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Review on statistical methods applied in pharmaceutical quality control and quality assurance

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Abstract: Global competitions have made the pharmaceutical industry undergo numerous obstacles to meet the pace of drug discovery, growth, and expansion. In order to effectively manufacture a quality product, statistical methods can be implemented for continuous improvement. Evolution in quality is accessed by determining the beneficial effects due to changes in process performance. The use of statistical tools and methods has increased exponentially to meet quality specifications during the development of a pharmaceutical product. Statistical process control is a segment of industrial statistics utilized to improve product quality continuously. The statistical process control technique is a method to analyze any variation by the process of timely evaluation of the manufacturing procedure.

Keywords: Statistical tool; statistical process control; control chart; quality improvement; process control

1 Introduction

Currently, the pharmaceutical industry uses statistical methods and techniques as a driving factor to solve a variety of obstacles. Difficulties have risen over the last few decades for the product to reach the narrow window of regulatory attributes.[1] The complexities of pharmaceutical companies have been exacerbated by threats such as generic competitors, patent-related concerns, and economic decline.[2] The foundation for achieving Quality by Design is the comprehension of systems and processes as well as the control and elimination of variance, i.e., the main aspects of statistical thinking. Scientifically informed approaches to quality and conformity are encouraged by new regulatory guidance from the Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and the International Conference on Harmonisation (ICH). A fresh, more scientifically robust, and risk-based approach would be needed to incorporate the principles expressed in those guidelines: process analytical technology (PAT), quality by design (QbD), and design room. Statistical approaches can significantly enhance the degree of comprehension of items and procedures. The role and requirement of statistics and statisticians can only grow greater in the industry as these patterns continue.[1] The global market's success is based on quality. Organizations do not produce bad performance; it is typically the result of a transition at the level of development. Product quality thus relies on the ability to monitor the method of output.[3] This is when it comes to Statistical Process Control-SPC.

Statistical processes control is a set of instruments that can result in process stability and variability reduction when used together.[4] Statistical process control (SPC) is a theory, a technique, and a collection of approaches for continuous system, process, and effect enhancement. The SPC method is based on data learning and has its roots in variation theory (understanding general and special causes). The SPC methodology combines the principles of critical analysis, process thinking, mitigation, stratification, consistency, energy, and prediction. Statistical process control assimilates proper calculation and measurements, appropriate methods for collection of data, a series of analyses, and pre-planned experimentation.[5] The use of various statistical tools supports augmented process control. The decision-making by the pharmaceutical company for the quality enhancement of the product can be made easy with the application of SPC.[4] Regulatory Trends affirms the scientific approach and continuous enhancement in the process and quality of the product. In order to meet the regulatory parameters, pharmaceutical companies demand the application of statistical methods. To improve the cost-effectiveness and product quality, the regulatory agencies such as FDA and ICH have shifted their focus on process validation, product quality testing, and process design effectiveness.[1]

2 Evolution of Pharmaceutical Regulations for establishing quality

It is important to consider the past regulation of the industry to understand the factors that have influenced the use of statistics in pharmaceutical production today (Table 1). The recent history of pharmaceutical regulation encompasses the era of regulatory interventions focused on science and technology that started and continues today with the beginning of the 21st century.[1] The 1906 Pure Food and Drug Act aimed to prohibit the entry of

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adulterated and misbranded food into interstate trade in the United States. In order to replace the Pure Food and Drug Act of 1906, pre-market alerts from drug producers to federal authorities were applied to the Food, Drug, and Cosmetic Act of 1938 to guard against the entry of harmful goods into interstate trade in the United States.[1, 6] As a condition for the approval of proposals to bring new medications into the interstate trade, the FDA has added significant proof of effectiveness.[6]

Table 1 History of regulations related to quality of drugs and pharmaceuticals

Year	Act	Description
1906	Pure Food and Drug Act	Prohibit the entry of adulterated and misbranded food into interstate trade
1938	Food, Drug and Cosmetic Act	Guard against the entry of harmful goods into interstate trade
1989	International conference of drug regulatory authorities	Exposed the need for harmonisation of criteria, leading to the creation of ICH
1990	International Conference on Harmonisation (ICH)	Registry of Pharmaceuticals for Human Use
2013	Quality by Design(QBD)	QBD became mandatory filling requirements for NDAs

Authority was also provided to the FDA to mandate compliance with the regulations on good manufacturing practice (GMP), good laboratory practice (GLP), and good documentation practice (GDP). In order to mitigate the risks that could affect the safety and robustness of pharmaceutical drugs, the pharmaceutical industry is governed by GMP and GLP. The aim is to ensure that a pharmaceutical product must satisfy the safety criteria in an attempt to have intended product identification and purity specifications. A framework that ensures proper design, supervision, and regulation of manufacturing processes and facilities is provided by the GMP and cGMP. This involves the development of a robust quality control scheme, the procurement of sufficient quality raw materials, the establishment of rigorous operating processes, the identification of anomalies in product quality, and the maintenance of effective laboratories for research. The FDA emphasized production processes information, the technologies used to generate and manage these systems, and the fundamental foundations of a rigorous quality system at the production site.

