International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 2; March 2018; Page No. 04-08

Regulatory framework of pharmacogenomics align with recent trends in USA

[1] Pallavi A Ghodke, [*2] Dr. Jignesh S Shah, [3] Dr. Dilip G Maheshwari

[1] M.Pharm, LJ Institute of Pharmacy, Ahmedabad, Gujarat, India

[2] Associate Professor, Department of Quality Assurance and Pharm Regulatory Affairs, LJ Institute of Pharmacy, Ahmedabad, Gujarat, India

[3] Head of the Department of Quality Assurance and Pharm Regulatory Affairs, LJ Institute of Pharmacy, Ahmedabad, Gujarat, India

Abstract

Pharmacogenomics is the study of how genes affect a person's response to drugs. Genomics is playing a major role in identifying information from the human body and applying it to current drug therapy. It raises significant regulatory complexities for the diagnostics arm of regulatory agencies. As it contains genetic testing (E.g. DNA, RNA), complexity of genetic arrangements makes it difficult to find correct gene that affect the drug response. As currently FDA is recommending the use of pharmacogenomics in drug development the USFDA regulations assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome, specifically DNA sequence variants, could affect a drug's pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety. The purpose of the regulations is to provide advice on general principles of study design, data collection, data analysis in early-phase trials, labelling and data submission.

Keywords: pharmacogenomics, regulatory requirements, early phase trial, data submission, labelling

Introduction [1, 2, 3]

"Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup."

Genomics is playing a major role in identifying information from the human body and applying it to current drug therapy. It has produced a new era of individualized drug therapy for patients to achieve higher efficacy and safety. Due to the enhanced development of today's technologies, the long-term benefits of pharmacotherapy management are becoming closer to implement in clinical practice.

It has been recognized through several healthcare management facilities that individuals respond differently to medications, and the correlation of the drug medication to the efficacy has led more pressure on physicians and pharmacists to apply the concept of personalized medicine into clinical practice.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions).

Pharmacogenomics aims to uncover genetic variants that influence drug response in order to tailor a patient's therapy based on their genetic make-up. At the same dose, a group of patients can experience no therapeutic effect while others develop serious adverse drug reactions (ADRs). This can lead to expensive and potentially life-threatening consequences. Each year in the United States alone, approximately 2 million people suffer drug-related adverse events, accounting for 7% of all hospital admissions. More importantly, serious drug toxicities cause over 100,000 deaths with costs estimated to be over $30–$100 billion dollars annually.

Initial pharmacogenomics studies have focused on candidate genes that encode proteins hypothesized to be involved in the absorption, distribution, metabolism and excretion (ADME) of specific drugs. Completion of the Human Genome Project, combined with advances in high-throughput genotyping and DNA sequencing, has shifted the focus of pharmacogenomics studies to explore a broader, genome-wide spectrum of potential genetic contributions. These studies have uncovered novel genes and biological pathways that influence drug response. By understanding a direct relationship between an individual's genotype and drug response, pharmacogenomics has the potential to empower clinicians with the ability to optimize the effectiveness and safety of drug therapy.

Applications of Pharmacogenomics [4]

Pharmacogenomics has the potential to provide modified drug treatment based on genetic alternation in efficacy and side effects. Some of the important applications of pharmacogenomics are given below:

- **More powerful medicines:** Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases.
- **Better, safer drugs the first time:** Instead of the standard trial-and-error method of matching patients with

the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning.

- **More accurate methods of determining appropriate drug dosages:** Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics.
- **Advanced screening for disease:** Knowing one's genetic code will allow a person to make adequate lifestyle and ecological changes at an early age so as to avoid or lessen the severity of a genetic disease.
- **Better vaccines:** Vaccines made of genetic material, either DNA or RNA, promise all the benefits of existing vaccines without all the risks.
- **Improvements in the drug discovery and approval process:** Pharmaceutical companies will be able to discover potential therapies more easily using genome targets.
- **Decrease in the overall cost of health care:** Decreases in the number of adverse drug reactions, the number of failed drug trials, and the time it takes to get a drug approved.

Why Pharmacogenomics needs to be regulated [4]?

Pharmacogenomics into clinical practice has the potential to improve efficacy and reduce toxicity, by choosing "the right drug for the right patient in the right disease at the right dose".

Pharmacogenomics raises significant regulatory complexities for the diagnostics arm of regulatory agencies. Firstly, there is the technical complexity of the tests and the need for standardization of platform technologies such as microarrays, and then there is the challenge of validating the results of tests that may analyses a vast number of biomarkers simultaneously.

