Pharmacogenomic data submissions to the FDA: clinical pharmacology case studies

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Introduction

This special report summarizes the key discussion points of case studies presented during the clinical pharmacology track of the FDA/DIA/PWG/PhRMA/BIO workshop on 'Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal' held in Washington DC in November last year [1,2].

At the 2002 FDA-PWG-PhRMA-DruSafe Workshop [3], the potential use of pharmacogenomics in the early clinical development of a drug was recognized, including in safety, tolerability, pharmacokinetic/pharmacodynamic (PK/PD), dose-ranging, drug–drug interaction and proof-of-concept studies. A distinction was drawn between the uses of variation at the chromosomal DNA level (single nucleotide polymorphisms [SNPs] and haplotypes) versus variation in gene expression (mRNA and protein). Many of the published pharmacogenetic data to date can be traced to inherited DNA variations affecting drug-metabolizing enzymes. Recently, data has emerged on drug targets, drug transporters and pharmacological pathways as 'candidate' genes to predict outcome, efficacy, or safety. Protein mass spectra have also begun to impact on predictions relevant to clinical pharmacology. Beyond differences in sample collection operations (imposed by the fact that genomic DNA is stable and invariant whereas RNA and protein are tissue and time specific), subsequent discussions are applicable to all pharmacogenomic data.

The fundamental question of pharmacogenomics is whether an initial, random segregation of gene markers in the patient population prior to drug administration can be 'organized' according to drug response in the same patients. Is the distribution of a given marker different between responders and non-responders or between subjects experiencing adverse events (AEs), or not? If it is, then a pharmacogenomic association exists between drug response and the segregated gene markers.

Issues specific to the various technologies and data sets are illustrated in the cases that were discussed in this second workshop. These cases highlight 'real world' scenarios in drug development and are meant to illustrate the potential utility of voluntary genomic data submissions (VGDS) and the basis for submitting information to the FDA as voluntary or required pharmacogenomic data submissions [4,101].

Case studies and workshop discussions

Scenario 1: Drug metabolism genes

A polymorphism of an enzyme in the glucuronidation pathway is shown to be associated with increased creatine kinase levels in response to statin therapy and risk of rhabdomyolysis. Individuals with the marker genotype are excluded from the trial to enhance the safety profile of a new statin for high-dose indications. The marker is not used for the trial on the low-dose indication.

Discussion

This case illustrated an emerging metabolism marker separate from the known, valid drug metabolism markers (e.g., *CYP2D6* and *CYP2C19*). The consensus was that because patients were excluded based on genotype, at least for one arm of the trial, the genetic information would be required as part of the investigational new drug application (IND), and not the subject of VGDS (Figure 1).

