Generic Medications: What we need to know
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Regulation of Generic Drugs
Office of Generic Drugs

OGD Mission
To ensure that safe and effective generic drugs are available to the American People.

Legislative History
- 1906 Pure Food and Drug Act - establishes regulation of Food and Drugs.
- 1962 Kefauver-Harris Amendments to the FDA&C Act - tightened safety standards and introduced requirement that drugs must be effective.
- 1984 Waxman-Hatch Act - created an abbreviated mechanism for approval of generic copies of all drugs approved after 1962, by stating that preclinical and clinical tests did not have to be repeated for generics.

Hatch-Waxman Amendments to FFD&C Act - 1984
• Considered one of the most successful pieces of legislation ever passed
• Created the generic drug industry
• Increased availability of generics
  • 1984 12% prescriptions were generic
  • 2000 44% prescriptions were generic - yet only 8% of revenue for prescription drug
  • 2009 71% prescriptions were generic
  • 2010 78% prescriptions were generic
  • 2017 99% prescriptions were generic
• Compromise legislation to benefit both brand and generic firms

Hatch-Waxman Amendments to FFD&C Act - 1984
• Allowed generic firms to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities (do not have to repeat expensive clinical and preclinical trials)
• Allowed patent extensions and exclusivities to innovator firms
Innovator Incentives (Patents)

• Prior to 1984, a patent would run for 17 years from issue date or 20 years from filing
• W/H set to restore some incentive for innovation because pre-market approval requirements have increased
• W/H may restore up to 5 years not to exceed 14 years from the product’s approval date

Innovator Incentives (cont.)

• URAA* (June 8, 1995) made all patents in force or filed as of this date have the longer term of 17 years from issuance or 20 years from filing
• All patents filed after June 8, 1995 have an expiration date of 20 years from filing
  *Uruguay Round Agreements Act

Exclusivity Incentives

• NCE protection - 5 years
• New salt or ester - 3 years
• New use or dosage form - 3 years
• Orphan drug status – 7 years

Generic Incentives

• All approved products eligible for generic competition
• Eliminated requirement for duplicative clinical trials
• Created a regulatory process for faster approval of generic drugs

Generic Drug User Fee Amendments (GDUFA)

• GDUFA aims to put FDA’s generic drug program on a firm financial footing and ensure timely access to safe, high-quality, affordable generic drugs. GDUFA enables FDA to assess user fees to fund critical and measurable enhancements to the performance of FDA’s generic drugs program, bringing greater predictability and timeliness to the review of generic drug applications.
• How is the FDA Office of Generic Drugs doing?
In 2017, FDA marked the final year of the first iteration of user fees for generic drugs—the Generic Drug User Fee Amendments of 2012 (GDUFA I) expired in 2017 and required Congress to pass reauthorization legislation.

Summer of 2017 the Generic Drug User Fee Amendments of 2017 (GDUFA II) were signed into law for the next 5 years. Under GDUFA II the FDA committed to performance goals, and industry agreed to pay user fees each year it is involved in the program.

Definition of a Generic Drug

A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.

Therapeutic Equivalence of Generic Drugs: Requirements

- Pharmacologically equivalent
  - Contains same amount of active drug
  - Meets USP standard for purity, strength, quality
- Bioequivalent (mean AUC values are typically within 3-4% of each other)
- Adequate labeling
- Manufactured in compliance with GMP

Bioequivalence of Drugs: FDA Accepted Parameters

- Single dose of reference drug and test drug given to 24 to 36 healthy adults in a crossover design.
- Bioequivalence accepted when the 90% confidence interval of the ratios
  - AUC
  - C_{max}
  - T_{max}
- Fall between 0.8 and 1.25 (log-transformed data)
- The generic manufacturer’s main challenge has been to make a generic that was absorbed as poorly as the brand (IE phenytoin delayed – Dilantin)
What are the Generic Drug Requirements?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Compared to reference listed drug (RLD) - (brand name product)

When can a Generic Drug be Marketed?

