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# Generics Life and Money Saving: A Review

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## Key Takeaways

Generic medications are critical in the United States' health-care system, saving payers and patients a total of $253 billion in 2016 and $1.67 trillion over the last decade.[1]

In 2016, generic drugs were used to complete 89 percent of all prescriptions written in the United States. Those, however, only 26% of overall drug expenses were attributed to prescriptions. Furthermore, generic manufacturers work in a cooperative environment. In contrast to branded enterprises, where the supply chain accounts for 64% of all income, the market for unbranded companies is significantly different. In the generic market, the manufacturers keep 76 percent of the revenue, whereas in the brand market, the producers keep 78 percent.[2]

## PRESCRIPTION REVENUE

The market dynamics of brand and generic medications are extremely different, as the brand business is often controlled by a single manufacturer with exclusivity, whereas the generic industry follows a multi-competitor model, with drug prices falling as more competitors enter the market. As a result, generic medicine prices have decreased since 2008.[3]

While brand-name prescription prices have risen by more than 60%, generic medicine prices have continued to rise.

With biosimilars entering the U.S. marketplace and poised to offer additional savings in areas of prescription drug spending that had not been available before, it is more important than ever that a healthy generic drug manufacturing market is cultivated to continue offering savings, assuring supply and broadening access to lifesaving medicine for all Americans. Currently, specialty drugs (that is, biologics, complex injectables and complex drugs) make up 42.9 percent of costs although they are used by fewer than 3 percent of patients.[4]

While the generic drug supply chain and the brand drug supply chain include many of the same stakeholders, there are different financial incentives at play

When considering solutions to the rising costs of prescription drugs, it is essential for policymakers to fully understand these differences so that policies can be tailored to the different situations of both the brand and generic markets.

## Overview of the Generic Drug Supply Chain

### BRAND AND GENERIC DRUGS

When a new drug product is developed and initially marketed, it is protected by a patent, which prevents other companies from marketing a similar product (i.e., based on bioequivalence). These drugs are typically referred to as “branded” or “originator” drugs. Once that protection has expired, other manufacturers may apply to the U.S. Food and Drug Administration (FDA) for approval of their own versions of the drug. “Generic,” or multiple-source drugs, are drugs for which the initial patent protection for the active ingredient has expired. Generic companies can also challenge patents ahead of patent expiration to bring more affordable medicines to patients as early as possible. Congress has provided the first company (is) to challenge such patents with the potential for 180 days of exclusivity to encourage generics to take on the significant risk and expense of such patent challenges. Generic drugs play an integral role in health care. The expiration of patents and the introduction of multiple generic manufacturers competing against each other on price results in significant cost savings for the health care system. Over the last 10 years, generic manufacturers saved

the U.S. health care system an estimated $253 billion and $1.67 trillion.5

**What Are Innovator Drugs?**

An innovator drug is the first drugs created containing its specific active ingredient to receive approval for use. It is usually the product for which efficacy, safety and quality have been fully established. When a new drug is first made, drug patent usually will be acquired by the founding company. Most drug patents are protected up to 20 years. During the patent period, other companies cannot make or sell the same drug until the patent expires.

**What Are Generic Drugs?**

A generic drug is made of the same active ingredient as its innovator drug. An active ingredient is the chemical contained inside a drug that makes it work. In other words, the pharmacological effect of a generic drug is exactly the same as those of its innovator counterpart. Other companies can manufacture the generic drugs when patent expires.

**Are innovator drugs and generic drugs similar?**

Yes, there are similarities between generic and innovator drug, such as:

- Active ingredient
- Strength (dose)
- Therapeutic effect
- Side effects
- How to take

**Examples of Innovator and Generic Drugs**

| Active ingredients | Innovator | Generic |
|---|---|---|
| Ranitidine HCL | Zantac | X'tac |
| Mefenamic acid | Ponstan | Mefetab |
| Piroxicam | Feldene | Apo-Piroxicam |

**Myths of Generic Drugs**

Some myths that are often associated with generic drugs:

- Generic drugs are not as safe as innovators.
- Generics drugs are not as effectives as innovator
- Generics drugs take longer time to act in the body.

