Guidance for Industry

Pharmacogenomic Data Submissions

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Guidance for Industry

Pharmacogenomic Data Submissions

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in informing regulatory decisions. The guidance provides recommendations to sponsors holding investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) on (1) when to submit pharmacogenomic data to the Agency during the drug or biological drug product[2] development and review processes, (2) what formats may be used for submissions, and (3) how the data will be used in regulatory decision making.

For the purposes of this guidance, *pharmacogenomics* is defined as the use of a pharmacogenomic or pharmacogenetic test (see glossary for definitions) in conjunction with drug therapy. Pharmacogenomics does not include the use of genetic or genomic techniques for the purposes of biological product characterization or quality control (e.g., cell bank characterization, bioassays). The FDA plans to provide guidance on these uses at a future time. Pharmacogenomics also does not refer to data resulting from proteomic or metabolomic techniques. This document is not meant to provide guidance on pharmacoproteomics or multiplexed protein analyte based technologies.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* or *drug product* includes human drug and biological drug products.

Paperwork Reduction Act Public Burden Statement: According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The valid OMB control number for this information collection is 0910-xxxx (expires x/xx/xx). The time required to complete this information collection is estimated to average 10 hours per response, including the time to review instructions, search existing data resources, gather the data needed and complete and review the information collection.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The promise of pharmacogenomics lies in its potential ability to identify sources of inter-individual variability in drug response (both efficacy and toxicity); this will help individualize therapy with the intent of maximizing effectiveness and minimizing risk. However, the field of pharmacogenomics is currently in early developmental stages, and such promise has not yet been realized. Pharmaceutical sponsors have been reluctant to embark on programs of pharmacogenomic testing during the FDA-regulated phases of drug development because of uncertainties in how the data will be used by the FDA in the drug application review process. This guidance is intended to help clarify FDA 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 efficacy (21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12). Because these regulations were developed before the advent of widespread animal or human genetic or gene expression testing, they do not specifically address when such data should be submitted. The FDA has received numerous inquiries about what these regulations require of sponsors who are conducting such testing.

From a public policy perspective, a number of factors should be considered when interpreting how these regulations should apply to the developing field of pharmacogenomics.

Because the field of pharmacogenomics is relatively new, most experimental results may not be well enough established to be suitable for regulatory decision making. For example:

- Laboratory techniques and test procedures may not be well validated. In addition, test systems may vary so that results may not be consistent or generalizable across different platforms. A move to standardize assays is underway, and much more information should be available within the next several years.

- The scientific framework for interpreting the physiologic, toxicologic, pharmacologic, or clinical significance of certain experimental results may not be in place.

- The findings from a specific study often cannot be extrapolated across species or to different study populations (e.g., various human subpopulations with different genetic backgrounds).

- The transmission, data processing, and storage of the large amounts of highly dimensional data generated from microarray technology has not been well validated nor widely tested.

Despite these concerns, some pharmacogenetic tests — primarily those related to drug metabolism — have well-accepted mechanistic and clinical significance and are currently being integrated into drug development decision making and clinical practice.

It is important for the FDA to have a role in the evaluation of pharmacogenomic tests, both to ensure that evolving FDA policies are based on the best science and to provide public confidence in the field. It is also important that FDA policy facilitate, not impede, the use of pharmacogenomic tests during drug development and, to the extent possible, encourage open and public sharing of data and information on pharmacogenomic test results.

To this end, the Agency has undertaken a process for obtaining input on these issues from the scientific community and the public. On May 16 and 17, 2002, the Agency held a workshop, cosponsored by pharmaceutical industry groups, to identify key issues associated with the application of pharmacogenetics and pharmacogenomics to drug development. Subsequently, on April 8, 2003, a public presentation was made to the FDA Science Board. This presentation contained a proposal for developing guidance on submission of information on pharmacogenomic tests and a potential algorithm for deciding whether a submission of such data is needed. The Science Board endorsed moving forward with both of these proposals.

