EDITORIAL

Drug Standardization: Its Regulation and Methods for Drug Testing

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Standardization of drugs is an evolving process, aiming to ensure safety, efficacy and quality of the drugs. The amount of drug substance and its release profile in every drug product should be uniform, within specified limits so that the required dose is delivered to the human body. This uniformity must align with the standards laid down in the pharmacopoeias, drug indexes, formularies and other books defining standards and specifications. All drug products manufactured by all the drug manufacturing facilities must be uniform and the product should be free of impurities for patient's safety and to avoid toxicity. [1]

Many countries have developed their own pharmacopoeias, like United States pharmacopeia (USP), British pharmacopeia (BP), International pharmacopeia (Ph. Int) and Japanese pharmacopeia (JP) and these are the most widely used pharmacopeias all over the word as well. Pakistan has not developed its own pharmacopeia, so the drug testing is relied upon USP and BP standards. There are approx. 11,000 prescription drugs actively marketed in Pakistan and sold through licensed pharmacies. Over the counter (OCT) products such as pain, cold, flu medicines contribute to significant market in our country as well. Collaborative efforts between the government, academia and industry stakeholders are essential to keep pace with global standards. [2]

A brief overview of bindingness of regulations according to state of law, state of technology and state of science is shown in Table I. In Pakistan, it is regulated by both Ministry of **National Health Services Regulations and Coordination** (NHSR&C) and **Drug Regulatory Authority of Pakistan** (DRAP). They ensure that drugs manufactured and distributed in Pakistan meet international standards. [3, 4] **National Essential Medicine List** (NEML), previously known as **National Formulary of Pakistan** (NFP) is an official publication that lists essential medicines approved for use within Pakistan. It has crucial role in promoting rational drug use and ensuring consistent health care standards. [5] **The International Council for Hormonisation of Technical Requirements for Pharmaceuticals for Human Use** (ICH) is distinctive in bringing together the pharmaceutical industry and the regulatory bodies to collaborate scientific and technical aspects of drugs and thus leading to the development of its guidelines. **Pakistan National Pharmacovigilance Center** (PNPC) was established in collaboration with US in year 2017, and became member of Uppsala Monitoring Center (UMC) by 2018. [6] **The National Pharmacovigilance Centre** (NPC) at DRAP highlights both legal requirement and

Table I: Binding and Non-Binding Regulations

		USA	International	Pakistan	British
Must be like this (State of law)	Law	Federal Food, Drug, and Cosmetic Act	-	The Drugs Act 1976 and DRAP* Act 2012	Medicine Act 1968, Misuse of Drugs Act 1971, Misuse of drugs Regulation 2001
	Rules and Regulation	Code of Federal Regulations	-	The Drug Rule 1976, 1978, 1986	MHRA*
Should be like this (state of technology)	Standard	USP*	ICH*, ISO*, WHO*, PIC/S*	NFP*, USP/BP*	BP*
	Guidance	FDA* Guidelines	PDA/ISPE*	PNPC* (GMP* + ICH* + WHO guidelines)	British Guidelines, EMEA* Notes for guidelines
Can be like this (State of science)	Publication	Articles, reviews, systemic analysis and meta-analysis of peer- reviewed, high impact factor journals			

BP: British Pharmacopeia, **DRAP**: Drug Regulatory Authority of Pakistan, **EMEA**: European Medicines Agency, **FDA**: Food and Drug Administration, **ICH**: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, **ISO**: International Organization for Standardization, **MHRA**: Medicines and Healthcare products Regulation Agency, **NFP**: National Formulary of Pakistan**, PIC/S**: Pharmaceutical Inspection Co-operation Scheme, **USP:** United States Pharmacopeia, **WHO**: World Health Organization

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Received: September 02, 2024; Accepted: September 13, 2024

https://doi.org/10.57234/jiimc.september24.2234

social responsibility. Effective pharmacovigilance not only ensures product quality and patient safety but also strengthens a company's reputation, credibility, and competitiveness in the global market. Non-compliance of binding regulations can lead to legal consequences, such as fines, penalties, or the suspension of licenses.[7]

The drug manufacturer companies label their products to indicate which standard was used to access the quality of finished drug product, this is commonly known as specifications. For example, if the manufacturer has claimed on the label of his product, that it complies with USP specifications, then it means that this product is tested as per testing method of US pharmacopeia. If the drug fails any quality test mentioned in its monograph, then it will be considered substandard drug product i.e. unsafe and ineffective. The drug testing methods can be chemical, biological or immunological, depending on the nature of drug. However, these also face distinct challenges that must be addressed to maintain the integrity of drug development and therapeutic applications.

Chemical assays have long been foundation of drug standardization, providing precise quantification of active ingredients. They involve the use of chemical methods like titrations, chromatographic and spectroscopic techniques. Their reliability and accuracy make them indispensable, particularly in the production of generics. The exact chemical nature of the drug must be known, and it should be available in pure form. Nevertheless, the complex chemical composition of some drugs and the need for increasingly sophisticated technologies highlight the ongoing challenge of maintaining the consistency across different batches and manufacturers.[8]

Bioassays, on the other hand, offer a more holistic approach by measuring the biological activity of a drug. These assays are crucial for assessing some antibiotics like cholistimethate, neomycin etc. A chemical assay is performed to identify the quantity of cholistimethate, then biological assay is done to measure its activity in IU. Biologicals (like insulin, erythropoietin, heparin, adalimumab) are checked for biosimilarity too, which is as crucial as their assays. Biosimilar means that it has been grown in same strain, with same protein sequence and folding. Moreover, the genetic material used in creating recombinant cell/organism should be 100% same. For example, if any pharmaceutical company wants to have multiple sources of insulin bulk, then insulin coming from all sources must be biosimilar. The inherent variability in the biological systems can lead to inconsistencies, necessitating rigorous validation and standardization of these assays to ensure reproducibility. [9] So, there is always ongoing research to shift analysis from bioassays to chemical method. For example, for insulin it has been changed to high-performance liquid chromatography (HPLC) method. [10] Among these bioassays, the 3-point and 4-point assays are particularly noteworthy. The 3-point assay, utilizing two submaximal doses of the standard and the one dose of unknown drug, allows for a reliable estimation of potency through response plotting. The 4-point assay, which involves two doses of both the standard and unknown drug, enhances the accuracy by calculating the log ratio of doses.[11]

Immunological assays are very specific and are used mainly for vaccines. A specific dose of vaccine is given to animals to access the immunogenicity of vaccine, then their blood is checked for antibodies. A specific dose of vaccine is required to make specific amount of antibodies. When desired level of antibodies is produced then this vaccine is considered “up to the standard”. Thus, this allows detection and quantification of therapeutic antibodies. While these assays are highly sensitive and specific, they are also susceptible to interference and cross-reactivity, posing challenges in ensuring their accuracy and reliability in clinical setting. They have also gained prominence with the advent of personalized medicine.[12]

In short, the integration of drug testing in drug standardization presents a multi-faceted approach. When harmonized, it can lead to more robust and reliable therapeutic products. However, the challenges associated with each method underscore the need for continuous innovation. As we look to the future, it is imperative that the researchers, regulatory bodies, and industry stakeholders should collaborate to enhance these methods, address their limitations, and develop new strategies for standardization.

Ultimately, the goal remains the same: to ensure that every patient receives a safe and effective medicine,

https://doi.org/10.57234/jiimc.september24.2234

regardless of where or how it is manufactured. It will continue to evolve as the drug development becomes more complex, and it is our responsibility to guide this evolution towards standards of quality and safety.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.