

# Accelerating Generic Approvals

## 5 Keys to Being First to Market

### In the game of generics, the first to market is the winner.

At a time when many of the most successful drugs are reaching the patent cliff, opening the floodgates for generic substitutes, generic companies are rushing to target the best candidates and enter the market first. And they are relying more heavily than ever on qualified outsource product development partners.

Competition in the generics market has never been greater. As patents on pharmaceutical products with sales of more than \$267 billion expire over the next six years,<sup>1</sup> companies worldwide are seizing the opportunity to introduce a generic alternative and rigorously competing to be first to market.



The U.S. generic drug market is booming. Where blockbuster drugs once ruled, bioequivalent generics are replacing them as welcome lower-cost alternatives for patients and are viewed as an important part of the solution to the economic burden of healthcare by the U.S. medical community. In the last decade alone, generic drugs provided more than \$824 billion in savings to the nation's healthcare system.<sup>2</sup> Today there are more than 7,800 generic versions of the approximately 10,668 FDA-approved pharmaceuticals.<sup>3</sup>

Saving time and costs in developing a generic product are extremely important for a generic drug's success. The first generic company to market wins the industry's Holy Grail -- the 180-day exclusivity period that is critical to a generic product's success. During that period, the manufacturer is able to build the product's access and acceptance without competition.

### Outsourcing Generic Development

Since time largely dictates the economic profile of a generic product, generic companies today are increasingly relying on qualified contract research organizations (CROs) to accelerate their development timelines. With a highly qualified partner, companies can gain broad expertise in development processes, advanced technology, scientific models, and infrastructure without adding significant capital investment. Further, this allows sponsors the flexibility to utilize the optimal level of resources and services they need to gain a competitive edge. Outsourcing generic drug research, development, and production can significantly reduce the time required to bring a generic to market.

"The key to successful development of a generic product goes beyond a successful bioequivalency study, regulatory filing, or a successful process validation study," says Michael Zhou, Ph.D., Senior Director, Global R&D, BASInc. "Successful generic drug development with a speed advantage requires a strong CRO laboratory partner. Developing a bioequivalent demands efficient, high quality, regulatory-compliant analyses at every step.

"BASi has considerable experience in efficient development of generic products. Its experienced team of development experts can help ensure flawless execution without costly delays. BASi delivers efficient bioanalytical method development and sample analysis as well as comprehensive pharmaceutical analysis, including stability program support, method validation, and final product release testing. Its scientists support clients from early phase R&D work to ANDA submission and post-market with sample analysis and stability testing."

### Five Common Development Challenges

Here are five of the most common challenges of developing a generic product, and how a qualified CRO can help you gain valuable speed to market.

#### 1. Preformulation and Formulation

Generic products must meet the same quality standards as branded products. Most countries require manufacturers to prove the efficacy of their formulation compared with the designated reference product by conducting a bioequivalence/ bioavailability (BE/BA) study. The U.S. Food and Drug Administration (FDA) requires bioequivalence to be between 80% and 125% of the innovator product.

The development scientist has a demanding role, as generic forms not only need to match innovator products within tight acceptance criteria, but should also circumvent restrictive formulation patents. Before preparing trial formulations, preformulation must be done to obtain as much information about the reference product and drug substance as possible. Preformulation includes determining the active



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ingredient(s), compounds, and excipients, as well as drug solubility, chemistry, flow and absorption, drug release and other characteristics.

Since labels for innovative drugs state only the main excipients, but not all of them, generic scientists are often challenged to determine the missing ingredients. Conducting analytical testing for each likely excipient is based on experienced guesswork, which can add considerable time to the development process if the scientists lack experience. An experienced CRO will know which ingredients to test for in various dosage forms and APIs and can shave time off this process by selecting the right ones the first time.

During formulation, scientists compare their recipe with the innovator drug to ensure it has a very close profile without impurities.

In addition to having the needed expertise, your CRO partner should already have the advanced equipment to conduct the tests efficiently, as well as quality systems and standard operating procedures (SOPs) in place.

## **2. Regulatory Expertise**

BE/BA studies must comply with specific requirements for each product and with the regulatory requirements of each country where the drug is intended to be marketed. In the U.S., the FDA has specific requirements for an Abbreviated New Drug Application (ANDA); for marketing abroad, there are different requirements for national submission in areas such as Europe, Japan, China and India.

Your service provider must be aware of and comply with all applicable regulations. The formulation scientist must ensure that a non-patent-infringing raw material can be incorporated into a non-patent-infringing formulation that will be at least as stable as the innovator drug product and bioequivalent. Submitting accurate BE studies will expedite regulatory approval, whereas submitting applications without all necessary information can result in costly delays.