The policies and processes outlined in this draft guidance are intended to take the above factors into account and to assist in advancing the field in a manner that will benefit both drug development programs and public health.

III. SUBMISSION POLICY

A. General Principles

Pharmacogenomic data submission policies must be consistent with the relevant codified regulatory submission requirements for IND, NDA, and BLA submitters and holders. At present, however, many pharmacogenomic results are not well enough established scientifically to be appropriate for regulatory decision making. This guidance interprets FDA's regulations for IND, NDA, and BLA submissions, helping to clarify FDA's current thinking about when the regulations require pharmacogenomic data to be submitted and when the submission of such data is voluntary. In some cases, complete reports of pharmacogenomic studies should be submitted, while in others, an abbreviated report or synopsis may be submitted.[3] Because FDA regulations establish different requirements for INDs, unapproved NDAs and BLAs, and approved NDAs and BLAs, this guidance sets out different submission algorithms for each of these categories. This guidance also clarifies how the FDA currently intends to use such data in regulatory decision making, that is, when the data will be considered sufficiently reliable to serve as the basis for regulatory decision making, when it will be considered only supportive to a decision, and when the data will not be used in regulatory decision making.

[3] For further information on when abbreviated study reports can be submitted in NDAs and BLAs, see the guidance for industry *Submission of Abbreviated Reports and Synopses in Support of Marketing Applications,* developed under section 118 of the Food and Drug Administration Modernization Act.

This guidance also makes a distinction between pharmacogenomic tests that may be considered *valid biomarkers* appropriate for regulatory decision making, and other less well-developed tests. Although currently most pharmacogenomic measurements are not considered valid biomarkers, certain markers (e.g., for drug metabolism) are well established biomarkers with clear clinical significance. Undoubtedly, the distinction between what tests are appropriate for regulatory decision making and those that are not will change over time as the science evolves.

For the purposes of this guidance, a pharmacogenomic test result may be considered a *valid biomarker* if (1) it is measured in an analytical test system with well established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results. For example, the consequences for drug metabolism of genetic variation in the human enzymes CYP450 2D6 and thiopurine methyltransferase are well understood in the scientific community and are reflected in certain approved drug labels. The results of genetic tests that distinguish allelic variants of these enzymes are considered valid biomarkers. The 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 have been independently replicated (see Glossary). When a sponsor generates, or possesses, data sufficient to establish a significant association between a pharmacogenomic test result and clinical outcomes, the test result represents a probable valid biomarker. The algorithms described below for IND, NDA, and BLA holders describe when to submit to FDA data on known valid biomarkers. Data on probable valid biomarkers need not be submitted to the IND if they are not used by the sponsor in decision making. However, we recommend that sponsors or applicants submit reports on probable valid biomarkers to unapproved NDAs or BLAs according to the algorithm in section IV.B.

Many pharmacogenomic testing programs currently carried out by pharmaceutical sponsors or by scientific organizations are intended to develop the knowledge base necessary to establish the validity of new genomic biomarkers. During such a period of scientific exploration, test results are not useful in making regulatory judgments pertaining to the safety or effectiveness of a drug and are not considered known or probable valid biomarkers. However, scientific development of this sort is highly desirable for advancing understanding of relationships between genotype or gene expression and responses to drugs and, therefore, should be encouraged and facilitated. For these reasons, although submission of exploratory pharmacogenomic data is not required under the regulations, the FDA is encouraging *voluntary submission* of such data, as described below.

B. Specific Uses of Pharmacogenomic Data in Drug Development and Labeling

As the field of pharmacogenomics advances, it is likely (and desirable) that sponsors will begin to use pharmacogenomic tests to support drug development and/or to guide therapy. Sponsors may choose to submit pharmacogenomic data that have not achieved the status of a valid biomarker to an IND, NDA, or BLA to support scientific contentions related to dosing, safety, or efficacy. For example, a sponsor may wish to provide supportive data demonstrating that changes in drug-induced gene expression differ between species that have different toxicologic responses to a drug, thus correlating changes in certain gene expression patterns with a specific

toxicity. A pharmacogenomic test result also might be used to stratify patients in a clinical trial or to identify patients at higher risk for an adverse event.

