

Do You Have Access to High Quality Generic Drugs?

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Access to High Quality Generic Drugs?

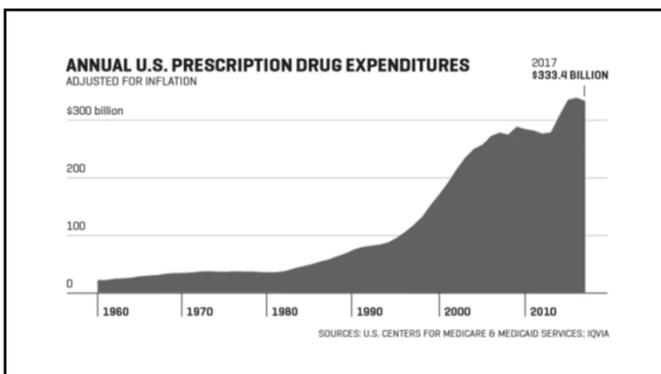
- TODAY – Background Discussion
 - Are generics identical to brand name products?
 - Does the FDA assure quality? What are the major issues?
- NEXT WEEK: Practical strategies for using generic drugs safely and effectively



Americans spend on average **\$1,000 - \$1,200** per capita annually on prescription drugs, according to OECD*. That's more than people pay in any other developed country.

This totaled about **\$333 billion** in 2017, according to the Centers for Medicare and Medicaid Services (CMS). This includes only retail drug spending, excluding hospital and other non-retail.

*Organization for Economic Cooperation and Development



Over the next decade, CMS predicts that growth in spending for retail prescription drugs will consistently outpace that of other health spending.

As a result, policymakers, providers, pharmacy benefit managers, and insurers are considering options to slow increases in prescription drug spending.

Increasing use of generic drugs is a leading approach.

- Generics account for 90% of prescriptions but only 23% of prescription expenditures.
- 80% of “active pharmaceutical ingredients” (API) & 40% of finished drugs come from India or China
 - This will probably increase in the near future
- There are serious issues with generic drug quality, especially from overseas

Claims About Generics

- **PHARMA:** brand name drugs are safer and more effective than generics
- **FDA:** we ensure the safety and effectiveness of generic drugs
- **Insurance Companies:** generics are identical to brand name drugs and are safe and effective. You “must” accept them

Questioning the Claims

- Are generics actually identical to brand name products?
- Does the FDA assure quality? What are the major issues?

A Case Study: Valsartan Recall

- July, 2018: **recall** of certain drug products containing **valsartan**, used to treat hypertension and heart failure. This recall was due to contaminants (NDEA and NDMA). These are probable **human carcinogens**. Their presence is thought to be related to changes in the way the valsartan was manufactured.

A Tangled Web

- Chinese drug manufacturer **Zhejiang Huahai Pharmaceuticals (ZHP)** is the main company that made the withdrawn valsartan. Here are some labeled manufacturers and secondary labels
- **Teva Pharmaceuticals** labeled as Major Pharmaceuticals, Actavis, A-S Medication Solutions LLC, AvKARE, Bryant Ranch Prepack Inc. Northwind Pharmaceuticals
- **Prinston Pharmaceutical Inc.** labeled as Solco Healthcare LLC. RemedyRepack Inc., H J Harkins Company Inc. dba Pharma Pac, NuCare Pharmaceuticals Inc.
- **Hetero Labs**, Inc. labeled as Camber Pharmaceuticals, Inc, RemedyRepack, Inc., AvKARE, Preferred Pharmaceuticals, Inc
- **Torrent Pharmaceuticals Limited** RemedyRepack, Inc.

RECALLS AND DRUG SHORTAGES

- Due to this recall, there is little replacement product containing valsartan available at this time and we anticipate **disruptions in supply** for some time. FDA recommends that patients not stop their medicine until they receive replacement product or an alternate medicine to treat their condition.(CVS/Caremark)

Brand Name Diovan and Entresto (Novartis)

- The recall does not affect any Novartis valsartan product but does include one lot of Sandoz valsartan in the United States. Evidently, Novartis valsartan is manufactured in Germany, Switzerland, and Ireland, not China
- Typical retail price for Diovan is around **\$260**, for generic valsartan is around **\$12.46**

Questioning the Claims

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Are Generics Really Identical to Brand Name?