- After patent & exclusivity protection ends, or
- Patent owner waives its rights, or
- Patent challenge is won, and
- FDA requirements are met

“Orange Book”

- All FDA approved drug products listed (NDA’s, OTC’s & ANDA’s)
- Therapeutic equivalence codes
  - "A" = Substitutable
  - "B" = Inequivalent, NOT substitutable
- Expiration dates: patent and exclusivity
- Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare their proposed products with
**FDA Ratings**

- “A” rated drugs are considered bioequivalent to the brand name original.
  - They either have been demonstrated to be so by human bioavailability study (“AB”) or considered inherently unlikely to have bioavailability problems (“AA”)
  - Other “A” designations (AN, AO, AP, AT) refer to non-oral formulations considered bioequivalent by the FDA
  - Only “A” rated products are interchangeable with their brand name equivalents by the FDA

**Levothyroxine Ratings**

- UNITHROID (STEVENS J) – 0.025MG AB1
- LEVOXYL (KING PHARMS) – 0.025MG AB1
- SYNTHROID (ABBOTT) – 0.025MG AB1

**Levothyroxine Ratings**

- SYNTHERID (ABBOTT) – 0.025MG AB2
- LEVOTHYROXINE SODIUM (MYLAN) – 0.025MG AB2
- LEVOT (ALARA PHARM) – 0.025MG AB2
- UNITHROID (STEVENS J) – 0.025MG AB2
- LEVOTHYROXINE SODIUM (GENPHARM) – 0.025MG AB2

**Levothyroxine Ratings**

- LEVOXYL (KING PHARMS) – 0.025MG AB3
- LEVO-T (ALARA PHARM) – 0.025MG AB3
- UNITHROID (STEVENS J) – 0.025MG AB3
- LEVOTHYROXINE SODIUM (MYLAN) – 0.025MG AB3
- LEVOTHYROXINE SODIUM (GENPHARM) – 0.025MG AB3

**Levothyroxine Ratings**

- LEVOTHROID (LLOYD) – 0.025MG AB4
- LEVOTHYROXINE SODIUM (MYLAN) – 0.025MG AB4

Therapeutic equivalence has been established between products that have the same AB+number TE code.

**FDA Ratings**

- “B” rated drugs have not been demonstrated to be bioequivalent by an in-vivo test.
  - These drugs are generally older drugs that were approved by the FDA on the basis of chemistry, manufacturing controls and in-vitro dissolution tests.
  - Less than 3% of marketed generic drugs have a “B” rating
FDA Ratings

No well documented therapeutic differences between brand name originals and FDA-approved generics have been reported.

FDA Estimate of Savings

Generic Competition and Drug Prices

<table>
<thead>
<tr>
<th>Number of Generic Manufacturers</th>
<th>Average Relative Price (% Generic: Brand)</th>
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<tbody>
<tr>
<td>1</td>
<td>100%</td>
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<tr>
<td>2</td>
<td>75%</td>
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<td>50%</td>
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<td>9</td>
<td>10%</td>
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<tr>
<td>10</td>
<td>8%</td>
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Economic Outlook Survey of US Healthcare Leaders

- Premier, Inc.'s spring Economic Outlook Survey polled 91 people representing a variety of roles in U.S. health systems, including physicians, C-suite members and supply chain management professionals.
- Almost every respondent agreed that increasing pharmaceutical prices pose a significant challenge to their operations. In addition, more than 90% said they would likely experience continued drug shortages over the next three years.
- Drug prices and shortages have consistently ranked among the biggest issues facing health systems over the past two years of surveys, according to an announcement from Premier. Part of the problem is a lack of generic drug options, so a solution to this is increased competition, the organization concluded.
- “In our view, one of the best ways to ensure fair pricing is by driving increased competition and greater use of generics and biosimilars,” Michael J. Alline, Premier’s chief operating officer, said in the announcement.
- “At the same time, we also need to provide prescribers with apples-to-apples mechanisms they can use to compare products in a therapeutic category, evidence-based facts around which products deliver optimal quality at the best value and aligned financial incentives.”
  — FierceHealthcare 4/25/2017
Kaiser Health Tracking Poll March 8-13, 2018

- This Kaiser Health Tracking Poll was designed and analyzed by public opinion researchers at the Kaiser Family Foundation (KFF). The survey was conducted March 8-13 2018, among a nationally representative random digit dial telephone sample of 1,212 adults ages 18 and older, living in the United States, including Alaska and Hawaii (note: persons without a telephone could not be included in the random selection process). Computer-assisted telephone interviews conducted by landline (421) and cell phone (791, including 483 who had no landline telephone) were carried out in English and Spanish by SSRS of Glen Mills, PA.
Counterfeit Meds and Internet Pharmacies

In 2016 there are an estimated 30-35,000 illicit internet pharmacies. Of these, 96% globally as well as in the US, fail to adhere to legal requirements, and 92% of them are operating in a blatantly illicit manner including the sale of prescription drugs without a prescription. 9% are selling controlled substances without a prescription with a focus on anabolic steroids to athletes.

The U.S. is far and away the primary focus of the illegal online prescription drug industry, with 82% on internet pharmacies in English and roughly 85% offering to ship drugs to the U.S.