As it contains genetic testing (E.g. DNA, RNA), complexity of genetic arrangements makes it difficult to find correct gene that affect the drug response. Certain ethical issues also come regarding handling of genetic samples and disclosing their data. Also depending on genetic information it is complicated process for physicians to write correct prescription. This also comes with another issue towards the pharmaceuticals as they need to re-label the drug product for which the Pharmacogenomics data is found or available.

Certainly this new developments will bring fresh challenges, and complexity towards regulatory as stringent regulations also needs to rationalize the frame work for Pharmacogenomics regulations. Regulatory agencies are keen to achieve a harmonized approach to this area and have made some progress in this regard.

Currently FDA is not only recommending the use of Pharmacogenomics in drug development but beginning to explore how they can forge a common approach. The development of transnational policies and regulatory standards and processes may assist regulators in guiding and promoting the adoption of Pharmacogenomics. Along with the FDA another leading regulatory authorities of Europe and Canada are also looking forward in the development of Pharmacogenomics field which keeps enormous rooms of growth as regulatory agencies to see Pharmacogenomics as a promising opportunity to improve the safety and efficacy of medicines. As an emerging area of clinical science it will require regulatory flexibility and a willingness to grow with industry.

Regulatory aspects of Pharmacogenomics as per USFDA [5]

The FDA is leading the way, in part because it simply has far greater resources, in part because the Agency has prominent champions of pharmacogenomics in its leadership. The work of the FDA in this area is marked by a high level of engagement with industry.

The USFDA regulations assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome, specifically DNA sequence variants, could affect a drug's pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety. This guidance provides pathway on when and how genomic information should be considered to address questions arising during drug development and regulatory review.

The purpose of the regulations is to provide advice on general principles of study design, data collection, data analysis in early-phase trials, labelling and data submission.

A) Regulations for Clinical Studies

Genetic differences between individuals can affect virtually all aspects of a disease and its treatment, including the rate of disease occurrence; the risk of disease progression or recurrence; the drug or drug class most likely to provide benefit; the therapeutic dose; the nature and extent of beneficial responses to treatment; and the likelihood of drug toxicity.

Pharmacogenomics (PGx) studies can contribute to a greater understanding of inter individual differences in the efficacy and safety of investigational drugs. PGx research depends on the collection and use of biological samples to generate data.

Across the drug development field, genomic data may be used for several purposes, including

(1) Identifying the basis for PK outliers and inter subject variability in clinical response;
(2) Ruling out the role of polymorphic pathways as clinically significant contributors to variable PK, PD, efficacy, or safety;
(3) Estimating the magnitude of potential drug–drug interactions;
(4) Investigating the molecular or mechanistic basis for lack of efficacy or occurrence of adverse reactions; and
(5) Designing clinical trials to test for greater effects in specific subgroups (i.e., use in study enrichment strategies).

In vitro studies of metabolism, transport, or drug targets could help identify the need for human PGx studies and contribute to the design and analysis of those studies. The following types of clinical pharmacology studies provide opportunities to prospectively integrate PGx factors for assessing inter individual variability and its implications for subsequent clinical studies.