When pharmacogenomic results are to be used in decision making in an animal safety trial, or during clinical development in a human trial as part of the protocol, the submission algorithms described below suggest that full information on the test system should be submitted to the IND. In contrast, results from earlier feasibility studies done under the same IND (or outside the IND) to establish the potential usefulness of the pharmacogenomic test (e.g., from samples taken during a dose-response study) should not normally be submitted unless they provide support for the use of the test in clinical decision making.[4]

If a pharmacogenomic test shows promise for enhancing the dose selection, safety, or effectiveness of a drug, a sponsor may wish to fully integrate pharmacogenomic data into the drug development program. This could occur in two ways:

1. The pharmacogenomic data are intended to be included in the drug label in an informational manner.

   For example, such data might be used to describe the potential for dose adjustment by drug metabolism genotype or to mention the possibility of a side effect of greater severity or frequency in individuals of a certain genotype or gene expression profile. In such cases, the pharmacogenomic test result may or may not be considered a valid biomarker, and an FDA-approved or widely used commercial pharmacogenomic test may not be available. Given this level of complexity, at the current time, sponsors should consult the relevant FDA review division for advice on how to proceed in a specific case. However, in all such cases, when a sponsor intends to include pharmacogenomic data in the drug label, we expect that complete information on the test and results would be submitted to the Agency as envisioned under §§ 314.50 and 601.2.

2. Dose selection, safety, or efficacy of a drug as described in its label will be contingent upon the performance of a pharmacogenomic test or tests. For example:

   - In the later phases of clinical drug development, patients will be tested for drug metabolism genotype and dosed according to the test results.
   - Patients will be selected for efficacy trial entry based on genotype (of patient or tumor) or gene expression profile.
   - Patients will be excluded from the trial based on genotype or gene expression profile (e.g., marker for adverse event).

   In all of these cases, the FDA recommends co-development of the pharmacogenomic tests and the drug and submission of complete information on the test to the Agency (in many cases, data on the test itself may be submitted to an IDE). The FDA plans to issue

[4] However, we recommend that a plan to perform any invasive test including phlebotomy, with the possible intent to conduct pharmacogenomic testing on a sample, be noted both in the protocol and the informed consent document.

further guidance on co-development of pharmacogenomic tests and drugs in the near future.

If a new pharmacogenomic test will be used in therapeutic decision making (choosing or dosing of drugs), we recommend that sponsors consider obtaining premarket review by the Center for Devices and Radiological Health (CDRH) in conjunction with their drug development program. By studying or considering diagnostic issues in conjunction with the introduction of new drugs, or changes to existing therapeutic claims, it is often possible to provide simpler and more consolidated studies.

The Office of In Vitro Diagnostics in CDRH is willing to meet with sponsors to discuss both scientific and regulatory issues with regard to new pharmacogenomic diagnostics and has both formal (IDE) and informal (pre-IDE) processes for helping to evaluate protocols.

C. Voluntary Submission of Exploratory Pharmacogenomic Research Data

At the current time, most pharmacogenomic data are of an *exploratory* or *research* nature, and FDA regulations do not require that these data be submitted to an IND, or that complete reports be submitted to an NDA or BLA. However, to be prepared to appropriately evaluate the anticipated future submissions, FDA scientists need to develop an understanding of relevant scientific issues, such as the following.

- The types of genetic loci or gene expression profiles being explored by the pharmaceutical industry for pharmacogenomic testing
- The test systems and techniques being employed
- The problems encountered in applying pharmacogenomic tests to drug development
- The ability to transmit, store, and process large amounts of complex pharmacogenomic data streams with retention of fidelity

Therefore, the FDA is requesting that sponsors conducting such programs consider providing pharmacogenomic data to the Agency voluntarily, when such data are not otherwise required under IND and NDA or BLA regulations. *Voluntary Genomic Data Submission*s (VGDSs) can be used for the submission of pharmacogenomic studies that are not required to be submitted. The FDA will establish a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDSs, to work on ongoing policy development, and to advise review divisions dealing with pharmacogenomic data.