There has been a shift from the illicit sale of controlled substances online to the sale of “psychoactive highs” such as synthetic cannabinoids, which have been linked to significant user harm.

The Internet Pharmacy Market in 2016: Prepared by LegitScript.com for The Center for Safe Internet Pharmacies

Counterfeit Meds and Internet Pharmacies

A Google and Bing search of 20 common medications identified about 33% of the 29,000 “hits” led to illicit internet pharmacies including “web-spam” and “hacked” web-sites, that is otherwise legitimate web-sites such as an.edu domain registered to a University that lined to an illicit internet pharmacy.

29 test buys from the illicit internet pharmacies were made, the majority came from India (none of the pharmacies was licensed even in India), other countries included Germany, Singapore, US, Canada and the UK

– Private carries including UPS, DHL and FedEx were not used for any of the shipments but 100% used the US Postal Service for US delivery.

– None of the shipments was seized by US Customs

* The Internet Pharmacy Market in 2016: Prepared by LegitScript.com for The Center for Safe Internet Pharmacies

Reynolds Drug Store, Andrews, SC

Some illicit internet pharmacies have hijacked web-sites previously operated by legitimate pharmacies, such as Reynolds Drug. Years ago EVApharmacy hijacked the pharmacies domain name: while reynoldsdrug.com retains the pharmacy’s address and branding, orders placed on the web-site are filled by EVApharmacy with drugs being shipped from Pakistan and China. When you click on buy now it takes you to a site called Canadian Online Pharmacy.

The site advertises Viagra 25mg - $1.85; 50 mg - $2.17; 75 mg - $1.89; 100 mg - $2.55; 120 mg - $4.88; 130 mg - $4.89; 150 mg - $5.45; 200 mg - $7.50

Brand Viagra only comes as 25, 50 and 100 mg tabs and costs $50.00 per tablet

* The Internet Pharmacy Market in 2016: Prepared by LegitScript.com for The Center for Safe Internet Pharmacies
This counterfeit drug manufacturing site in China produced fake Viagra and other drugs that were sold to customers in the European Union and the U.S.

Prescriptions Purchased on the Internet

• A credit card (MasterCard) was obtained and medicines were ordered to a central location in the UK. Over 36 prescription-only medicines were ordered, comprising two packets each of 18 medicines commonly purchased via the internet.

• These included medicines indicated to treat neurological disorders, cardiovascular disease, mental health, obesity and erectile dysfunction

— The Counterfeiting Superhighway, 2008 European Alliance for Access to Safe Medicines

Prescriptions Purchased on the Internet

• Results of the laboratory analysis indicated that an alarming 62% of the products received were counterfeit, substandard or unapproved generic medicines. This figure closely reflects the findings of the expert panel during their visual analysis of the medicines.

• While 38% of the medicines received were found to be genuine branded medicines, 16% of these were illegal non-EU imports (genuine products, imported into the EU illegally from a non-EU country).

— The Counterfeiting Superhighway, 2008 European Alliance for Access to Safe Medicines

Prescriptions Purchased on the Internet

Analysis of purity and active pharmaceutical ingredient concentration (using high-performance liquid chromatography) of 55 samples labelled ‘Viagra 100 mg’ ordered via the Internet (Data on File. New York, NY: Pfizer Inc.)

CAUTION Buyer Be Ware!

The Counterfeiting Superhighway landmark research by the European Alliance for Access to Safe Medicines in 2008 found that:

• 96% of online pharmacies researched were operating illegally

• 94% of websites did not have a named, verifiable pharmacist

• over 90% of websites did not require a prescription to sell prescription only medications

• More than eight in 10 internet pharmacies do not ‘physically exist’ – in order to comply with the law all online pharmacies must be traceable to a verifiable bricks and mortar address.

• Fewer than five in 100 internet pharmacies are licensed by a board of pharmacy or appropriate pharmacy listing.

• 86% of internet pharmacies link to a bogus ‘approval’ web page ‘stamp of approval’ from a recognized society or association
FDA Campaign: BeSafeRx – Know Your Online Pharmacy

- Patients should only buy prescription medicine through online pharmacies that:
  - require a valid prescription from a doctor or other health care professional;
  - are located in the United States and provides a physical address and telephone number;
  - have a licensed pharmacist available for consultation; and
  - are licensed by the patient’s state board of pharmacy.
- Are Verified Internet Pharmacy Practice Sites (VIPPS) by National Association of Boards of Pharmacy
  - http://www.nabp.net/programs/accreditation/vipps/find-a-vipps-online-pharmacy/  
  - http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321470.htm  