i) PK and PD Studies in Healthy Volunteers

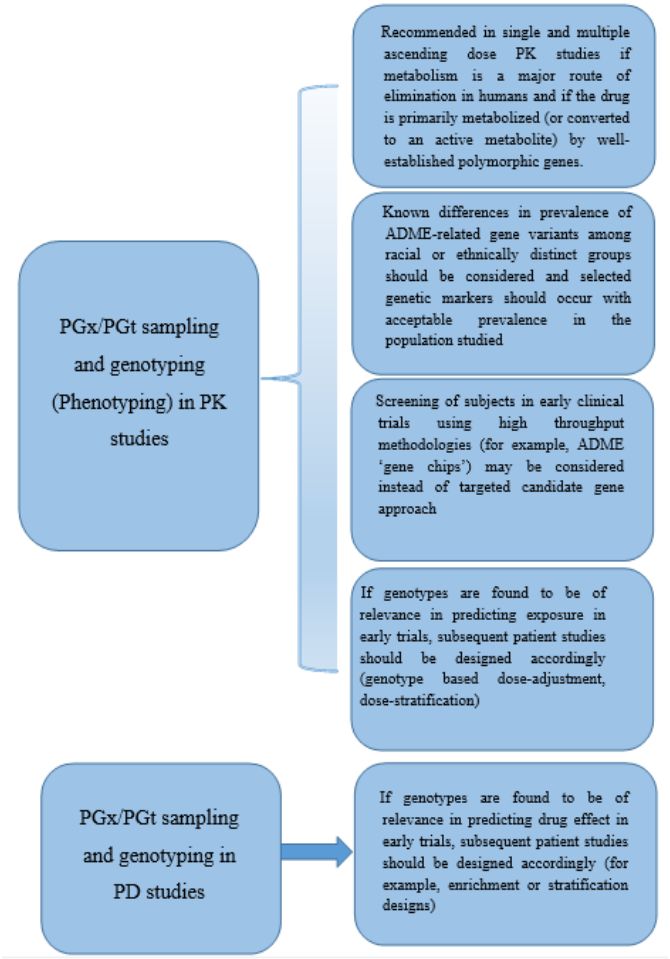

Fig 1

ii) PK and PD Studies in Patients

If important variability in PK of active species is observed in healthy volunteers, the significance of this finding should be considered in the design of subsequent studies in patients e.g., in dose/response studies in genotype-defined subgroups. This knowledge can be used in the subsequent design of other clinical trials, for example, by using genotypes to

(1) Select patients for trials e.g., enrichment with potential responders and elimination of patients likely to experience toxicity;
(2) Stratify groups within trials; and
(3) Adjust doses in trials.

These steps can increase the average effect, decrease toxicity, and improve the chances of overall success of the study.

iii) Dose-Response (D/R) studies

D/R studies are usually conducted in phase 2 using biomarkers or clinical end points that are relevant to clinical efficacy and safety to

(1) Provide proof of concept,
(2) Identify doses for phase 3 trials, and
(3) Establish dose-response for relatively common adverse effects.

Both PK differences i.e., metabolism and transport and PD differences e.g., shift in concentration-response curves can lead to differences in D/R in individuals. If previous PK and/or PD studies suggest that a genotype is important in influencing systemic exposure-response or efficacy and safety responses, D/R studies that stratify dose groups by genotype or specific genotype-guided D/R studies (PK adjusted D/R or even a concentration controlled study) should be considered.
Genetic information can be included in D/R or concentration/response (C/R) models much like any other clinical covariate. Explanations related to genomic factors can sometimes be convincing on their own or can lead to hypotheses to be tested in further studies, where patients would be stratified by genotype.

B) Regulations for Data Submission [6]

This section of regulation provides guidance intended to facilitate scientific progress in the field of Pharmacogenomics and to facilitate the use of pharmacogenomics data in drug development. It provides recommendations to sponsors holding investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) on

(1) When to submit pharmacogenomics data to the Agency during the drug or biological drug product development and review processes,
(2) What format and content to provide for submissions, and
(3) How and when the data will be used in regulatory decision making.

There was always an issue for pharmaceutical sponsors have been reluctant to embark on programs of Pharmacogenomics testing during FDA-regulated phases of drug development because of uncertainties in how the data will be used by FDA in the drug application review process. This process of FDA clarifies the policy in this area. Sponsors submitting or holding INDs, NDAs, or BLAs are subject to FDA requirements for submitting to the Agency data relevant to drug safety and effectiveness. This interprets FDA's regulations for investigational and marketing submissions, with the goal of clarifying FDA's current thinking about when the regulations require pharmacogenomic data to be submitted and when the submission of such data would be welcome on a voluntary basis with the set.
This guidance makes an additional distinction between known valid biomarkers that have been accepted in the broad scientific community and probable valid biomarkers that appear to have predictive value for clinical outcomes, but may not yet be widely accepted or independently verified by other investigators or institutions.

Voluntary Genomics Data Submission (VGDS)

The FDA invites submission of exploratory pharmacogenomic data on drugs or candidate drugs whether or not the molecules are currently the subject of an active IND, NDA, or BLA. Exploratory genomic data may result from, for example, microarray expression profiling experiments, genotyping or single-nucleotide polymorphism (SNP) profiling experiments, or from other studies using evolving methodologies that are intended to facilitate global analysis of gene functions.

VGDSs will be reviewed by the Interdisciplinary Pharmacogenomic Review Group (IPRG). The review process is intended to ensure that scientific staff experienced in the evaluation of genomics studies participate first-hand in analysis and review of the data. Any data evaluation will be conducted for scientific and informational purposes - not for regulatory decision making. If additional information becomes available after a sponsor submits a VGDS that triggers the submission requirements under 21 CFR Part 312, 314, or 601, the sponsor must resubmit the data to the investigational or marketing application and should follow the appropriate algorithm described in this guidance for a required submission.