## **3. In Vitro/In Vivo Testing**

To demonstrate bioequivalence, the formulation must have the same amount of active ingredient and the same dissolution and release profiles as the reference product. Oftentimes, clinical BE testing may be necessary, and sometimes toxicology studies are needed. A service provider knowledgeable in this area with an onsite toxicology facility can provide the needed expertise, continuity, and effective study oversight.

For in vitro and in vivo testing, it is critical to have highly qualified medical and technical staff, both clinical and laboratory principal investigators. If human testing is necessary, the investigators must be able to efficiently recruit qualified subjects and conduct the study. A deep understanding of pharmacokinetic (PK) variability is needed when designing such studies.

## **4. Quality by Design**

Development of a generic product, as with any other drug, must be governed by Quality by Design (QbD) principles and incorporated into the development planning. This requires a thorough understanding of the product and development process along with a knowledge of risks and how best to mitigate them.

Scientists must not only gather test data, but know how to interpret the data to determine whether the formulation's pharmacokinetic and dissolution profiles are comparable to those of the reference drug. They should also have an understanding of the quality target product profile (QTPP).

Incorporating QbD, scientists must justify why and how the formulation was chosen through actual experimentation, including identifying the critical excipients and justifying the concentration of each excipient in the formulation. Modeling and simulation can aid generic developers in determining what drug release profile is needed to provide bioequivalence to the reference list drug/product.

Then the challenge to the generic developer becomes selecting the excipients and designing a formulation and release mechanism that provides the intended in vivo release profile. A mechanistic understanding of how the physical properties of a drug substance and excipients affect drug product performance can enable a rational choice of excipients and reduce the number of experimental formulations that need to be produced.

Because it is usually not feasible to test every trial formulation in an in vivo study, better in vitro/in vivo correlations (IVIVC) will improve an iterative design process. When an in vitro dissolution test can be related to the in vivo dissolution of a product, a generic sponsor will have an efficient tool to evaluate different formulations and select the optimal formulation for use in the pivotal bioequivalence study.

However, the correlation of dissolution testing with in vivo performance varies from product to product. The FDA's data from dissolution tests and pharmacokinetic studies can help external collaborators develop and test models capable of predicting the connection between dissolution and bioavailability/bioequivalence.

In addition, companies need to quickly develop a Chemistry, Manufacturing, and Controls (CMC) strategy, the part of drug development that deals with the nature of the drug substance and product, the manner in which they are made, and the manufacturing process. However, many companies lack expertise on how to fully address complex CMC guidelines.

## **5. Planning**

Early, thorough planning, supported by a solid understanding of generic development science and regulatory requirements, is essential for timely delivery of data for an ANDA submission. Experienced CROs can provide consultation and advice for regulatory compliance and ANDA submission, which result in considerable time and cost savings.

The key to a successfully developed generic product goes beyond a technically correct bioequivalence study, a regulatory filing, and a successful process validation study. A truly successful generic product is one that can be made repeatedly by any trained manufacturing operator without problems. Considerable effort and careful planning during development will improve the chances of generating a robust product.

A manufacturer typically begins searching for the right product to develop about two years in advance and invests many resources early into product development. Once selected, the product development path needs to be scheduled and its progress closely tracked and managed with the goal of being first to market. The company then begins preformulation following guidance by the FDA, and if successful, develops and tests the formulation to demonstrate bioequivalence to the innovator product.

### Choosing The Best CRO

The following checklist is a guide to choosing the best CRO to produce a bioequivalent formulation expeditiously at the lowest cost. Find out if the CRO has the following qualifications:

- Highly qualified staff who efficiently, thoroughly, and accurately carry out every step, including method development, analytical testing, data interpretation, and support for regulatory submission
- Knowledgeable in generic regulatory requirements
- An exemplary regulatory compliance record
- Adheres to Chemistry, Manufacturing, and Controls (CMC) guidelines, and has standardized protocols for development and quality SOPs
- An excellent track record of speed, quality and cost efficiency
- Provides consultation and guidance
- Has the development infrastructure, capacity, technology and sites for efficient development, as well as onsite temperature- and humidity-controlled stability storage
- State-of-the-art technology and facilities
- Provides a broad array of services, from bioanalytical method development and sample analysis to ANDA submission and post-commercialization product testing
- Knowledge of formulation, process design and development of a generic product
- Experience in lab-testing generics, including in vitro/in vivo testing capability
- Excellent reputation and history of satisfied customers

### CROs = Faster Drug Development

Why will a well qualified CRO get your generic product to market faster? Simple. R&D is a CRO's core competency, the focus of its business. Outsourcing generic development offers broad expertise, the needed infrastructure, and the ability to quickly solve formulation challenges, which enable generic manufacturers to achieve substantial time and cost efficiencies. In the generic race to market, companies who outsource development to a qualified CRO will gain a competitive advantage – and have the best shot at first-to-market success.

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