The international conference of drug regulatory authorities organized by the World Health Organisation in Paris in 1989 exposed the need for harmonization of criteria, leading to the creation in 1990 of the Registry of Pharmaceuticals for Human Use (ICH). QBD became mandatory filing requirements for NDAs in 2013. Science- and risk-based regulatory systems would guarantee that FDA efforts are concentrated on product stability and higher-risk regions. All such variables have directed the organization towards the use of advanced technologies involving the statistical approach, such as process tracking, control charting, and validation for risk reduction.[7]

3 Emerging approaches for statistics

Nowadays, tools like descriptive statistics are used to analyze the quality attributes of essential process measures, quality management, and statistical methods. Example- Normality plot, capability histogram, and control chart and capability plot.[8] The primary goal of a production operation is to differentiate between random variables and assignable sources of variance. A production process often influences the setting, materials, processes, equipment, and even staff.[9] The major approach of application and deployment of statistical tools is to create an informative background of the processes and limit the variations.[2]

4 Statistical Process Control (SPC)

Statistical Process Control is a subset of statistics that incorporates systematic time series evaluation techniques with graphical analysis, mostly generating information from data quite easily and clearly to lay decision-makers.[10] It is a control process that aims to analyze the operation over time by eliminating the variation in the process, hence maintaining the quality attributes using a statistical approach.[2] When the process is robust, the system's efficiency can be enhanced by minimizing the causes of variation.[4] SPC assists in studying variations, their comprehension, and, ultimately, their reductions to hold them under limits that comply with requirements or targets. Production processes are prone to degradation over a period of time. Statistical process control keeps a record of such degradation to measure it and accurately fix its causes. SPC helps reverse the trend; hence, it assists in continuous quality improvement.[3] In the case of assignable or unique causes of deviation, a control chart is a helpful method for detecting out-of-control conditions. Researchers may use SPC and its main device, the control chart, to help interpret data leading to quality improvement. SPC leads us to better improve productivity and quality enhancement by differentiating cause and variation, whether common or special, and eliminating such causes.[4] Subbulakshmi et al. (2017) reviewed 41 published studies between 1980 to 2014, evidencing the application and utility of SPC and the need for research in this domain. Concluding the understanding of the review work, SPC can be taken as a beneficial element that can reduce the variability hence reducing the burden of scrap, rework, and losses due to defectives for the company. It can have control over the quality of the product and continuous improvement.[11] Yonatan Mengesha Awaj et al. (2013) applied the SPC techniques to study waste management. They applied the Pareto chart and p-chart. They have concluded that the application of fishbone analysis, Pareto chart, and cause and effect diagram helped minimize the problem related to the improvement in productivity.[12]

5 Control Chart

Shewhart designed the control chart, a comparatively simplistic statistical method for separating between normal and special cause variance.[10] The information

and data gathered upon applying the control chart are aimed to be utilized for the quality improvement of the processes and products by limiting and correcting the variations.[3] A control chart is indeed a basic and effective graphical analysis that can be used right away. Any control chart possesses a group of data points that are sequentially marked that corresponds to the feature of significance throughout processing, a central line that represents an approximation of the process mean, process standard deviation, and lower and upper limits that can be used to measure the data.[9] Proper control charts can be implemented by having a brief account of the basic distribution being used for common cause process variation.[10] Control charts are the most well-known statistical process control methods. Such graphical depictions of process results, when used properly, allow the participants to see what is going on with certain systems in real-time, making effective decisions. The ability to quickly grasp procedures and variation has resulted in the most rapid, immediate, and long-term developments of any management strategy.[5] A variation can be analyzed as a result of common cause when all the values of the data-set are falling within the upper control limit and the lower control limit, and the special cause is interpreted when any of the values falls beyond the upper control limit and lower control limit. While most conventional statistical procedures in clinical studies utilize 2SD as the statistical criteria in reaching to judgments, control charts use 3SD for numerous reasons.[10]