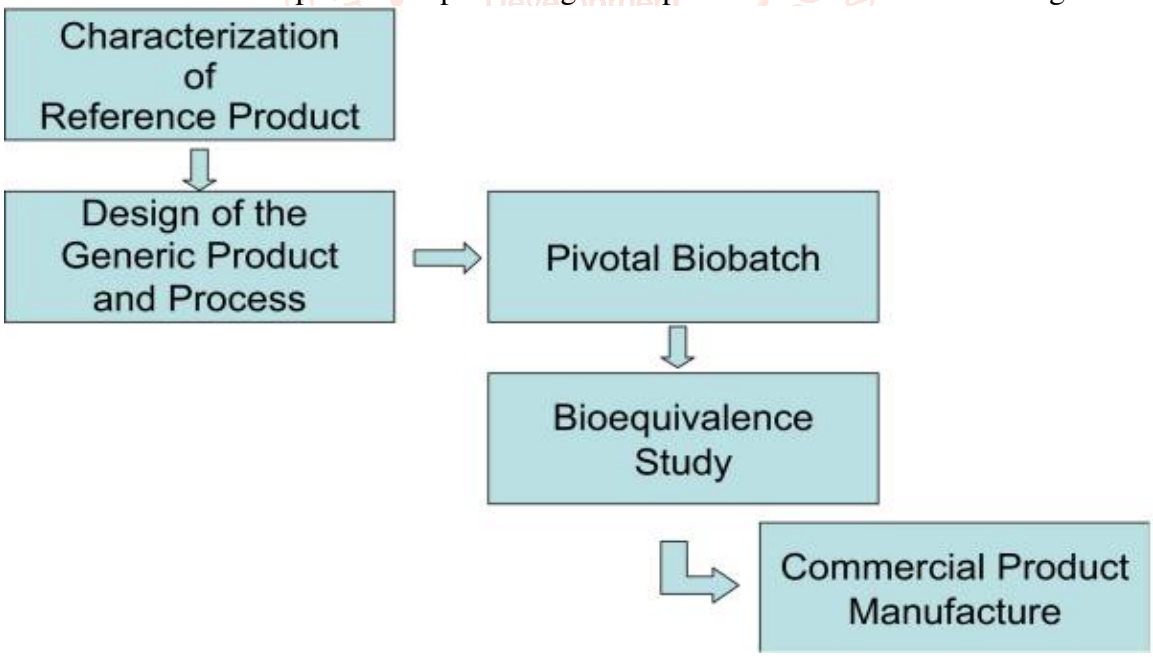
Generic drugs use the same active ingredients as innovator drugs and work the same way+. So, they have the same risks and benefits as the innovator drugs.

Generic drugs may look different because of certain inactive ingredients, such as colours and flavourings agents, may be different. These ingredients do not affect the safety, effectiveness or performance of the generic drug.

So, there's no truth in the myths that generic drugs are inferior in quality as compared to innovator drugs.

**GENERIC DRUG DEVELOPMENT PROCESS**

The steps involved in the development of a potential generic product can be described in Fig. 1:




Unlike the case for new drugs, the risk of total failure is low because the safety and efficacy of the active ingredient have already been established, but cost efficiency is more important because of much lower profit margins and competition with other generic manufacturers. Time efficiency is important to both generic and new drug manufacturers with neither wanting unanswered scientific questions to slow the progress of products through the development process. Another aspect to efficient drug development is to use scientific understanding to limit unnecessary human testing of drugs. Bottlenecks to the efficient development (in the senses of resources, time, and appropriate use of human subjects) of a generic product can occur at every stage in the development process.