- What is a **brand name** drug product?
- What is a **generic** drug product?
- What is the **quality** of a drug product?
- Is process an important aspect of quality?
 - What is the importance of process patents in addition to product and formulation patents?

Brand Name Drug Product

Usually means a drug marketed under the original **New Drug Application (NDA)**. It is more accurate to call these **original** or **originator** products or a **reference listed drug (RLD)**.

The procedure for approving an NDA requires evidence of safety and efficacy from rigorous clinical trials, submission of samples, manufacturing processes, and often specific plant inspections. It takes 10 to 15 years to develop a new medicine

Brand Name Drug Product (2)

- By the way, developing a new drug product is risky and expensive.. Only 20% of approved medicines generate revenues that exceed average R&D investment. In 2013, Merck reportedly spent \$7.5 billion on R&D, representing 17% of net sales.

M Rosenblatt in HBR

What is a Generic Drug Product?

- A generic drug is a medication **created to be** the same as an existing, approved, brand-name drug in dosage form, strength, route of administration, and performance characteristics.
- A generic is **seldom identical** to the brand-name product because the original manufacturer may hold a complex of product and process **patent** rights

What Is A Generic Drug Product?

A generic drug product is legal in the US if it has an **Abbreviated New Drug Application** (ANDA) approved by the US Food and Drug Administration

Example of Multiple Patents

- AbbVie says the U.S. Patent and Trademark Office has granted it more than **30 patents** on the ways in which Humira is administered; more than **25 patents** on various formulations of the drug; more than **50 patents** related to manufacturing processes; and about **20 patents** on devices that customers use to take the medicine.

Authorized Generic

“Authorized generic” usually means an approved brand name drug labelled without the brand name. Except for that, it is the exact same drug product as the branded product. An authorized generic may be marketed by the brand name drug company, or another company with the brand company’s permission.

<https://www.fda.gov/media/77725/download>

Branded Generic

- **Branded Generic** is a marketing ploy with a bit of hype. At best the brand name is meant to be easier to remember. At worst, it is a copy pretending to be original.

QUALITY OF PRESCRIPTION DRUGS

Quality of a drug product means the totality of

- (1) safety and effectiveness (the ability of the drug product to satisfy fitness-for-use)
- (2) the **consistency and reliability** of (#1) across individual instances and time.

QUALITY OF PRESCRIPTION DRUGS (2)

- Product quality cannot be assured by testing alone. It must **also** be supported by evidence of acceptable raw materials, production, documentation and assessment procedures (called GMP) in order to claim that product not tested is equivalent to product tested. **GMP complicated & \$\$\$**

QUALITY OF PRESCRIPTION DRUGS (3)

- Therefore one sample submitted with an ANDA does not prove equivalent quality. GMP enforced by frequent plant inspections are necessary.

Bioequivalence

Bioequivalence of two drug products means that the active ingredient is absorbed by the body at about the same **rate** and to the same **amount**

21 see C.F.R. § 320.1(e) (1996)
<https://openjurist.org/107/f3d/868/united-states-of-america-v-robert-shulman>

Orange Book

Lists drug products approved on the basis of safety and effectiveness by the FDA. The main criterion for inclusion of any product is that the product has a current, approved application (ANDA)

Also, the Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products.

- https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface#_ftn8

Modern Examples of Unsafe or Ineffective Drug Products

Drug recalls are common. Most are minor, in the sense that they involve relatively few people. They are usually “voluntary” at the request of the FDA, but note that the FDA is authorized to seize drugs shipped in interstate commerce.

Classification of Drug Recalls

- **Class I** if there is a reasonable probability that the use of the product will cause serious adverse health consequences or death.
- **Class II** if use of or exposure to a product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- **Class III** if use of or exposure to a violative product is not likely to cause adverse health consequences.