Verified Internet Pharmacy Practice Sites (VIPPS) by National Association of Boards of Pharmacy

- The VIPPS accreditation program (Verified Internet Pharmacy Practice Sites), is a strong indicator of an internet pharmacy’s compliance with state and federal laws and regulations and NABP’s criteria.
- To date, NABP has reviewed over 9,600 sites — only 3% of those online sites appear to be in compliance with pharmacy laws and practice standards.
- To date there are 69 VIPPS Accredited Internet Pharmacies. The complete list can be found at:
  - http://www.nabp.net/programs/accreditation/vipps/find-a-vipps-online-pharmacy/  

The Campaign for Sustainable Rx Pricing

- Prescription spending is growing faster than any other part of the health care dollar.
- In 2015 the prices of prescription drugs had the largest increases in 24 years. In fact, prescription drug prices rose more than 7% since last year, the largest one-year hike since 1992.
- May 2017, The Campaign for Sustainable Rx Pricing launched a national TV and digital advertising campaign, featuring a commercial for the mock drug “Price Gougi$ol,” that delivers a harsh rebuke of direct-to-consumer advertising of prescription drugs.
  - https://www.youtube.com/watch?v=175rbyp3C80

Direct To Consumer Advertising

- In 2008, the House Commerce Committee reported that every $1,000 spent on drug ads produces 24 new patients, and a 2003 research report found the prescriptions derived for drugs promoted with DTC ads were nearly seven times greater in number than those without such promotions.
- Prior to 1997, drug ads could only be run along with lengthy consumer information warning of risks and side effects, therefore, few companies used them. In 1997, the U.S. Food and Drug Administration (FDA) revised the rule so that rather than providing a full disclosure, companies only needed to meet an “adequate standard” when it came to describing risks to consumers.
- The US and New Zealand are the only two countries where direct to consumer advertising of prescription medications is allowed.

Direct To Consumer Advertising

- November 17, 2017 the American Medical Association (AMA) called to ban all DTC advertising for drugs and medical devices. Billions of dollars are being spent promoting prescription only products driving demand and expensive treatment at the expense of less costly alternatives. DTC demonstrates the anticompetitive behavior of the consolidated pharmaceutical marketplace.
- June 29, 2016 the American Society of Health Care Pharmacists ASHP) called to ban all DTC of prescription drugs and medication containing devices. DTC has been shown to influence consumers to pursue medication treatment without knowing all the risks, costs and side effects. DTC has increased drug spending more than drug spending on research and development.
Basaglar is taking Market Share from Lantus

<table>
<thead>
<tr>
<th>Medication</th>
<th>ATORVASTATIN</th>
<th>LOBARTAN</th>
<th>AIMOVIGE</th>
<th>METOPROLOL</th>
<th>METFORMIN</th>
<th>ROVASTATIN</th>
<th>SABAPATIN</th>
<th>OXTICOBAM</th>
<th>INACTIVATED INFLUENZA VIRUS</th>
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<tbody>
<tr>
<td>2017 6-Month</td>
<td>10.3</td>
<td>8.6</td>
<td>6.1</td>
<td>7.5</td>
<td>7.0</td>
<td>6.8</td>
<td>6.1</td>
<td>4.8</td>
<td>4.4</td>
</tr>
<tr>
<td>2017 6-Month Change (%)</td>
<td>-16.4</td>
<td>-8.8</td>
<td>-4.7</td>
<td>-4.6</td>
<td>-4.5</td>
<td>-2.8</td>
<td>-4.7</td>
<td>-2.4</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

Fastest and Slowest Growing Mail and Retail Molecules by Absolute Rx Change (12 month comparison)
Adjusted for 90-Day Rx

Top 10 Corporations by Unbranded Generic Non-Discounted Spend

Without generics, annual spending on cholesterol drugs would have reached $38.2Bn in 2016
Generic cholesterol medicines generated $28.2Bn in savings in 2016

GoodRx Top 10 Prescriptions Dispensed

1. Atorvastatin (Lipitor) | 15.7 | 13.6 | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.9 |
2. Levothyroxine (Synthroid) | 13.9 | 12.6 | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.9 |
3. Lisinopril (Zestril) | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 |
4. Hydrocodone/acetaminophen (Vicodin) | 15.5 | 13.6 | 14.9 | 13.5 | 15.9 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 |
5. Amlodipine (Norvasc) | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 |
6. Ibuprofen (Motrin) | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 |
7. Omeprazole (Prilosec) | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 |
8. Losartan (Cozaar) | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 | 14.9 |
9. Gabapentin (Neurontin) | 15.5 | 13.6 | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 |
10. Sertraline (Zoloft) | 15.5 | 13.6 | 14.9 | 13.5 | 15.9 | 15.5 | 13.6 | 14.9 | 15.5 | 13.6 |