For candidate drugs or standalone voluntary submissions (submissions not related to any application), sponsors should submit the package clearly labeled as VOLUNTARY GENOMIC DATA SUBMISSION (VGDS). For VGDSs related to an existing IND, NDA, or BLA, please include the reference number on the voluntary submission cover sheet.

Submission of Pharmacogenomics Data during IND Phase

In case the patients were dosed based on genotypes, this genetic information would be required as part of IND submission but not for VGDS.

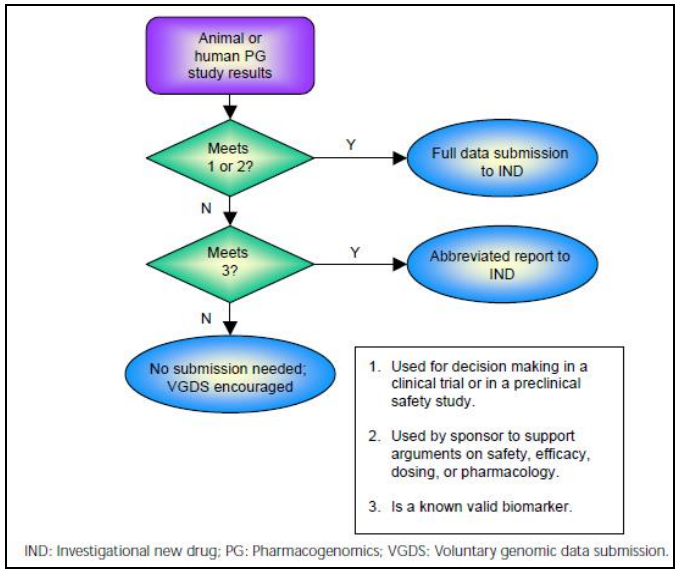

Fig 2: Data Submission to an IND

Pharmacogenomics data that must be submitted to IND as per 21 CFR Part 312 requirements are

(1) The test results are used for making decisions pertaining to a specific clinical trial, or in an animal trial used to support safety (e.g., the results will affect dose and dose schedule selection, entry criteria into a clinical trial safety monitoring, or subject stratification).

(2) A sponsor is using the test results to support scientific arguments pertaining to, for example, the pharmacologic mechanism of action, the selection of drug dosing and dosing schedule, or the safety and effectiveness of a drug.

(3) Test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or the test is a known valid biomarker for a safety outcome in animal studies. If the information on the biomarker is not being used for purposes 1 or 2 above, the information can be submitted to the IND as an abbreviated report.

Submissions that are not required for IND but are encouraged by FDA to submit voluntary in VGDS are

1) Information is from exploratory studies or is research data, such as from general gene expression analyses in cells/animals/humans, or single-nucleotide polymorphism (SNP) analysis of trial participants.
2) Information consists of results from test systems where the validity of the biomarker is not established.

Submission of Pharmacogenomics Data during NDA, BLA or Supplement

Provide full (complete) reports on pharmacogenomic investigations intended by the sponsor to be used in the drug label or as part of the scientific database being used to support approval as complete submissions (not in the form of an abbreviated report, synopsis, or VGDS), including information about test procedures and complete data, in the relevant sections of the NDA or BLA.

If the data needs to be submitted for already approved NDA or BLA application than results of nonclinical or clinical pharmacogenomic investigations on known or probable valid biomarkers must be submitted in the annual report as synopses or abbreviated reports.

If Pharmacogenomic study results of other types do not meet the submission requirements outlined in the regulations as per 21CFR Part 314.81. However, such reports can be voluntarily submitted to the NDA or BLA as a VGDS.

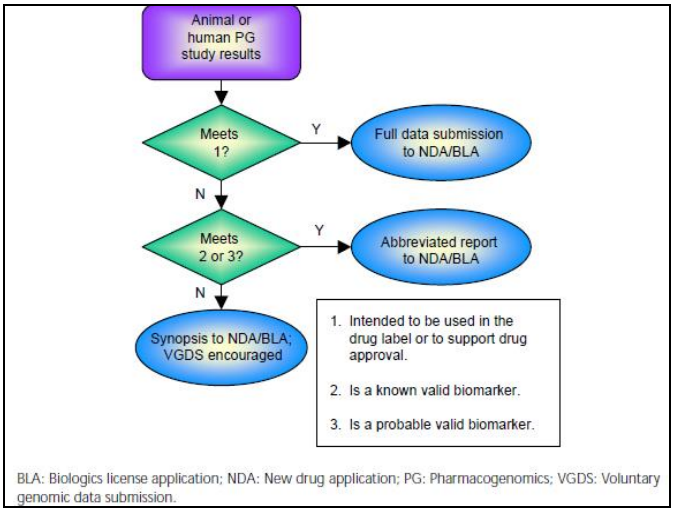

Fig 2: Data submission to NDA or BLA Application

For required submissions, complete reports, abbreviated reports, or synopses of pharmacogenomic studies should be submitted to INDs, NDAs, or BLAs in the usual manner.