IV. SUBMISSION OF PHARMACOGENOMIC DATA

FDA regulations establish different requirements for INDs, unapproved NDAs and BLAs, and approved NDAs and BLAs. For this reason, there are different submission algorithms for the submission of pharmacogenomic data.

A. Submission of Pharmacogenomic Data During the IND Phase

Section 312.23 outlines information submission requirements for an IND, including for data generated or available during the IND phase. Section 312.23(a)(8) lays out the requirements for pharmacology and toxicology information: "Adequate information about pharmacologic and toxicological studies of the drug involving laboratory animals or in vitro, *on the basis of which* the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations" (emphasis added). The in vitro and animal studies needed to establish a basis for proceeding with human trials of various types are well established internationally. Therefore, pharmacogenomic data relevant to, or derived from, animal or in vitro studies should ordinarily be submitted under § 312.23(a)(8) when the sponsor wishes to use these data to make a scientific case, or when the test is well established as a predictive biomarker (i.e., is a known valid biomarker).

Section 312.23(a)(9) sets forth the requirements for submission of previous human experience with the investigational drug. A summary is required on trials or human experience relevant to an evaluation of the safety or effectiveness of the drug. Therefore, sponsors must submit human data of known relevance (e.g., known valid pharmacogenomic biomarkers). In addition, sponsors or applicants must submit "any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support the marketing of the drug" (312.23(a)(10)(iv)) and "if requested by the FDA, any other relevant information needed for review of the application" (312.23 (a)(11)). Human pharmacogenomic data intended to be used in decision making in the drug development process is such data. In cases when the validity of the test is not well established, such data will be viewed by the FDA as supportive only for the purposes of regulatory decision making.

Sponsors holding INDs who generate or possess pharmacogenomic data related to an investigational drug can comply with FDA requirements using the following algorithm:

Pharmacogenomic data must be submitted to the IND under § 312.23 if ANY of the following apply:

1. The test results will be used for decision making in any clinical trial, or in an animal trial used to support safety. (For example, the results will affect dose selection, entry criteria, safety monitoring, or subject stratification.)
2. The sponsor is using the test results to support scientific arguments pertaining to, for example, the safety, effectiveness, dosing and pharmacology of the drug.
3. The test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known valid biomarker for a safety outcome in animal studies. If the information on the biomarker (example, human P450 2D6 status) is ***not*** being used for purposes 1 or 2 above, the information can be submitted to the IND as an abbreviated report.

Submission to an IND is NOT needed, but voluntary submission is encouraged (i.e., information does not meet the criteria of § 312.23) if

4. 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.
5. Information consists of results from test systems where the validity of the biomarker is not established.

Although submission of such data in cases 4 and 5 is not required under the regulations, the FDA would welcome voluntary submission of the data in a VGDS. See Appendix A for additional guidance on assessing whether to submit pharmacogenomic data to an IND.

Note: Regardless of requirements for submission, the fact that samples will be collected for potential analysis must be noted in any clinical protocol (312.23(a)(6)) and informed consent documents (50.25).

Data from a VGDS submission to an IND will not be used for regulatory decision making. However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted under §§ 312, 314, or 601, the sponsor must submit the data to the IND, NDA, or BLA, respectively, and should follow the appropriate algorithm.

B. Submission of Pharmacogenomic Data to a New NDA, BLA, or Supplement

Section 314.50 outlines the NDA submission requirements; section 601.2 generally outlines BLA submission requirements. As the introduction to § 314.50 states, "the [NDA] application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug product pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source." Therefore, to comply with these regulations, sponsors will need to provide reports of pharmacogenomic investigations in their NDAs, and to permit a thorough analysis of a biologics application, a sponsor would want to submit such a report in its BLA. However, the extent and format of such reports will depend on the relevance and application of the information.