6 Cumulative sum Control Chart (CUSUM)and Exponentially weighted moving average (EWMA) control charts

These charts were initially introduced in 1950s, having the ability to extract information from different samples and combine them to obtain information, unlike Shewart control chart. As EWMA can predict the operational mean, it can be utilised to govern dynamic processes in real-time. The EWMA chart's ability to forecast time series values has contributed to its use in automated adaptive controllers. Multivariate quality control issues can be solved by the utility of CUSUM and EWMA control charts.[2]

7 Design of Experiments (DoE)

R.A Fisher introduced an effective strategy approach, Design of Experiments (DoE), during the 1920s. DoE is a method of study design wherein the input factors of the procedure are systemically adjusted to see how they affect the output variable as well as which ones have been the most impactful. These method are very useful in identifying the crucial few elements that drive the process and its interactions, along with determining the values that these factors should have to ensure that the response is as close to the limit as achievable with least amount of variability. DoE experimental processes are based on a mathematical foundation, thus they deliver information for a specific amount of information, resulting in experimental resources and improved efficiency. It determines the operational ranges that ensure completed product quality by exploring the operational space for all selected inputs in connection to a given response or reactions of a process. DoE can be utilized for a variety of purposes, ranging from factor screening through process optimization. Using DoE, it is also possible to monitor many responses at the same time, making it an extremely effective technique in industries like pharmaceuticals, wherein quality is accomplished by optimizing multiple product features. When dealing with mixed components, significant use of DoE quite common in the formulation development domain. When correctly incorporated for process understanding, optimization, and monitoring, DoE and SPC tools have such a clear greater efficacy; consequently, their usage in QbD method is particularly beneficial.[2]

8 Role of statistics in pharmaceutical development

Process monitoring and improvement are integrated into existing studies and statistics methods. Quality control using statistical approaches is a new and advanced subdivision of industry that identifies factors that impair the quality and optimal productivity.[13] SPC is a flexible tool that can help healthcare professionals navigate growth and achieve the monitoring of patients' health status.[5] SPC tools can assist performance management professionals and scientists in making an informed decision based on statistical reasoning.[10] The major role of the statistical approach in evaluating the data accumulated from manufacturing procedures based upon which a decision is given for monitoring and controlling the variation.[2] To meet the FDA's demand, the pharmaceutical organisations have moved their focus on gaining efficient knowledge of their manufacturing procedures and they also aim to estimate the risk associated with Out of Specification (OOS) and Out of Trend (OOT) products. In accordance to meet the parameters set as per FDA, the industries have started to utilize a broader aspect of statistical approach over the conventional techniques, promoting initiatives such as PAT for improved technology transfer.[1] Statistical tools could be utilised for obtaining the retrospective validation to ensure that quality attributes are complying as per the specifications.[8] Cur- rent research shows the use of statistics in Non-clinical and clinical testing. In pharmacovigilance and epidemiology, many statisticians are contributing. Over the last 20 years, statistics has expanded massively. Statistics play a part wherever quantification is required. Statisticians are a major element in the establishment of innovative pharmaceutical products because of their ability to think in terms of variability.[14] In today's clinical growth, bio-statistics is a well-established function. The statistical approach quickly adapted for taking tasks in research trials, and statistician is now a key element in clinical study design. Today, many statisticians work on operational activities such as composing analysis plans, paperwork, validation of programs, and report writing.[15] Statistics can be extremely useful in establishing experimental designs and trying to draw relevant conclusions from gathered data.[16] In the pharmaceutical sector, organizations need to work on various domains to comply with the product's quality attributes. Statistical approaches and concepts can be applied in diverse manners among the different operational fields of pharmaceutical and

biological sciences like drug discovery, prediction modeling of any disease, statistical aspect of non-clinical studies, process monitoring during manufacturing, application of SPC and its tools such as the design of experiment and control chart, development of bio-marker, competitive intelligence, pharmacovigilance, and epidemiological research.[15]

9 Conclusion

Developments of new technologies are becoming extremely complex and costly hence, the pharmaceutical industry is experiencing profound change. In today's operational setup, statistics combine operational and strategic work. Pharmaceutical development today is divided into different pathways, each of which necessitates the use of specific statistical methods. Statistical societies and institutions should adapt their training programs for statisticians employed in the pharmaceutical industry. It will be critical for statisticians to actively develop and seize opportunities as the pharmaceutical industry grows. Statistical societies and institutions should adapt their training programs for statisticians employed in the pharmaceutical industry.

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