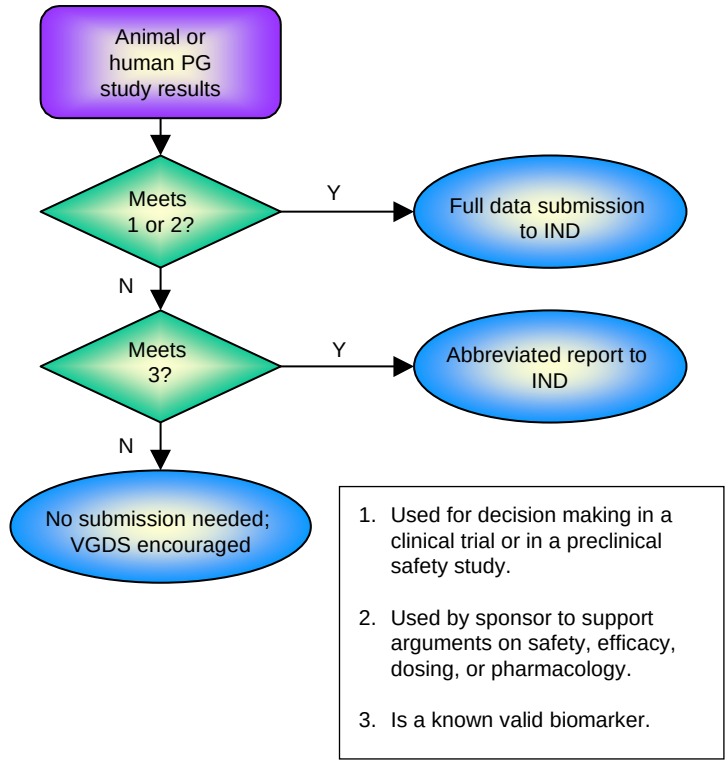
Scenario 2: Drug transporter genes

ABCB1 (multi-drug resistance 1 [MDR1]) markers are utilized as a surrogate for an anti-seizure drug level in a dose-ranging study. The *C3435* allele for high levels of drug efflux transporter correlates with low response. The *T3435* allele for low activity of drug efflux transporter correlates with high response. The sponsor proposes to achieve the same response based on genotype status using two different regimens. Individuals with the *T3435* allele receive a lower dose than individuals with the *C3435* allele.

Discussion

This case illustrated another emerging marker. The consensus was that because patients were dosed based on genotype, the genetic information

Figure 1. Submission of data to an investigational new drug [4,101].



IND: Investigational new drug; PG: Pharmacogenomics; VGDS: Voluntary genomic data submission.

would be required as part of the IND and not the subject of VGDS (Figure 1).

After presentation of cases 1 and 2, various issues arose concerning the determination of the validation status of this type of marker. For example, if one sponsor considered a certain measurement to be a non-valid biomarker but the FDA, with additional information from other sources (e.g., other applications or literature), considered it to be a valid biomarker, what would the process be to inform the sponsor? What if the source of alternative information is proprietary and patent protected by another sponsor but gathered by the FDA as part of its regulatory purview. Does the informed consent for genetic testing in such a trial cover voluntary submission to the FDA? Are the only known valid biomarkers metabolic genotypes? What other features in the laboratory analysis of such markers would be required by the FDA, such as Clinical Laboratory Improvement Amendments (CLIA) certification? Does CLIA certification automatically validate a biomarker? It was suggested that the FDA provide a list of known valid biomarkers in the guidance, as well as their scientific rationale. Furthermore, it was suggested that the FDA regularly update such information and provide an ongoing tally of the biomarker roster, and each marker's valid versus probably valid status.

Scenario 3: Receptors

A sponsor has developed a new inhaler device and nebulizing technology for emergency asthma treatments with albuterol. Patients would be recruited and screened for genotyping for assignment to five therapeutic arms defined by the five most common haplotype pairs. The design required an equal number of patients in each of the five arms, and included a gradual screening out of patients with the common haplotype pairs and selective inclusion only of patients with the low frequency haplotype pairs, in order to achieve balance among the arms. Various effective doses of albuterol were administered in the initial dose-ranging study by adjustments on the device's nebulizing technology. At low delivery dose the various groups evidenced pulmonary function improvements in response to albuterol, which

were predictable by haplotype pair. At this point, the sponsor chose to escalate the delivery of albuterol with the inhaler device until the haplotypically determined differences were effectively abolished among arms. The subsequent clinical development did not include genotyping and used only the high delivery setting of the device.

Discussion

This case illustrated the enrichment of a trial with patients having equal genetic representation. Whether these haplotype markers in this study are valid or probably valid was not an issue, as the study incorporated them in the design of the trial and, thus, should be submitted in filings to the agency (Figure 1).

Scenario 4

The *5HT1A* Gly22 allele is shown to be associated with favorable response to selective serotonin re-uptake inhibitor antidepressants. Patients are recruited according to genotype to enrich for but not limit, the trial for responders.

Discussion

This case illustrated genotype specified recruitment of patients. The consensus was that such design would require genetic information to be submitted as part of the IND (Figure 1).

Enrichment of a trial for responders according to genetic markers could compensate for lower frequency in the general population. Related issues arose concerning the nature and extent of such recruitment criteria. For example, if the genetically defined population is < 200,000, would the submission qualify for orphan drug products status? What if the recruitment had been carried out blinded to the genotype but the size of the cohort scaled according to the expected genotype frequencies to capture sufficient numbers of patients in a less frequent genotypic class? Would such retrospective stratification warrant the data analysis to be required or would it be appropriate for VGDS. In such cases, the situation was much less clearcut, but the consensus was that it should be covered by VGDS. A combination of scenarios could arise if part of the analysis is performed with validated biomarkers and some with 'probably valid' experimental markers. Would the sponsor submit validated and non-validated biomarkers separately? This issue was further discussed in Scenario 6 below.