Subsequent paragraphs of § 314.50 outline the submission requirements in specific disciplines. Nonclinical pharmacology and toxicology filing requirements are described in § 314.50(d)(2); human pharmacokinetics and bioavailability requirements in §314.50(d)(3); and clinical data requirements in § 314.50(d)(5).

Section 601.2 outlines the BLA submission requirements. Section 601.2 states that the BLA manufacturer shall submit data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency. Like NDA sponsors, BLA sponsors should provide reports of pharmacogenomic investigations in their BLAs. However, the extent and format of such reports will depend on the relevance and application of the information.

Sponsors who have generated or possess pharmacogenomic data related to a drug can comply with the regulations' requirements using the algorithm below.

1. Provide 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 pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

   The following examples would fit this category.

   – Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection, or effectiveness

   – Pharmacogenomic test results that the sponsor proposes to describe in the drug label

   – Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label

2. Submit reports of pharmacogenomic test results that constitute known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species, but that the sponsor is not relying on or mentioning in the label, to the Agency as an abbreviated report (not in the form of a synopsis or VGDS). (If a pharmacogenomic test of this type was conducted as part of a larger overall study, the reporting of the pharmacogenomic test results can be incorporated into the larger study report.)

3. Submit reports of pharmacogenomic tests that represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species to the NDA or BLA as an abbreviated report. (If the pharmacogenomic testing of this type was conducted as part of a larger study, the abbreviated report can be appended to the report of the overall study.)

4. There is no need to submit detailed reports of general exploratory or research information, such as broad gene expression screening, collection of sera or tissue samples, or results of pharmacogenomic tests that are not known or probable valid biomarkers to the NDA or BLA. Because the Agency does not view these studies as germane in determining the safety or effectiveness of a drug, the submission requirements in §§ 314.50 or 601.2 will be satisfied by the submission of a synopsis of the study. However, the Agency encourages the voluntary submission of the data from the study in a VGDS submitted to the NDA or BLA.

See Appendix B for additional guidance on how to assess whether to submit pharmacogenomic data to an unapproved NDA or BLA.

C. Submission to an Approved NDA or BLA

The requirements for submitting new scientific information to an approved NDA or BLA are outlined in §§ 314.81(b)(2) and 601.12. 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 (21 CFR 314.81(b)(2)).

Pharmacogenomic study results of other types do not meet the submission requirements outlined in the regulations (§ 314.81(b)(2)). However, such reports can be voluntarily submitted to the NDA or BLA as a VGDS.

D. Compliance with 21 CFR Part 58

Questions have been raised about the need for pharmacogenomic studies to comply with the requirements of 21 CFR part 58, which describes good laboratory practices (GLPs) for nonclinical laboratory studies that support INDs and NDAs. Section 58.3(d) (21 CFR 58.3(d)) defines *nonclinical laboratory studies* as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility…."

The requirements of part 58 apply to nonclinical studies submitted to support safety findings, including nonclinical pharmacogenomic studies intended to support regulatory decision making. Any studies eligible to be submitted in an abbreviated report, synopsis or VGDS under the algorithms discussed above do not fall under part 58.

V. FORMAT AND CONTENT OF A VGDS

This section provides recommendations on the format and content of VGDS reports and data. The FDA invites submission of exploratory pharmacogenomic data on drugs or candidate drugs whether or not the drugs are currently the subject of an active IND, NDA, or BLA. Exploratory genomic data may result from, for example, DNA microarray gene expression profiling experiments, expression biomarkers from single or limited gene expression profiles, genotyping or single-nucleotide polymorphism (SNP) profiling of clinical study participants, or from other studies using evolving methodologies that are intended to facilitate global analysis of gene structure or gene function.

The purpose of the VGDS process is to provide the FDA access to emerging pharmacogenomic data so that a foundation can be built for developing scientifically sound regulatory policies. The Agency intends to gain experience and to develop an aggregate genomic knowledge database from multiple VGDSs that could be used to rationally facilitate the use of pharmacogenomics in drug development and to share what general knowledge is learned from the data repositories, where appropriate. The VGDS process will also provide a forum for scientific discussion of exploratory data within the FDA outside of the application review process.