Examples of Fraud: Bribery

- 1989 *bribery* of FDA officials to get favored treatment (Charles Chang) A total of 42 people, including officials and executives; and ten companies, plead guilty to, or were convicted of, fraud or corruption charges.

Examples of Fraud: Switching Samples

This is the fraud of submitting brand name product in place of one's own generic for analysis in support of ANDA

- 1989 Vitarine Pharmaceuticals submitted brand-name Dyazide in support of its ANDA for its generic
- Bolar did the same for dyazide, thioridazine, (Mellaril), & nitrofurantoin.

Examples of Fraud: Fake/Forged Documents

- "Coversheet" scheme: Bolar kept changing manufacturing ingredients and process without notifying FDA
- Ranbaxy forged, destroyed, and altered documents; and interfered with FDA inspections from 2004-2013

Examples of Fraud: Intentional Contamination

81 deaths in 2007 from intentionally contaminated heparin from top-tier company Baxter. API supplier in China had not been inspected by Baxter or FDA. China refused to disclose original source of contaminated heparin.

Import Alert

August 11, 2016: FDA placed Laxachem Organics Pvt. Ltd., India, on import alert for refusing to allow FDA to inspect its facility.

- This alert stops all Laxachem pharmaceutical products from entering the U.S. legally.
- Laxachem will remain on import alert until it has been fully inspected by FDA and found to meet U.S. standards.

Nationwide Recall

PharmaTech's 2017 recall of all liquid products due to possible bacterial contamination.

- Water at the plant was contaminated for years
- These products were manufactured in Davie, Florida, and distributed and labeled by six firms – Rugby, Major, Bayshore, Metron, Centurion, and Virtus.

Tiered Quality

- SOME pharmaceutical manufacturer dump substandard products to countries with weaker or nonexistent quality enforcement
- Imports from Canada seem OK BUT
- It is essential that policies allowing private drug imports require disclosure of supply chain
- AND that importers account for that

The FDA's Competing Interests

FDA regulates about one-fifth of the U.S. economy, most of the products Americans consume.

- Pharmaceutical manufacturers, investors, and insurance companies apply pressure to **speed** drug approvals or to **keep** product on the market.
- Consumer and patient safety advocates demand better protection from danger, and cheaper drugs

FDA's Competing Interests (2)

- Medicare spent **\$129 billion** on prescription drugs in 2016 (about 20% of Medicare spending)
- In fiscal year 2012, DOD and VA spent a combined **\$11.8 billion** to purchase drugs on behalf of about 18.5 million beneficiaries (GAO 2013) Availability of generics lowers this expense substantially.

FDA's Competing Interests (3)

- Drug recalls, manufacturer debarments, etc. sometimes result in **shortages** of essential drugs.
- Adverse actions against foreign manufacturers may have serious repercussion in international affairs

Spotty Regulatory Compliance

FDA inspectors often flag the same violations again and again.

Over the past decade 70 drug plants — most of them domestic — were penalized for the same violation at least four times. And more than a third of those plants has issued a recall at some point. Lupkin, Sydney. *Tainted Drugs: When Medicine Makes Patients Sicker*

SUMMARY – A Balanced View

- Benefit of well-made generic drugs indisputable.
 - Essential to our health care system, & quality is critical to us all.
 - Save \$millions in expenditures compared to brand-name drugs.
 - Most seem to be well-made.
- Yet their quality is not guaranteed. Things can go wrong. We must **take care** with generics

Conclusion(1) Bad Advice from President Reagan



"Government is not the solution to our problem!
Government is the problem."

— Ronald Reagan —

January 20, 1981: From Reagan's Inaugural Address

Conclusion (2)

- The facts show that there are still many pharmaceutical manufacturers here and abroad who will put their own interests (\$) ahead of public safety and the needs of sick people.
- Some will commit any kind of fraud to get or to keep their drugs on the market
- This may be due to greed or incompetence, but the result is the same -- unsafe and ineffective drugs

Conclusion (3)

- 80% of API & 40% of finished drugs come from India or China
- This proportion may increase as originator and generic manufacturers respond to governmental and market pressure to lower prices
- The FDA is unable to maintain proper (complete) and regular inspections even of US plants

Conclusion (4)

- The FDA is our only defense against unsafe and ineffective drugs.
- Some people want to weaken the FDA to prevent it from doing its job
- It is in our interest to support the FDA's role in protecting us.