C) Regulations for Inclusion of Pharmacogenomics information in Labelling[5]

In general, labeling should include information on PGx only if it is useful to inform prescribers about the impact (or lack of

impact) of genotype on phenotype; or to indicate whether a genomic test is available, and, if so, to indicate whether testing should be considered, is recommended, or is necessary. If applicable, a "Pharmacogenomics" subsection should be included in the Clinical Pharmacology section of the prescribing information (PI) and should include clinically relevant data or information on the effect of genetic variations affecting drug therapy.

When the information has important implications for the safe and effective use of a drug and the consequences of the genetic variations result in recommendations for restricted use, dosage adjustments, contraindications, or warnings, this information will be summarized in other sections of the labeling, as appropriate (e.g., Boxed Warning, Indications And Usage, Dosage And Administration, Contraindications, Warnings And Precautions, Drug Interactions).

Detailed information about clinically relevant genetic information should be consolidated into the most appropriate labeling section. The following Table shows types of PGx information that could appear in various sections of labeling.

Table 1: PGx Information to be covered in Label

Section of Label	Types of Information
Indications and usage	PGx information related to proper patient selection (e.g., the need for PGx testing)
Dosage and administration	Dosing recommendations for subgroups of patients based on genetic makeup
Boxed warning, contraindications, warnings and precautions, and/or adverse reactions	PGx information affecting drug safety
Warnings and precautions and use in specific populations	Genotype(s) that are known to be associated with an adverse reaction in a specific population
Drug interactions	Relevant information concerning the role of genetic variations in drug-drug interactions, and the clinical consequences of the combination of genetic polymorphisms in protein(s) in the context of the drug's metabolism, transport, and action
Clinical pharmacology	PGx impact on PK or PD
Clinical Studies (if studied and the evidence is substantial; or if observed neutral findings (i.e., lack of a pharmacogenetic effect) would be pertinent clinical information)	Efficacy differences related to PGx

Conclusion

Personalized medicine through Pharmacogenomics as choosing the right drug, and the right dose, for the right patients based on patient's genetic makeup-is gradually being realized in many countries now a days. Yet, the practice of pharmacogenomics was lagging behind. As next-generation gene sequencing technology advances quickly, previous technical challenges for performing pharmacogenomic studies or practices in this have been mostly resolved by the help of the guidance provided by USFDA. This study gives insight on how the clinical study has be performed in the field of Pharmacogenomics along with the data submission for the IND, NDA or BLA application. Also gives a glance on the kind of information that can be added in the label of the Pharmaceutical product. Though this process makes easy to follow the regulations awareness and appropriate training can have the capacity to provide expert pharmacogenomic supports for both physicians and patients.

Acknowledgement

The authors are thankful to Dr. K. Pundarikakshudu, Director of L.J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities and encouragement to carry out the work.

Reference

1. Kumar V, Majumdar D. Pharmacogenomics - The New Trend for Personalized Medicine, Indian Journal of Pharmaceutical and Biological Research (IJPBR). 2016; 4(1):39-49.
2. Lee JW, Aminkeng F. The emerging era of pharmacogenomics: current successes, future potential, and challenges, https://www.ncbi.nlm.nih.gov /pubmed/24684508
3. Stuart Hogarth, Dr. Kathy Liddell. Regulating pharmacogenomics an overview of developments in various countries and industry response to regulatory initiatives. A report for Health Canada, 1-57.
4. Aneesh TP, Sonal Sekhar M. Pharmacogenomics: The Right Drug to the Right Person.
5. USFDA Guideline. Guidance for Industry- Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling (Last Accessed 02 Jan 2018)
6. USFDA Guideline. Guidance for Industry-Pharmacogenomic Data Submissions. (Last Accessed 01 Jan 2018)
7. Gouleberto Ruano, Jerry M. Collins. Pharmacogenomics data submission to the FDA: clinical pharmacology case studies, Special Report 2, Pharmacogenomics. 2004; 5(5):513-517.