In the characterization stage, some generic products are challenges to develop because of the complexity of the reference product. Complex reference products may include drug substances with many potentially active molecules. Molecular diversity can arise in products with a natural source origin or even in synthetic molecules that are polydisperse mixtures. Other challenging reference products include products with complex supra-molecular structures such as iron complexes and products containing liposomes. The use of nanotechnology in drug delivery will lead to even more complex pharmaceutical structures to characterize. To make a copy of these products, an ANDA sponsor may need better characterization than the originator.

In the formulation development stage, generic formulations may be developed that do not pass the bioequivalence study or meet other requirements and formulation development must be repeated. These failures can sometimes be linked to the inability of dissolution or lack of an IVIVC to evaluate proposed formulations and processes during development. For new or complex dosage forms the formulation and product development stage can fail because of an inability to identify the critical quality attributes of new or complex dosage forms. Inhalers are complex combination of device and formulation and many are breath actuated and thus must perform equivalently to the reference product over a range of flow rates. Transdermal products must be bioequivalent to the RLD in terms of the rate and extent of drug delivery, but must also be equivalent in terms of adhesion, irritation and sensitization to the RLD when applied to the skin. Concern about the interaction of modified release formulations with alcohol (6), has introduced a new potentially critical quality attribute for some drug products.

The type of bioequivalence study required can determine whether the development process is economically and scientifically feasible. Expensive, extensive or unpredictable BE tests can limit the development of a generic product. A highly variable drug may require a large number of subjects using the usual FDA

recommended study. However, the biggest limitation to generic competition is when FDA recommends a clinical endpoint bioequivalence study. Many generic companies do not develop products that need clinical endpoint bioequivalence studies because of the relative cost, time and risk of failure involved. Clinical endpoint studies can add up to $2–6 million to the cost[1]. Thus, when expensive and risky (to the sponsor) clinical endpoint trials are needed to establish bioequivalence, the number of generic competitors is reduced significantly.

Finally, a generic drug that demonstrates bioequivalence to the reference product can be delayed in reaching the market because of the final scale-up step in the generic drug development process. Problems on scale up include wasted commercial batches, failure to meet specifications, and process variability.

These problems may require the sponsor to reformulate product or revise the process

## CRITICAL PATH OPPORTUNITIES

Based on this analysis of generic drug development, there are several areas of opportunity where scientific progress could accelerate the development and approval of generic products and expand the range of products for which generic versions are available, while maintaining high standards for quality, safety, and efficacy. FDA presented these opportunity areas in its May 2007 document (7).

- Improve the science underlying quality by design for the development and manufacture of generic drug products.
- Improve the efficiency of current methods for assessment of bioequivalence of systemically acting drugs including products that use complex and novel drug delivery technologies.
- Develop methods for the assessment of bioequivalence of locally acting drugs such as topical and inhalation products.
- Develop methods for characterizing complex drug substances and products.

Figure 02 indicates how these opportunity areas link into the generic drug development process. Progress in these areas will accelerate approval of generic drug products. More importantly, it will expand the range of products for which generic versions are available, while maintaining high standards for quality, safety, and efficacy. Methods for equivalence based on sound science build the confidence of health care providers, patients, and the public that generic products are equivalent to innovator products.

