WHITE PAPER

Generics and Biosimilars: Ensuring Quality from Beginning to End

Scaling the Summit of Quality – An Impeccable Journey in Drug Manufacturing

Introduction

When a new drug is first developed by a pharmaceutical company, it is initially sold under a brand name and the product is covered under patent protection. This means that the only company allowed to manufacture, market, and profit from the drug is the innovator company that holds the patent. However, once a patent expires, opportunities arise for companies other than the innovator to manufacture and sell the product as a generic or biosimilar medicine. "The term generic drug applies to small molecule drugs and the main advantages of these products are that they will lower the cost and create competition," explained Dr. Mansoor Amiji. "Biosimilars on the other hand are protein or biotechnology-based products. Again, the requirements are to produce the same type of drug as the innovator by a different company to create competition for the brand name product."

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Manufacturers of generics and biosimilars must adhere to stringent quality, safety, and efficacy requirements during drug development; however, there are key differences between the two. "Generic products must demonstrate bioequivalence to the brand name drug whereas biosimilars must show biosimilarity," said Dr. Amiji. "Generics must be identical in chemical composition to the innovator while biosimilars, which are far more complex, must show that they are highly similar."

Demonstrating Bioequivalence and Biosimilarity

For a company to demonstrate bioequivalence for their generic small molecule drug, they must carry out a Phase I clinical trial in healthy individuals to ensure that the area under the curve and maximum plasma concentration for their drug is equivalent to that of the brand name drug. "They will run crossover studies in healthy individuals who will receive the brand name and the generic drug. The plasma concentration-time profile results will be compared to see if the two are bioequivalent," explained Dr. Amiji. In the United States, if bioequivalence is demonstrated, an abbreviated new drug application (ANDA) containing the data from the study is sent to the FDA to review and potentially approve.

The process for biosimilars is slightly more complicated, as these are protein-based drugs. "You have to consider factors such as the method of manufacturing, the technology, or the cell line," said Dr. Amiji. "There are many variabilities with biosimilars and the brand name protein drug." For this reason, biosimilarity is often considered on a case-by-case basis. "There is no general guidance for biosimilars, at least not in the United States. Some countries are starting to implement general guidances, but this is mainly due to cost pressures. Protein-based drugs are extremely expensive and so if you can create a biosimilar and potentially lower the cost, then this is an incentive for many companies to try to get into that marketplace, but also for regulators to encourage development."

Dr. Amiji added that there is additional scrutiny when assessing biosimilarity, especially relating to toxicity. "Even minor amounts of biological contaminants in your sample could cause unwanted biological effects. This is especially the case if they derive from cell-based systems or microorganisms like *E. coli,* where small amounts of contaminants could cause significant toxicity. They may be therapeutically as effective, but the safety aspect is a key concern in approving biosimilarity."

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Another interesting aspect to consider for biosimilars relates to the process and analytical methods. "In a lot of small molecule drugs, you rely on sophisticated analytical methods to ensure the quality of your active ingredient and excipients. In the case of biosimilars, parameters such as specificity and limits of detection also need to be analytically validated and continuously improved upon." For example, if you have a mass spectrometer that can detect impurities, but the level of detection needed is very low, you could miss certain impurities in your sample. This could potentially be a cause for concern when you are approving that product – you may still have a contaminant in your sample, but the instrument is unable to detect it. Creating various protocols that allow for greater sensitivity and specificity is therefore critical.

There have been continued efforts in the United States, most European countries, and some parts of Asia to harmonize and create similar types of requirements for biosimilars. However, Dr. Amiji believes that the United States has taken a more cautious approach than other countries and continues to approve biosimilars on a case-by-case basis.

Ensuring Quality Standards

Irrespective of whether it is a brand name, generic, or biosimilar drug, all pharmaceutical products must ensure product quality assurance using Quality by Design (QbD) measures. "QbD is a universal principal when it comes to the quality of pharmaceuticals. Once you start manufacturing a drug for the masses, you must follow the same QbD principles that you would if you were producing it for the first time," said Dr. Amiji.

"For example, the standards for generics are the same as the brand name company; they will produce the drug,

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control the process parameters, and ensure that their product meets the target product profile. Again, that target product profile will be very similar to that of the brand name drug. Ultimately, they need to ensure they are meeting the same safety and efficacy standards."

Considering the high levels of scrutiny and quality control relating to the approval of generics and biologics, it comes as no surprise that there are few concerns relating to their safety from the consumer. "In the case of generics, the only concerns you might see is where the brand name and generic drug contain different excipients. A patient may have a hypersensitivity to one of those excipients and will then be prescribed the brand name because of the reaction to the generic." explained Dr. Amiji.

As healthcare costs in the United States and other parts of the world have risen dramatically in recent years, there is pressure on various groups to ensure that generic products continue to reach the marketplace. "In the United States, pharmacists are required to dispense generics if the prescription does not specify the brand name, this is the law," said Dr. Amiji. For biosimilars, the situation is slightly more complicated because the onus is on the regulatory agency to ensure that these products perform the same way as the brand name drug and have the same safety and efficacy profile. "Once it is approved, the level of confidence by the consumer is going to be the same as the brand name as they will automatically assume that this product performs the same way, so there is minimal scrutiny of biosimilars from the consumer side."

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Next-Generation Biologics

Recently, there has been a rise in the development of biobetters – a new class of biologics that have entered the market. As the name suggests, biobetters are considered to be better and improved versions of existing biologics. "There is a very fine line between a biobetter and a new active ingredient," noted Dr. Amiji. "With biobetters, you are not producing a completely new drug, but you are trying to do a little bit better than the existing one. Take insulin as an example, if you could produce a biosimilar that was longer acting, or combine two forms of insulin in one vial, this could reduce the number of times a patient has to inject."

Dr. Amiji concluded that this is an interesting point in history as we see more and more complex pharmaceuticals being developed. "From a company perspective, as a commercializing entity, innovators are trying to develop products that are hard to create a generic or a biosimilar for. However, there is also the cost factor which is the main motivator for companies to do this less expensively, and that is the main driving force behind these ideas of generics and biosimilars."

About Mansoor M. Amiji, PhD

Dr. Amiji received his undergraduate degree in pharmacy from Northeastern University in 1988 and his PhD in pharmaceutics from Purdue University in 1992. Over the years, his research has received over $40m in sustained extramural funding from the National Institutes of Health (NIH), National Science Foundation (NSF), foundations, and biotech/pharma industries.

Dr. Amiji has supervised research efforts of over 120 post-doctoral associates and graduate students. He has also edited 10 books, along with over 70 published book chapters and over 360 peer-reviewed articles.

Dr. Amiji has received several awards including the 2006 NSTI Award for Outstanding Contributions towards the Advancement of Nanotechnology, Microtechnology, and Biotechnology, and the 2007 American Association of Pharmaceutical Scientist's (AAPS) Meritorious Manuscript Award. He is a Fellow of both AAPS and the Controlled Release Society. He has also received the Distinguished Alumni Awards from both Northeastern University School of Pharmacy and Purdue University College of Pharmacy.

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