A narrative “life” journey of a prescription drug molecule: From chemical synthesis to receptor binding in fish brain

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Introduction

Many health care providers have only a cursory knowledge of the numerous steps involved in the production and supply of the pharmaceutical products we provide to our patients. The purpose of this article is therefore to provide a short, explicit overview, via a case study, of the many steps involved in a typical “journey” of a pharmaceutical drug molecule. It is the hope that, by elucidating this process more thoroughly, readers will appreciate the complex linkages as well as the potential pitfalls that may implicitly occur at each step in the overall global distribution process. Such an understanding is increasingly important, given Canada’s major drug shortage issues that have complicated pharmaceutical care for patients since the early 2010s.¹ Furthermore, this narrative will also briefly detail contributions from the pharmaceutical sciences towards ensuring the continuing supply or integrity of routinely used pharmaceutical products.

Active pharmaceutical ingredient

Production

Our story begins with the batch organic synthesis of the commonly used Selective Serotonin Reuptake Inhibitor (SSRI) drug molecule, escitalopram, in an offshore production facility of a company whose services have been contracted by a multinational generic pharmaceutical firm.² This company, located in India, is primarily devoted to the bulk chemical production of active pharmaceutical ingredients (APIs). While our escitalopram molecule (in the oxalate salt form) may have been synthesized elsewhere in the world, upwards of 40% to 50% of generic API production occurs in China or India.³ (In this instance, I searched *escitalopram oxalate* as the API on Pharmacompass.com and restricted the facilities to those that have

an actively approved Drug Master File [DMF] with the US Food and Drug Administration [FDA]. Of the 21 facilities that met these criteria, 15 were in India.)

The synthesis of the compound itself occurs in multiple sequential phases of controlled chemical reactions followed by purification and analysis.⁴ In this case, there are at least 2 readily viewable patents (since expired), each detailing a different step-by-step process involved in synthesizing escitalopram oxalate, including the potential enantiomeric separation of the target API from the racemic mixture.^{5,6} In many cases, intermediate precursors are synthesized at 1 site and then transported to another facility for further steps in the synthesis of the API.⁷ Lastly, in addition to the organic chemistry involved in producing the API, a number of physical processes, including crystallization, freezing, drying and filtration, may variably be involved in the preparation of an API as a bulk powder.⁸

In-house quality control testing and packaging

After the “birth” of our escitalopram oxalate molecule, the batch that it was produced in is brought to an adjacent room/building at the plant for analytical quality testing to ensure the yield is acceptable and the batch is free from impurities.⁴ In our case, the batch with our escitalopram molecule meets requirements and the batch is weighed, separated and appropriately packaged into multiple containers for further distribution.

Ordering and shipment

As of February 2019, Health Canada’s drug product database listed 26 pharmaceutical companies currently marketing oral tablets of escitalopram in various strengths.⁹ Many of these companies import escitalopram oxalate in its bulk API form or as a finished dosage form from another manufacturer.¹⁰ This is in accordance with Health Canada’s mutual recognition

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allowance regulations, which enable importation of a foreign company's API or finished dosage form if it is documented to have met the requirements for good manufacturing practices (GMP) by other recognized international governmental authorities (such as the US FDA).¹¹

In our case, multiple standard 1 kg drums of the finished API bulk powder, one of which contains our specific escitalopram oxalate molecule, were purchased by 1 of the 26 pharmaceutical companies marketing escitalopram oxalate oral tablets in Canada. With receipt of the transaction, the Indian API chemical plant arranges export to Canada.