Scenario 5: Drug-induced QT prolongation

A sponsor is developing a previously known phosphodiesterase inhibitor for a new indication. In a retrospective analysis, individuals evidencing drug-induced QT prolongation on electrocardiogram assessments were rerecruited and consented for genetic analysis of carrier status for QT syndrome mutations. Data from individuals with any of these mutations were then excluded from the safety analysis of the drug.

Discussion

This case motivated considerable debate. One current opinion was that the data would be amenable to VGDS since the exclusion was performed analytically through retrospective stratification and required no actual screening out of patients. However, as critical data were excluded to support safety, the genetic information used to exclude patients could not be considered VGDS and should be submitted as part of the IND/new drug application (NDA)/biologics license application (BLA) (Figures 1 and 2).

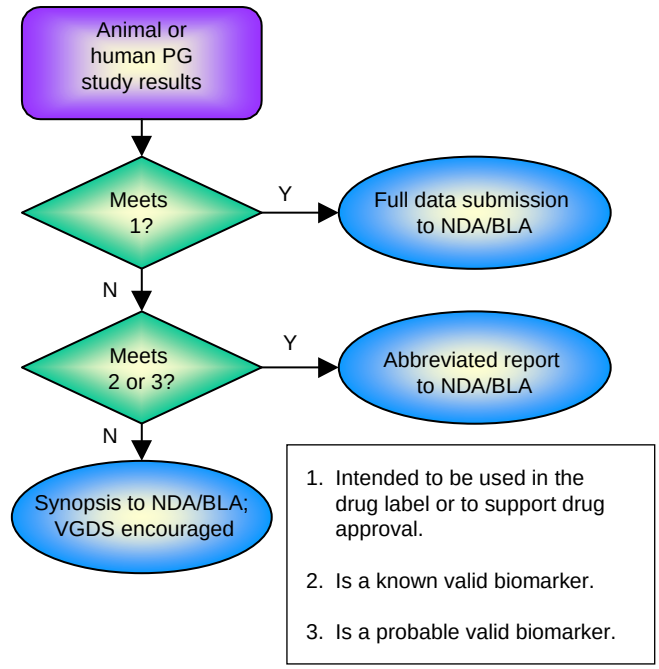
The issue of biomarker validation status again came to the fore, as there are no drug-induced QT prolongation markers but various mutations leading to the disease long QT syndrome.

The labeling implications, including whether the test would be required, were controversial because of the safety implications. If patients were excluded from safety analysis, then the label must exclude those patients, as safety data were not reported on those genotype classes.

Scenario 6: Gene expression

In a Phase II clinical study of neoadjuvant chemotherapy, gene expression profiling was performed on primary breast cancer tissue biopsies obtained prior to chemotherapy. Gene expression profiles were correlated with tumor response to compound A as measured by tumor size changes after four cycles of the drug. Response of the tumor to neoadjuvant chemotherapy is considered a valid surrogate marker of patient survival. In this study, tumor resistance or sensitivity (tumor response) was arbitrarily defined using residual disease percentage to divide the patients into equivalent groups for statistical purposes (patients with ≤ 25% residual disease were called sensitive and those with > 25% were labeled resistant). Using this definition, a 92-gene profile (out of 3000 genes evaluated) was identified that correlated with response to compound A. Interestingly, the prognostic gene set did not contain many genes previously

Figure 2. Submission of data to a new drug application or new biologics license application [4,101].



BLA: Biologics license application; NDA: New drug application; PG: Pharmacogenomics; VGDS: Voluntary genomic data submission.

associated with response to other drugs in this class. This predictor gene set displayed 88% accuracy and 85% sensitivity upon validation on the same sample set. Validation on a limited set of samples that were not used in the derivation of the classifier set was 100% accurate. This exploratory pharmacogenomics study will be used as the basis for the validation of a prognostic expression pattern in a larger Phase III clinical trial. The sponsor plans to utilize the pretreatment expression to stratify patients in the Phase III trial and compare tumor response in the patient subgroups.