Better advice from Reagan:

"Trust but verify"

comment after the signing of the INF Treaty with Mikhail Gorbachev in December 1987

Major References

Eban, Katherine. *Bottle of Lies*
Harper-Collins 2019 Kindle edition.

Lupkin, Sydney. *Tainted Drugs:*

When Medicine Makes Patients Sicker January 07, 2019 <https://www.medscape.com/viewarticle/907263>

Open FDA <https://open.fda.gov/tools/downloads/>

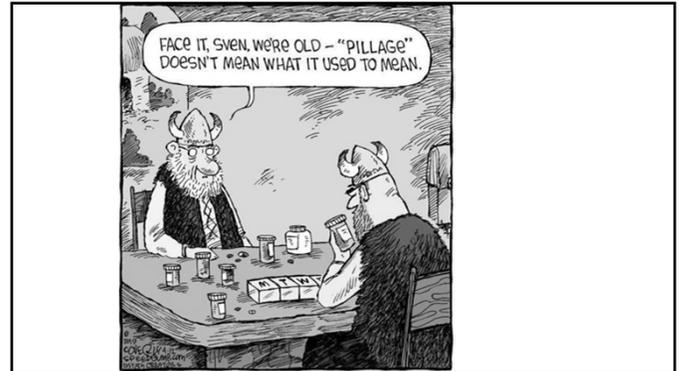


FURTHER
COMMENTS/QUESTIONS?

Part II Next Week : Practical Advice for
Using Generic Drugs

Do You Have Access to High Quality Generic Drugs? PART II

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Practical strategies for using generic drugs safely and effectively

1. Be Vigilant
 - Appearance
 - Response
2. Consult Pharmacist
Consult prescriber before stopping any prescribed medication
3. Avoid switching manufacturer for certain medications and delivery systems (inhalers)
4. Learn the generic name of your medicines
5. Be aware – use – the “Orange Book”
6. Evaluate the manufacturer

Practical Advice (1)

Be vigilant, skeptical, and proactive . . .

- a. regarding the appearance, odor, etc of generics
- b. regarding your responses if you have changed the source (manufacturer), especially if you can monitor drug effects (BP, blood sugar)

Practical Advice (2)

If you have concerns about a drug product --

- A. Speak to your pharmacist. Pharmacist is obliged to evaluate bioequivalence
- B. Do not discontinue a prescription medicine until you have consulted the prescriber.

Practical Advice (3)

Avoid switching generic manufacturer if you take a NTI drug or one known to have bioequivalence issues (3-letter designations in Orange Book)

Narrow therapeutic index (NTI) Drugs

NTI drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions.

- Serious events are those which are persistent, irreversible, disabling, or life-threatening, (L.X. Yu, FDA, 2010)

NTI Drugs(2)

NTI drugs generally have the following characteristics:

- Steep drug dose-response relationship within the usual dose range or
- Narrow span between effective drug concentrations and concentrations associated with serious toxicity

Examples of NTI Drugs

warfarin	digoxin
levothyroxine	lithium carbonate
carbamazepine	phenytoin
theophylline	

NTI Drugs (3)

Patients taking NTI drugs should receive regular therapeutic drug monitoring based on . . .

- clinical response (e.g., blood sugar, blood pressure), and/or
- pharmacokinetic or pharmacodynamic measures to ensure safe and effective use of the drug,

Variable Drug Absorption

- digoxin (Lanoxin), propranolol (Inderal), procainamide (Pronestyl)
- phenytoin (Dilantin)
- Lithium
- amitriptyline, nortriptyline (Aventyl), desipramine (Norpramin), trimipramine (Surmontil)

Variable Drug Absorption (2)

- Diltiazem, (Cardizem)
- Nifedipine (Procardia)
- Theophylline
- Sustained release dosage forms

Practical Advice (3)

Avoid switching manufacturer if you take a drug known to have bioequivalence issues (3-letter designations in Orange Book) or variable drug absorption

Orange Book

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Orange Book Bioequivalence AA Codes

AA designates products in conventional dosage forms not presenting bioequivalence problems

- Multisource drug products coded as AA contain active ingredients and are in dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues.