Finished oral dosage form

Production

Three weeks later, when the order of bulk API is received by the Canadian generic drug manufacturer, the first thing that is done is to retain any accompanying documentation of the importer company for proper record-keeping. Once the API is unpackaged, the powder enters a rather complex series of steps in the machinery of industrial pharmaceuticals, scaled for mass production of tablets.¹² Granulation of the blended powder containing API and excipients (with the latter often outsourced or made in-house) is a standard technique with some variation (i.e., wet or dry) depending on the properties of the API powder and desired characteristics of the solid oral dosage form.¹² (Due to the competitive nature of the pharmaceutical industry, the exact production procedure is often not publicly available for particular products due to either intellectual property law [patents] or confidentiality clauses in regulatory agreements between Health Canada's inspectors and the manufacturer.) The final stage is the compression of the granules in tablet press machinery to output single, content uniform, solid oral dosages.¹²

Intermediary packaging and distribution

Many of the tablets produced are placed into sealed stock containers, appropriately labeled as per Health Canada standards, of 100 tablets each containing 10 mg of escitalopram, for sale to pharmacies or wholesalers. However, in the case of our specific escitalopram oxalate molecule, it finds its temporary home in the core of a tablet that was placed in a sealed package of 9999 other 10 mg escitalopram tablets for sale to an independent pharmacy distributor, a company preferentially procuring pharmaceuticals for certain partner pharmacy chains or businesses, operating in Canada.¹³

Finished product distribution

Approximately 1 week after their production, the 10,000-tablet package, having gone through transit from 1 province to another within Canada, arrives at the operation site of the purchasing distributor. This package is opened and the tablet contents are equally separated into 100 stock bottles, each containing 100 tablets and labeled to Health Canada standards, with the

stylistic details and information of this particular generic pharmaceutical firm.

The bottle with our drug molecule happens to be shipped in a routine daily order to a community pharmacy within the city limits of where the distributor is located (although this company warehouse, one of many nationally, distributes regionally). The next day, 2 stock bottles of 100 tablets of escitalopram oxalate 10 mg arrive at the community pharmacy, both labeled with the same lot number from the generic "manufacturer."

Pharmacy dispensing

From this point, all pharmacists know the next part of the story. Two weeks later, a refill request from a regular patient (a 31-year-old man we will call Saraj) results in 30 tablets of the second stock bottle (the first one was already used) being counted out by a pharmacy technician and placed into a 7-dram clear vial, labeled with the prescription information. During a routine follow-up conversation immediately after dispensing (to encourage adherence and address any new medication-related concerns), Saraj makes the off-handed mention that a cousin of his "works for a drug company back home in India that makes these drugs."

Patient ingestion

Twenty-one days later, on a Friday, as Saraj suddenly remembers mid-afternoon to take his 15th tablet (he is not perfectly adherent), our drug molecule is finally introduced into a patient's body. Given the average pharmacokinetics of escitalopram, our molecule has an approximate 80% chance of being absorbed into the systemic circulation.¹⁴ This particular escitalopram molecule is among the ~8% of the dose that did not undergo hepatic biotransformation by cytochrome P450 microsomal enzymes.¹⁴ Saraj just so happens to be visiting his in-laws at their cabin, overlooking a lake, when he has the urge to use the washroom. The molecule is renally excreted unchanged 2 days after its ingestion.

Environmental epilogue

Within a matter of hours, our molecule finds itself adrift in the natural lake system. In its cationic form, stable to hydrolysis, it nevertheless eventually permeates into the neural tissue of a northern pike.¹⁵ Our India-born escitalopram finds its place in the company of its peers—sertraline from China and fluoxetine from south of the Canadian border.^{16,17}

Conclusion

This case study is meant to make pharmacists reflect on the multitude of complex distributive forces ("cogs" in the globalist, pharmaceutical machine) that bring various medicines to our patients, as well as the consequences of different consumer behaviours involving pharmaceuticals (postdispensing) on health and the environment. This is especially important to properly frame issues of medication access in the current

era of drug shortages, although the lack of API availability is only one among a multitude of reasons for shortages. Cameo appearances in this narrative from the pharmaceutical sciences, medicinal chemistry, pharmaceuticals and pharmacokinetics serve as a reminder to community pharmacists of the “behind-the-scenes” expertise that forms some of the scientific

foundation of our modern pharmaceutical care practices. Lastly, while it may be impractical to imagine drugs at the molecular scale when thinking of pharmaceutical distribution, this mental exercise nevertheless enables an appreciation for both basic science and the interconnectedness between the micro (i.e., molecular) scale and the macro (i.e., global) scale. ■

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