WHITE PAPER

Drive Pharmaceutical Quality Excellence

Tackling the Suboptimal – A Process-Driven Approach to Ensure Pharmaceutical Quality

Introduction

Globalization of the pharmaceutical industry has led to increasing demands on regulatory agencies across the globe to ensure the quality, safety, and effectiveness of medicines. To meet the required standards and regulations mandated by the regulators, quality assurance and quality control measures must be implemented during the clinical, manufacturing, and distribution stages of the product life cycle. "If you consider the continuum of the supply chain you can identify various areas where things can go wrong and ultimately the patient receives a poor-quality product," said Dr. Amiji, University Distinguished Professor, Professor of Pharmaceutical Sciences and Professor of Chemical Engineering at Northeastern University (Boston., MA, U.S.A.). "Anywhere along the pipeline can be impacted – everything from raw material quality tothe manufacturing and distribution of the finished goods needs to be assessed."

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Quality assurance is a regulatory term relating to the governance of quality by regulatory agencies, for example the FDA in the United States or the EMA in Europe, whereas with quality control the onus is on the company developing the product. "The main purpose of quality control is to test and verify the product quality against predefined standards; for example, if a company is developing a tablet, one of the quality control measures would be to test whether the tablet has the same amount of active ingredient as stated on the label," explained Dr. Amiji.

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Poor-quality medicines can have far-reaching consequences, from placebo pills or subtherapeutic doses through to contaminated products that could potentially cause harm to the consumer. The development of these products can arise from various factors, such as poor-quality raw materials, poor manufacturing, inadequate quality control, or counterfeiting. It is important to distinguish between products that simply fail to meet the quality standards (substandard medicines) and those that have been intentionally altered (falsified medicines).

Substandard medicines are those which are made legitimately but fail to meet either their quality standards or specifications, or both. The product may be contaminated, poorly packaged, or contain too much or too little of the active ingredient. "If you take the example of COVID-19 vaccines, the Pfizer/BioNTech vaccine requires a cold chain to be distributed. If the cold chain is not utilized, you are now dealing with a product in the clinic that is substandard because the requirements have not been followed," explained Dr. Amiji.

In contrast, falsified medicines are those that have been deliberately and fraudulently tampered with. A well-known example of this occurred in 1982 in Chicago, where a series of poisoning deaths resulted from drug tampering. The victims had all taken Tylenol-branded acetaminophen capsules that had been intentionally laced with potassium cyanide. A less serious case occurred in 2012, where the FDA warned of counterfeit versions of Avastin, an injectable biopharmaceutical to treat metastatic cancers. The fake injectable contained cornstarch, acetone, and other chemicals, but no cancer-fighting ingredients, meaning the product did not provide the efficacy expected and could cause harm. The driving force behind intentional falsification of medicines is the potential lucrative nature of the business. "The people developing these products are not conducting quality control tests; they are there to make money out of vulnerable individuals," said Dr. Amiji.

Preventative Regulatory Measures

To prevent the manufacture and distribution of substandard medicines, a concerted effort is required by the regulators, drug manufacturers, and law enforcement to ensure that only drugs of acceptable quality reach the patient. When it comes to the approval of any therapeutic product, the most important criteria for regulatory agencies is the notion that these products are safe and effective. However, regulators have historically acted in isolation and the quality requirements have varied significantly from country to country. This means that products are sometimes differentially approved depending on the quality assurance criteria. An example of this is the AstraZeneca COVID-19 vaccine, which is currently approved in the UK and Europe, but not in the United States.

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In an attempt to achieve greater harmonization in standards, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was introduced in 1990, whereby guidelines are developed to ensure the assessment of safety, quality, and efficacy of medicines. Current good manufacturing practice (GMP or cGMP) is another system for ensuring that products are consistently produced and controlled according to quality standards. "The FDA, EMA, and other regulatory bodies have formulated requirements for GMP that have to be met when developing products for human use," said Dr. Amiji "These guidelines cover the whole spectrum of production; it is a complete cycle that runs from the start of the process to the product's expiry."