Orange Book Bioequivalence AB Codes

AB designates multisource drug products with identical active ingredient(s), dosage form, route(s) of administration and strength that meet necessary bioequivalence requirements

AB1, AB2, AB3... Three-character codes are assigned when *more than one reference drug* of the same strength has been designated. If a study demonstrates bioequivalence to a reference drug product, the generic product will be given the same three-character code as the reference drug it was compared to.

Orange Book Bioequivalence Codes (2)

"B" CODES Drug products that FDA . . . considers not to be therapeutically equivalent to other pharmaceutically equivalent products. These often have a problem with specific dosage forms rather than with the active ingredients.

Practical Advice (4)

To avoid unintentional duplication

- Carry a list of your medications including OTC's
- Learn the generic name of your medications

Practical Advice (5)

Ask about the Orange Book

If you receive a drug from a new manufacturer, ask your pharmacist/PBM about the Orange Book rating

Orange Book

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Practical Advice (6)

Evaluate the manufacturer – your pharmacy should be able to help you identify who made the finished product.

Evaluate the Manufacturer

- It can be very hard to track where your drugs come from. Sometimes drugs are repackaged and rebranded along the way. The package need include only one of packager or manufacturer or distributor.
- If contacted, some manufacturers will disclose what country the medication came from and some will not.

Find Manufacturer
I got lucky with my generic lansoprazole because the capsules were imprinted



Practical Advice (6) *Use the internet to research your generic manufacturers*

My search for NATCO product recall yielded a story about adverse action by FDA against a NATCO plant.

“Natco Pharma . . . [has] received an adverse observation report, known as Form 483, after inspections conducted . . . earlier this year by the US Food and Drug Administration. The letter was issued after the regulatory body found deviations from the standard quality control practices.”

FURTHER
COMMENTS/QUESTIONS?

A BRIEF HISTORY OF US DRUG LAW

US drug law has evolved slowly since 1902, against fierce resistance, usually in response to horrific events that stimulated the public to demand congressional action.

The *Biologics Control Act of 1902*

- First federal regulation of biological products.
- In response to the deaths of 22 children who had contracted tetanus from contaminated horse serum. (Serum had been collected from a horse known to have tetanus).

The Pure Food and Drug Act (Wiley Act) 1906

- Main purpose was to ban foreign and interstate traffic in adulterated or mislabeled food and drug products.
- Required that active ingredients be placed on the label of a drug's packaging and that drugs could not fall below purity levels established by the USP or the NF.
- Response to Sinclair's *The Jungle*

Federal Food, Drug and Cosmetic Act (Copeland Act) 1938.

- Created the U.S. Food and Drug Administration (FDA)
- Authorized FDA to oversee the safety of food, drugs, medical devices, and cosmetics.
- Required that drugs be labeled with adequate directions for *safe* use.

1938 Act (Continued)

- Required pre-market approval of all new drugs based on proof of *safety (not efficacy)*.
- Prohibited false therapeutic claims for drugs. (Federal Trade Commission jurisdiction over drug advertising).
- Authorized factory inspections, and injunctions (seizures) as an enforcement tool.

1938 Act (Continued)

- Stimulated by Elixir of Sulfanilamide and the "American chamber of horrors" Lash Lure, Koremlu, Radithor, and the Wilhide Exhaler, which falsely promised to cure tuberculosis and other pulmonary diseases.

"Chamber of Horrors"

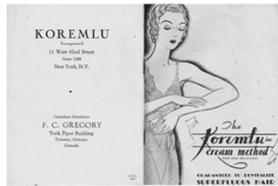
Elixir of Sulfanilamide caused the death of more than 100 people from kidney damage. Diethylene glycol was used to dissolve the drug. Manufacturer desired a liquid for marketing (not medical) purposes. No testing or research into solvent



"Chamber of Horrors"

Koremlu, a depilatory, contained thallium acetate. Widely marketed in the 1930s. It sold at \$10 a jar, (\$150 today). It caused baldness, pain and paralysis.

