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Pipeline

Thoughts on improving medication use

There is growing concern about the cost to the patient for medications. While the concern is global, it is an especially important issue in the United States (U.S.) due to the complexities of the system for payment of health care. Patients and physicians explore many options to attempt to reduce their drug costs, including using reformulated or generic drugs, outdated drugs, and drugs imported from Canada. While I have written about many of these topics over the years in this journal and elsewhere, I thought it might be useful to address these issues in one, current article.

1. Price as paid by the patient

First, the factors determining what a patient pays for their medication in the U.S. are not transparent. Intuitively, it would seem that the price the patient pays should be related to the price charged by the pharmaceutical manufacturer to the distributor. However, this is not the case due to many competitive factors, and undisclosed rebates and discounts, and variability due to insurance company formularies and policies [1]. A flow chart of payments for a branded, pharmacy-dispensed drug for a patient with private insurance is shown in Fig. 1. In this theoretical example where there are multiple drugs available for the treatment of the disease, the nominal price of the medication to the wholesaler or distributor is US$100 (Wholesale Acquisition Cost [WAC]). The manufacturer negotiates with Health Plans and/or Pharmacy Benefit Managers (PBMs) to secure a preferred tier position on formularies relative to competing drugs in the same class. This negotiation involves a competitive rebate to the specific payers based on the competitiveness of the market. These rebates commonly range from 10 to 50% of the drug price [2]. This position on the formulary then determines the patient's co-pay. Pharmacy-advertised discounts for patients do not apply to patients with medication insurance [3]. Manufacturers' coupons for patients do *not* apply to patients whose prescriptions are paid for by Medicare [4].

In the example shown, for a drug with a nominal WAC of $100, the net revenue to the manufacturer is $67.50, and the net cost to the patient is $40 (not counting the insurance premium). For patients without medication insurance, pharmacies set the price of medications, and these prices can vary widely [5]. Important in any calculations of the cost of medications is that WAC is NOT a good estimate of what patients pay – most (those with insurance) pay much less. Most Americans have insurance coverage for medication. A 2015 survey conducted by Consumer Reports found that one-third of Americans regularly take at least one prescription drug, and that 96% of these users of pharmaceuticals are covered by prescription insurance [5]. The proportion of payment for outpatient prescription drug expenditures paid for by patients (in contrast to public funds or insurance) decreased from 26% in 2003 to 17% in 2013, and it is estimated that it will decrease to 12% by 2023 [6]. The rebates and discounts are not always disclosed to the insured patient.

2. Generics

Another way to attempt to lower the costs of medication to the patient is to use generic drugs. At the time of writing this column (November 2017), there are generic therapeutic options for most topical ocular hypotensive medications. However, that is *not* true for prescription pharmacotherapy for dry eye disease in the U.S. at present, as the two approved agents are both still on patent, and no other agents in the same classes are available.

For therapeutic classes where generics *are* available, the patient and physician rightly ask: Are generic alternatives to the branded product truly equivalent? [7]. First, a clarification. By definition, a generic product (505[j] in the parlance of the U.S. Food and Drug Administration [FDA]), is an *exact* copy product of the innovator – the active, the nature of the formulation (e.g., solution), and the excipients (also known as *inactives*). If an excipient differs either *qualitatively or quantitatively* from the reference listed drug, some information is required to demonstrate that this difference does not affect the proposed generic product. The analytical limit is within 5%. By definition, in a solution, all of the ingredients are dissolved. If chemistry, manufacturing and compliance (CMC) is followed in a Good Manufacturing Practice (GMP)-compliant manner, then the generic product is the same as the innovator product [5].

The U.S. requirements for generic ophthalmic drugs derive from a 1984 law ("Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Hatch-Waxman Amendments), some of the provisions of which came into effect in 1992. These were reviewed by Cantor several years ago [2]. Wiley A. Chambers, MD, Deputy Director of the Division of Transplant and Ophthalmic Products at the FDA Center for Drug Evaluation and Research wrote an editorial clarifying those requirements [3]. Note that the bottle for the generic may be different than the innovator.

If the product is not a solution (e.g., a suspension or an emulsion), then even with exactly the same active and excipients, the product may be pharmaceutically different. Thus, the current practice of the FDA is to require comparative clinical trials for the non-solution products. For topical corticosteroids, the Office of Generic Drugs (OGD) issued draft guidances proposing similarity of the aqueous bioavailability between the generic and innovator product.[1] For Restasis® (cyclosporine ophthalmic emulsion), OGD has

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281453.pdf.

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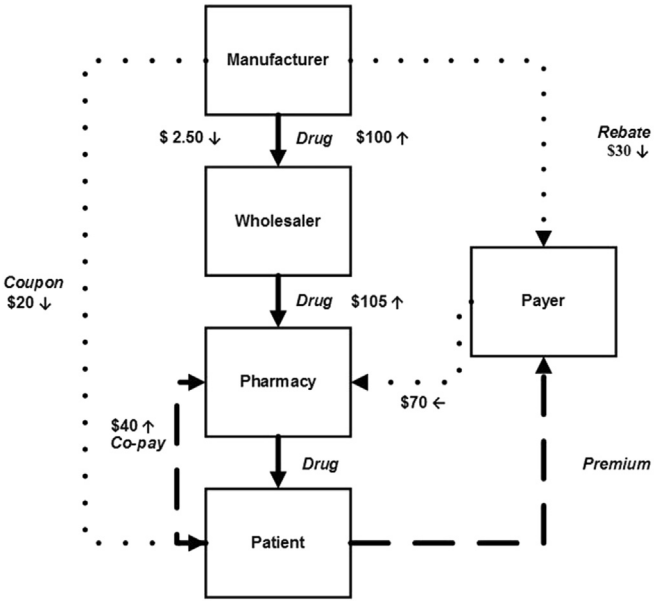