Discussion

This case study illustrated the use of DNA microarray data and the process by which it is generated and distilled. The consensus was that the data generated from the Phase II trial, which formed the basis of the hypothesis that the 92-gene profile may correlate with the clinical response, can be VGDS and submitted as an abstract/synopsis in the NDA/BLA submission. For the Phase III trials, since the pretreatment expression will be utilized to stratify patients, the data on the 92 genes from the Phase III trial will need to be submitted to the IND (Figure 1). The data from the other genes (e.g., 2908 genes) can be submitted as VGDS. In order for the VGDS data to be useful, many expressed the opinion that it would be desirable to have the entire data set (3000 genes) included in the VGDS submission. Another opinion was that in order to evaluate the validity of the 92 genes used in the Phase III trials, the FDA would include the 92 genes for a complete report but statistical analysis may require the data from some of the other 2908 genes (i.e., the house-keeping genes) to assure the quality of the study or to affirm the appropriateness of the selection of the 92 genes.

The FDA would benefit from reviewing the format, analytical plan and statistical issues of array data. It was suggested that microarray data should be validated by other technologies (e.g., protein, reverse transcriptase-polymerase chain reaction). However, in the case of patterns composed of a large number of genes, this may not be feasible. To the extent that array technologies introduce learning sets and validation sets in series or in parallel, VGDS should allow non-sequential trials to be presented in a logical fashion but not according to chronology. Participants felt that the guidance needed to address procedural differences

between the IND and NDA/BLA phases of VGDS. Finally, multiple clinical trials may be ongoing to generate the learning and validation data, which is not trackable by conventional reporting requirements. Array data, more than any others, illustrate the need for analytical and statistical standards that would arise from VGDS and cumulative databases collected at the FDA from multiple industry submissions.

Scenario 7: Biologics

A sponsor is developing Immumab, a (hypothetical) mouse-derived humanized monoclonal antibody against tumor necrosis factor, for Crohn's disease. Major histocompatibility complex (MHC) markers previously determined to be predictive of hypersensitivity infusion reactions are genotyped in the entire patient population in a prospective study. Those patients genetically predicted to be at risk of infusion reactions are given intravenous hydrocortisone and intramuscular promethazine 30 min before infusion. With this strategy, infusion reactions to Immumab are lowered from 25 to 10% of patients. The sponsor highlights the reduced AE rate of this trial in the description of the safety aspects of the drug.

Discussion

This case study illustrates a prominent safety consideration for biologics, development of auto-antibodies and hypersensitivity reactions. The consensus was that the data should be reported as part of the BLA because attenuation of predicted side effect was possible by genotyping markers of the hypersensitivity (Figures 1 and 2). The scenario involved no exclusion by retrospective stratification nor actual screening out of patients. Instead hydrocortisone and promethazine were given to patients with a marker of hypersensitivity to reduce the AE rate.

Outlook and expert opinion

There appeared to be no great discordance on cases where submissions are clearly required. However, when debating how the microarray data are to be submitted (either required or as VGDS), participants expressed the urgent need for analytical and statistical standards. Definition of 'known valid' and 'probable valid' biomarkers was central to the discussions. Although some favored the broad definition as listed in the draft guidance, many requested more clarity and that the FDA provide a list of 'valid biomarkers' and their scientific rationale. In addition, the intellectual property issues, the composition of the proposed FDA Interdisciplinary Pharmacogenomics Review Group, and the process of receiving and reviewing VGDS remain critical issues that will need further clarification in the final guidance. Although many participants have already been involved in retrospective analysis of genetic data in various phases of clinical trials, some indicated no perceived advantages to share those data with the FDA, as these data may not be used in subsequent trials. Additional guidance on the benefits to a sponsor in submitting data under VGDS and further transparency in the evaluation of these data from emerging technologies are needed to provide incentives for the industry to share data.

Disclaimer

The views presented in this article do not necessarily reflect those of the FDA.

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