Thallium was a rat poison. Now banned in the US as too toxic. Koremlu didn't qualify as a drug and the FDA did not yet have power to regulate cosmetics.

**"Chamber of Horrors"**

Radithor advertised as "A Cure for the Living Dead" claimed to cure impotence, among other ills.

Eben Byers, American athlete and industrialist died from Radithor radium poisoning in 1932. He was buried in a lead-lined coffin; in 1965 his remains were still highly radioactive.

A 1990 *WSJ* article describing the Byers incident was titled "The Radium Water Worked Fine Until His Jaw Came Off"

**Brief History of US Drug Law (6)**

- **Durham-Humphrey Amendment 1951.** Defined/distinguished prescription and over-the-counter drugs.
- **Kefauver-Harris Amendments 1962.** Required proof of **efficacy** as well as safety before a new drug could be marketed, (retroactive to all drugs introduced after 1938)

1962 act (Continued)

- Gave FDA strict control over drug trials (required informed consent by subjects),
- Transferred regulation of *prescription* drug advertising from the FTC to the FDA,

1962 act (Continued)

- Established Good Manufacturing Practices (GMP) to be followed by pharmaceutical industry
- Increased FDA authority to access company production and control records to verify GMP was followed.
- Stimulated by the worldwide thalidomide disaster (narrowly averted in the USA).

Drug Efficacy Study Implementation (DESI)

- Response to the Kefauver-Harris requirement that all drugs be efficacious as well as safe.
- Classified pre-1962 drugs (already on the market) as either effective, ineffective, or needing further study.
- By 1984, final action taken on 3,443 products; of these, 2,225 were found to be effective, 1,051 were found not effective, and 167 were pending

The Drug Price Competition and Patent Term Restoration Act, (Hatch-Waxman) 1984

- Outlined process for pharm mfg to file an Abbreviated New Drug Application (ANDA) for FDA approval of a generic drug
- Five-year period of market exclusivity awarded when the FDA approves an NDA for new chemical entity; during that period the FDA cannot approve a generic version of the drug.

Hatch-Waxman 1984 (continued)

- Extends patent life covering a drug by a portion of the time the drug is under regulatory review by the FDA, ensuring innovator companies that regulatory review will not unduly consume patent life
- Limits FDA evaluation of ANDA to (1) how generic applicant it is going to manufacture the drug and assure its quality and (2) a study showing that the drug they manufacture is bioequivalent.
- Stimulated by very few generics coming to market.

Generic Drug Enforcement Act (1992)

Authorized FDA to withdraw any application containing false data or to debar corrupt companies entirely, if need be.

User Fees Permitted

- **The Prescription Drug User Fee Act (PDUFA) (1992)** allows the FDA to collect a substantial fee from a drug manufacturer to fund the new drug approval process at the time a New Drug Application (NDA) In order to continue collecting such fees, the FDA must meet performance benchmarks, primarily related to the speed of the NDA review process.
- **Generic Drug User Fee Amendments (GDUFA) (2012)** enables FDA to assess industry user fees to bring greater predictability and timeliness to the review of generic drug applications.

FDA Documentation

- **FDA Drug Safety Communications**
- <https://www.fda.gov/drugs/drug-safety-and-availability>
- **Enforcement Reports**
- <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports>
https://www.accessdata.fda.gov/scripts/ires/index.cfm#tabNav_advancedSearch

FDA Documentation

- **Warning Letters**
- <https://www.fda.gov/drugs/warning-letters-and-notice-violation-letters-pharmaceutical-companies/warning-letters-2019#OPDP>

FDA Warning Letter to ZHP

“Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).”

FDA Documentation**• Inspection Citation**

<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-citation>

• Inspection (Form 483) Database

<https://www.fda.gov/media/107480/download>