Do You Have Access to High Quality Generic Drugs?

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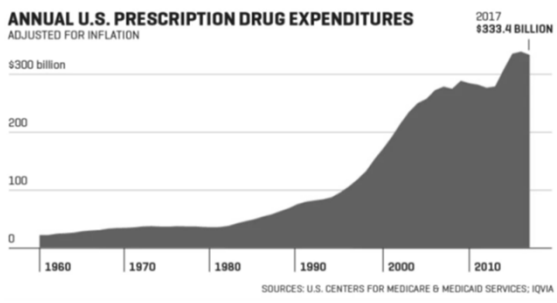
Access to High Quality Generic Drugs?

- 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 hyper-tension 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 manu-facturing 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 contam-inated 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."

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

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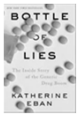

FURTHER COMMENTS/QUESTIONS?

Part II Next Week : Practical Advice for Using Generic Drugs