:

[1, 4, 6] "How Drugs are Reviewed in Canada," Health Canada, 2015, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examenfd-eng.php. Retrieved: November 12, 2015.

[2] "It's Your Health: Clinical Trials and Drug Safety," Health Canada, 2013, http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/clinical_trials-essais_cliniques-eng.php; retrieved: November 12, 2015. "Phases of Clinical Trials," Canadian Cancer Society, 2015, http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/clinical-trials/phases-of-clinical-trials/?region=on&p=1; retrieved: November 18, 2015. "How drugs are approved in Canada," Consortium of Canadian Centres for Clinical Cognitive Research, http://c5r.ca/how%20drugs%20are%20approved/; retrieved: November 13, 2015.

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[5] "It's Your Health: Clinical Trials and Drug Safety," Health Canada, 2013, http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/clinical_trials-essais_cliniques-eng.php. Retrieved: November 12, 2015.

BEHIND THE COUNTER

REVIEWING HEALTH CANADA'S DRUG ASSESSMENT PROCESS

In each issue of *Follow the Script*, we interview a member of our pharmacy team about a current topic. In this issue, we talk to **Ned Pojskic,** our pharmacy strategy leader, about Health Canada and drug approvals.

FtS: What is Health Canada assessing when approving new drugs?

Ned: Health Canada reviews new drug submissions for safety, efficacy, and quality of a drug.

FtS: Health Canada's review doesn't look at how much the new drug is going to cost?

Ned: No, the Patented Medicine Prices Review Board is the organization that regulates the prices of brand-name drugs. And keep in mind that GSC also looks at the prices of drugs when we're considering adding them to our formularies. We need to be sure new drugs offer value for our plan sponsors and plan members, relative to existing therapies already on the market.

FtS: I understand that sometimes new drugs are approved with conditions. What does that mean?

Ned: Approving drugs for use by the public always involves some risk, so Health Canada issues either a Notice of Compliance (NOC) or a Notice of Compliance with conditions (NOC/c) for the drug. The NOC/c means Health Canada recognizes that more information is needed about the clinical benefits of the drug but does not want to delay patient access. This happens for drugs where the benefit to patients outweighs the risks.

FtS: Can you give me an example?

Ned: Health Canada is always considering unmet needs when assessing drugs for approval, so some cancer drugs are a good example. This is where the potential immediate impact of the drug therapy for patients with no other options is balanced against other considerations.

FtS: We sometimes hear about drug recalls. Why does that happen when it takes so much time and so many trials before the drug is even submitted to Health Canada?

Ned: Some studies are better than others. But studies try to replicate ideal conditions, and those conditions don't happen in real life – real life is never ideal. And new drugs tend to be studied for a limited period of time; often not long enough to truly evaluate long-term effects. As well, drug trials don't always involve patients with the level of complexity and co-morbidities seen in the real world.

It's impossible for drug trials to test for every factor that could come up with patients – what other conditions they have, what other drugs they end up taking – there are endless possible combinations. So once a drug is sent out into the world, its true effects are seen. That's when recalls happen. For example, sometimes a drug will have a very rare side-effect that isn't revealed during a clinical trial that involves a relatively small number of people. The side-effect might only become apparent after the drug is approved and being used by a much larger and diverse population.

FtS: So Health Canada could easily approve a drug that's not as safe as the drug submission makes it out to be?

Ned: Absolutely. Remember Vioxx? It was a blockbuster drug for arthritis and other acute pain. It was released in 1999 but had to be pulled off the market in September 2004 because it was causing patients to have heart attacks.

FtS: How often are drugs recalled?

Ned: Drug recalls are actually rare and almost always happen because of safety issues not efficacy. If there was more consistent reporting of side-effects, as well as issues with efficacy, there likely would be more drug recalls.

Side-effects are supposed to be reported to Health Canada by health care providers – patients can also report drug issues to Health Canada – but reporting is voluntary, so we don't know the extent to which it happens. This is important because Health Canada bases its decisions to recall drugs or release drug information on these reports.

FtS: Do drug companies voluntarily recall drugs or does Health Canada have the power to force them to issue recalls?

Ned: It used to be that Health Canada could only ask manufacturers to withdraw a drug, but since 2013, we have the *Protecting Canadians from Unsafe Drugs Act*, which is also called Vanessa's Law. Now Health Canada has the power to recall unsafe drug products and can enforce the recalls through fines and penalties, including jail time.

FtS: Let's talk about natural health products since they've been in the news recently. Do they go through the same submission and assessment process as pharmaceutical drugs?

Ned: When Health Canada assesses natural health products it looks at safety, quality, and effectiveness – the same as drug products. The evidence required to support safety and efficacy depends on whether the manufacturer makes "traditional health claims" or "non-traditional health claims" for the product.

Non-traditional claims require scientific evidence of safety and efficacy. Traditional claims are based on the knowledge, skills, practices, and experiences of the specific culture using the product over at least 50 years. In the absence of scientific evidence, Health Canada is really only ensuring that the products won't harm anyone. But, because these products are approved and given a number the same way drugs are, it's a bit misleading to the public since it appears that Health Canada is giving these products credibility and legitimacy. And a lot of people think that anything that's "natural" must be safe. So, many patients don't worry about side-effects or interactions with other drugs and don't typically report the usage of these products to their pharmacists or physicians.

FtS: This has been an interesting topic, thanks Ned!