Fig. 1. Flow chart for payments in theoretical example of prescription in the United States. Shown are payments for a prescription, branded pharmaceutical with a nominal Wholesale Acquisition Price of US$100. The pharmaceutical is produced by a manufacturer, sold to a wholesaler, who in turns sells to a pharmacy, who in turn dispenses to a patient with medical insurance. Bolded lines indicate the primary direction of product and payment. Dollar values and arrows indicate the amount and direction of payments. The insurance premium paid by the patient to the payer (insurance companies and pharmacy benefit managers) is highly variable depending upon the nature of coverage, whether the patient is also covered by Medicare, and cannot be assigned to one prescription. See Congressional Budget Office report for additional information. [Anonymous. Prescription drug pricing in the private sector. Available at https://www.cbo.gov/publication/18275. Accessed February 9, 2016.].

proposed either a clinical efficacy study or a pharmaceutical (*in vitro*) study. However, the Office of New Drugs (OND) proposes that only a clinical efficacy study will suffice for comparability. To date, there have been no publicly available products which test this difference in policy between Offices of the FDA.

3. Re-formulation products (505(b)(2))

There is a development pathway for a product in between a copy product (generic) and a new chemical entity (NCE). This is the 505(b)(2) New Drug Application (NDA), legislated as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Waxman-Hatch) [8]. As the drug substance in not an NCE, there is typically a lower risk. This is a popular route, as 505(b)(2) NDAs represented 63% (284/451) approved original NDAs in the period 2009–2015.[2] Conceptually, a 505(b)(2) application is one where the applicant refers to some piece of information that the applicant does not have the right to reference.

Typically, products submitted under a 505(b)(2) application have a different formulation, which may lead to a different dosing regimen, but similar indication. For example, Timoptic-XE® is a reformulation of Timoptic® solution (timolol maleate), both for the treatment of glaucoma. However, this approach may be used for a different indication and a different route of administration. For example, Retisert® (fluocinolone acetonide intravitreal implant) changed both the route (intravitreal) and the indication (posterior uveitis) from the referenced drug, Synalar® (fluocinolone acetonide cream, ointment and solution), a dermal product for the treatment of dermal inflammatory conditions. The 505(b)(2) pathway is also the regulatory approach used by the many reformulations of cyclosporine or prostaglandin drug delivery systems currently in clinical research.

Assuming that the systemic exposure to the molecule with the new product is not greater than the innovator product, then there is a "savings" in development cost and timing with respect to the systemic toxicology assessment of the molecule. As well, there is a savings on manufacturing the drug substance (i.e., the active pharmaceutical ingredient), as technical issues were worked out by the innovator. However, nonclinical safety and clinical efficacy and safety data are required for the new ophthalmic product. Sometimes, there is a great savings for this over an NCE. However, sometimes, the development of a new delivery system is non-trivial, and the savings over an NCE is not so apparent. For example, drug delivery systems for now off-patent prostaglandin systems have been in development for at least ten years. Also, a recent analysis by the Tufts Center for the Study of Drug Development found the review times for 505(b)(2) NDA's is longer than for traditional 505(b)(1) NDA's.[2]

4. Expiration date

For various reasons, patients may possess medications that are past their expiration date. It seems wasteful *not* to use these medications – but are they as safe and effective for the patient to use as those medications within their shelf life? [9]. For example, Cantrell et al. chemically evaluated a number of long-expired *oral* medications and found that many medications still had at least the labelled amount of drug. Some even had 20–25% more, and one had 300% more. A few had much less than the labelled amount [1]. However, ophthalmic products are a bit more challenging. I covered details of ophthalmic manufacturing in a previous article in this journal [10]. Ophthalmic drug products are typically liquids and sterile. The assignment of an expiration date is based not only upon the potency of the active pharmaceutical ingredient, but also that of the preservative, and its antimicrobial efficacy, as well as pH and volume. Ophthalmic products may undergo degradation due to light, and there may also be concentration of the drug due to evaporation through the container. Shelf-life is set for a time at which the drug product is still within about 5–10% of the specifications at time of manufacture and initial release.

Some have a perception that manufacturers would prefer to have a short expiration date, so that patients have to buy more product. This is not the case. The shorter the shelf life, the more challenging the logistics for the manufacturer to produce the product, ship it to wholesalers, who, in turn, ship it to pharmacies, who maintain stock until they receive and fill prescriptions for the product. As manufacturers must compensate wholesalers for the expired product, there is actually a financial incentive to manufacturers to assign a longer shelf life, rather than a shorter shelf life.

5. Canadian imports

There are many issues and perceptions about importing products from Canada. The FDA created the "Personal Importation Policy" (PIP) in 1954, and updated it in 1988.[3] In this guidance, they state that although importing unapproved prescription drugs is illegal, the FDA's guidance on importing prescription drugs for personal use recognizes that there may be circumstances in which the FDA can exercise discretion to not take action against the illegal

[2] http://csdd.tufts.edu/news/complete_story/pr_ir_mar_apr_2017.

[3] https://www.fda.gov/forindustry/importprogram/ucm173751.htm.