Medication | 0.8-12.0 |
Brand Cost | 450.00-600.00 |
Generic Cost | 10-12.00 |

1. Amlodipine (Norvasc) | 10.0 mg #30 | $270.00 | $7-15.00 |
2. Buspirone (BuSpar) | 800 mg #90 | N/A | $8-12.00 |
3. Omeprazole (Prilosec) | 40 mg #30 | $340.00 | $10-13.00 |
4. Losartan (Cozaar) | 100 mg #30 | $165.00 | $4-11.00 |
5. Sertaline (Zoloft) | 100 mg #30 | $300.00 | $7-11.00 |
6. Gabapentin (Neurontin) | 300mg #180 | $1,000.00 | $16-24.00 |
Price Gouging

• When a drug shortage happens or one is anticipated, a “gray market” may spring up, with the potential for price gouging. The practice of price gouging by secondary wholesalers, which largely comprise the “gray market,” is unacceptable and presents serious concerns for patient safety, as it cannot be assured that the products have been handled in a way that maintains their integrity. The manufacturer of a drug has no influence or control over the prices charged by a secondary wholesaler to a hospital or pharmacy.

— Pharmaceutical Research and Manufacturers of America®

### Table 1. Case Studies of the Four Companies

<table>
<thead>
<tr>
<th>Company</th>
<th>Pharmaceutical</th>
<th>Specialty and</th>
<th>Closed Distribution</th>
<th>Price Gouging</th>
</tr>
</thead>
<tbody>
<tr>
<td>ValueHealth (2016)</td>
<td>50% market share</td>
<td>Mylan</td>
<td>Implemented closed distribution to prevent generic companies from obtaining generic necessary to develop generics.</td>
<td>Increased the price of Thalidomide from $15.70 to $170 per 100 mg.</td>
</tr>
<tr>
<td>Vivastor (2004)</td>
<td>20% market share</td>
<td>Teva</td>
<td>Increased the price of Mylanta from $1.50 to $50 per 100 tablets. The increase was of such magnitude that patients were no longer able to use the product.</td>
<td></td>
</tr>
<tr>
<td>Zolux (2004)</td>
<td>1% market share</td>
<td>interstate pharmacies</td>
<td>Increased the price of Zolux from $500 to $8,600 for 25 mg. At $50 per tablet—20 fold increase.</td>
<td></td>
</tr>
<tr>
<td>Zostar (2016)</td>
<td>5% market share</td>
<td>Sandoz Division of Novartis</td>
<td>Increased the price of Zostar from $3.40 to $8.78 per 100 tablets. Increase from $0.72 to $3.61.</td>
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### Non-Profit Hospitals Entering the Generic Drug Manufacturing Business

- Intermountain Healthcare system is teaming with the Mayo Clinic, HCA Healthcare, Catholic Health Initiatives, Providence St. Joseph Health, SSM Health and Trinity Health to form a non-profit company called Civica Rx to manufacture or contract with existing manufacturers for FDA approved generic medicines.
- The U.S. Department of Veterans Affairs, the company said, “will also work in consultation with Civica Rx to address its particular needs.”
- The effort is aimed at combating drug shortages and skyrocketing prices.
- The seven organizations represent about 500 U.S. hospitals.
- The initial focus will be a group of 14 generic drugs (primarily generic injectables) that are administered to patients in the hospital and have either been in short supply and/or had excessive price increases.
- Civica has named a chief executive: Martin Van Trieste, former chief quality officer for biotech giant Amgen.

### Generic Medications

1. Which of the following statements about the use of generic medications is NOT True?
   - A. In 2017 unbranded generic medications made up over 86% of the total prescriptions dispensed and accounted for only about 13% of the total costs.
   - B. The US Healthcare system has saved about $1.67 trillion over the last 10 years through the use of low cost generic medications.
   - C. 4 of the 5 largest generic drug manufacturers by market share are Teva, Mylan, Sandoz Division of Novartis, and Greenstone Division of Pfizer.
   - D. None of the above (All are true)
Generic Medications

2. Which of the following is NOT an FDA requirement for approval of a generic version of a branded medication?

- A. FDA does not have to comply with the delays in review and approval that the patents and exclusivities impose prior to approving a generic medication.
- B. The medication must contain the same active ingredients in the same dosage form and dose.
- C. The generic medication must have similar blood level concentrations (bioavailability) as the brand medication.
- D. The generic medication must be manufactured according the current FDA good manufacturing practices (GMP’s)