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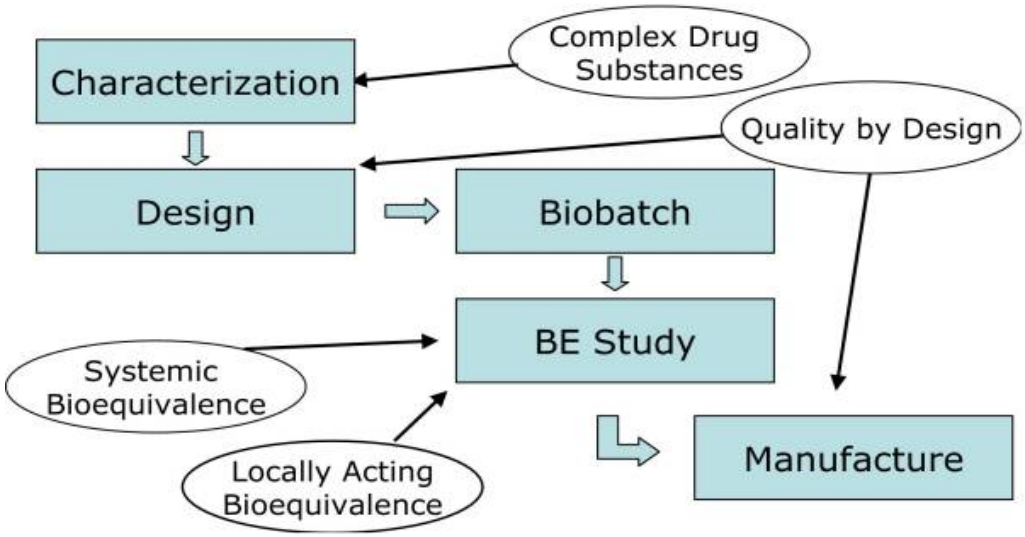


**BIOEQUIVALENCE ON THE CRITICAL PATH**

In this paper we focus on the critical path opportunities that are connected to the evaluation of bioequivalence.

- Quality by design tools to aid in the design and manufacture of bioequivalent products
- Bioequivalence of systemic drugs
- Bioequivalence of locally acting drugs

Category, would give a large return on investment to the public. However, any individual generic manufacturer that invested $10 million in a bioequivalence method for a product might never be able to recover that investment because of competition with other generic manufactures. Thus, identifying the source for resources to apply to these critical path opportunities is a challenge.

**Bioequivalence for Systemically Acting Drugs**

For systemically acting drugs, the critical path goal is to increase the efficiency of a process that already is providing safe and effective generic drugs to the public. The use of the Biopharmaceutics Classification System (BCS) (8,9) in the development of both new and generic drug products is an example of how critical path approaches can improve the efficiency of pharmaceutical development and improve product quality. Expanding the use of biowaivers in appropriate cases and improving dissolution methods are efficient ways to accelerate the approval and development of high-quality generic products. FDA has also identified other issues for which resolution could lead to more efficient bioequivalence testing. Many of these areas were discussed in scientific detail at the May 2007 AAPS BE, BCS and Beyond workshop and examples included

- Expansion of BCS bio waivers to some class II and class III drugs (10)
- Development of bio relevant dissolution (11,12,13)
- Mechanistic understanding of food effects
- Bioequivalence methods for highly variable drugs (14)

**Bioequivalence Methods for Locally Acting Drugs**

Bioequivalence of locally acting drugs is a long-standing challenge to the generics program, has the biggest impact on generic competition, and raises the most challenging scientific issues. Locally acting drugs are primarily found in the following categories: topical dermatological products, orally inhaled and nasal drug products, and GI acting drug products. They often require exploration of alternative bioequivalence methods because plasma concentration profiles of these products are not always appropriate surrogates of pharmacological activity. There was little discussion of these issues at the May 2007 AAPS BE, BCS and Beyond workshop. It is the intention of the "Critical Path Opportunities for Generic Drugs" report to attract the attention of leading scientists to address these complex challenges.

Difficulty in demonstrating bioequivalence of local acting drugs also has consequences to NDA sponsors across a product's life cycle. In initial development, process scale-up and optimization become difficult if there is not a method to compare pre and post change products. After approval, manufactures are reluctant to make major manufacturing improvements if a clinical study is required to validate the changes.

The selection of the bioequivalence method for a locally drug is based on product specific factors and a scientific understanding of the products' mechanism of action. FDA's regulation 21 CFR 320.24 lists approaches that are acceptable for determining the bioavailability or bioequivalence of a drug product. All of the approaches listed have been used for bioequivalence of locally acting drugs. A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that "For a drug

that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action".

## CONCLUSIONS

In the above study we studied total information of generics, difference between branded and generics, processes of development of generic, critical path opportunities, myths of generic drugs**.**

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