Quality by design (QbD) principles, which were first introduced in 2005, are also important for ensuring product quality. "QbD was introduced to change the paradigm of pharmaceutical product quality from being product orientated to process orientated," said Dr. Amiji. One of

the goals of QbD is to ensure that all sources of variability affecting a process are identified, explained, and managed by appropriate measures so that the finished medicine consistently meets its predefined characteristics from the start of development. "There is a lot of precedent in terms of utilization of QbD in existing pharmaceuticals," said Dr. Amiji. "By addressing quality in the processes rather than the end-product, the agencies have become much more streamlined and conscious of cost savings. If you can identify problems during one of the initial processes, you can hopefully solve them before the product is made."

Ensuring Quality of Generics and Biosimilars

An interesting area of quality control relates to generics and biosimilars, which are marketed as cheaper versions of costly brand-name drugs. Although the process of developing generics and biosimilars is less time-consuming or costly than the development of the innovator product, manufactures still need to demonstrate that they meet certain safety and efficacy standards. "Generic products must demonstrate bioequivalence to the brand name drug whereas biosimilars must show biosimilarity," explained 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."

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. 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 by the regulators.

The Challenge of Complex Medicines

When it comes to the development of biologics and gene therapies, manufacturers must adhere to stringent quality, safety, and efficacy requirements during drug development. However, these complex medicines are presenting some interesting and unique challenges for the regulators. Biological products, which are derived from living organisms and frequently have a complex molecular structure, require special quality considerations due to the biological nature of the starting materials, the manufacturing process, and the test methods needed to characterize batches of the product. Likewise, the emerging field of gene therapy, which involves the introduction of genetic material into a cell to create a therapeutic benefit, also requires careful consideration of the critical quality attributes (CQAs) that could impact product safety, purity, and potency.

"With biologics and gene therapies, the science is often a little ahead of the regulators and so the agencies are having to adapt in real time," said Dr. Amiji. "Ensuring quality along the supply chain requires constant dialogue between the company developing a product and the regulatory agencies." An example of this was during the development of the mRNA COVID-19 vaccines by Moderna and Pfizer/BioNTech in the United States. The FDA was in constant dialogue with the companies to provide guidance on what types of studies had to be conducted, what quality requirements had to be in place, and how those quality and regulatory standards had to be satisfied.

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Another area where quality assurance becomes paramount is vaccine development, where the benefits and risks associated with the drug require careful consideration. "If you think about a cancer treatment, although the drug may have various side effects, it will still get approved if the therapeutic benefit overwhelms the effect," said Dr. Amiji. "When it comes to vaccines, you are dealing with healthy individuals and broad demographics, so the risk tolerance becomes a lot lower and subsequently the safety margin has to be much higher."

The Shift Toward Artificial Intelligence

Artificial intelligence (AI) has become an increasingly popular tool to support drug discovery and development efforts. "There is a lot of interest in the use of AI and machine learning in all aspects of pharmaceutical product development, from discovery and development to further along the clinical path toward manufacturing and approval," said Dr. Amiji. "What I am excited about is the possibility of identifying the good from the bad early on in the cycle, which could enable us to make more discriminatory choices during the development and manufacturing process."

Another area where Dr. Amiji believes AI could facilitate research relates to patient demographics; for example, when unique findings are only seen in certain patient subsets. "When using animal models, there is a tendency to homogenize pre-clinical studies despite the fact we have a very heterogenous population in the context of clinical application to the masses. If we could learn from that heterogeneity and bring it back to the pre-clinical level, that would be a really important step for the use of AI in drug development."

Dr. Amiji concluded that pharmaceutical companies and regulators must continue to be vigilant and monitor activities to ensure that products are not compromised, and public safety is protected. "This is the most challenging aspect of quality control because you have to look at the entire manufacturing chain and not just the end product," he said.

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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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