Currently, consensus standards do not exist for presenting and exchanging genomic data, although such standards are evolving. Therefore, this guidance does not recommend a specific format for the VGDS. We recommend only that, to achieve the goals of the VGDS process, the data submitted in a VGDS and the level of detail be sufficient for the Agency to interpret the information and independently analyze the data, verify results, and explore possible genotype-phenotype correlations across studies. We do not, however, want submission of a VGDS to be overly burdensome and time-consuming for sponsors. Therefore, we offer the following examples of possible VGDS formats:

- An article submitted to a peer-reviewed scientific journal
- An evolving public standard for specific types of experiments, such as the Minimum Information About a Microarray Experiment (MIAME) standard for microarray expression data.[5] An analogous approach could be used for formatting a VGDS containing genotyping or other genomic data derived from technology platforms other than nucleic acid hybridization arrays.
- A report on a gene expression microarray experiment containing the following:

  Title page
  Background and scientific rationale
  Primary and secondary study goals
  Synopses and summary of findings
  Study design and sample collection
  Array design and description
  Quality control tests performed on arrays
  Sample processing and preparation
  Demonstration of quality of RNA or DNA
  Hybridization procedures and parameters
  Measures of performance of hybridization such as spike-in control
  Measurements and quantification
  Normalization controls
  Number of repeats (array hybridized), number of biological assays performed
  Statistical analysis
  Bioinformatics tools and software used. Source of gene annotation
  Validation of gene expression by conventional assays such as Northern blot, real time PCR (polymerase chain reaction), RT-PCR (reverse transcriptase-PCR), immunohistochemistry, or Western blot, if reagents available
  Validation of SNP by SSCP (single-strand conformation polymorphism) or other assays
  Submission of electronic file containing raw images, raw data, scatter plots for all experiments reaching the conclusion, as well as an electronic data file of the background-corrected gene expression data (spot intensities) from microarray experiments that were used for analysis
  Results and conclusions
  References

[5] Brazma, A., et al., *Nature Genetics*, 29, 365-371, 2001 and http://www.mged.org/workgroups/miame.html.

The Agency will develop more specific guidance on how to submit detailed reports of genomic research data to INDs, NDAs, and BLAs.

VI. PROCESS FOR SUBMITTING PHARMACOGENOMIC DATA

Depending on the type of pharmacogenomic data, sponsors should submit reports according to the following recommendations.

- Complete reports, abbreviated reports, or synopses of pharmacogenomic studies to INDs, NDAs, or BLAs should be submitted in the usual manner.

- Sponsors who wish to voluntarily submit pharmacogenomic data to the FDA should submit the report to the relevant IND, NDA, or BLA, clearly labeled as a Voluntary Genomic Data Submission (VGDS), or as a pre-IND submission in the case of candidate drugs.

VII. FDA REVIEW OF PHARMACOGENOMIC DATA

The FDA has received many questions about the use of pharmacogenomic data in the application review process. Many questions reflect the concern that the Agency will raise new questions and require additional data based on findings from exploratory pharmacogenomic studies, that new studies will be required or suggested based on preliminary human pharmacogenomic data, that indicated populations will be narrowed or restricted based on the pharmacogenomic results in subpopulations, or that new studies in subpopulations will be required after retrospective analysis suggests differential responses based on pharmacogenomic subgrouping. There is also concern about the availability of staff who are expert in interpretation of such data.

The FDA will not use information submitted through the voluntary process for regulatory decision making on INDs or NDAs. VGDS filings will be analyzed by the Interdisciplinary Pharmacogenomic Review Group (IPRG) and the relevant review division staff. This process is intended to ensure that scientific staff experienced in the evaluation of such studies participate in analysis of the data. Any data evaluation will be for scientific and informational purposes. However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted under §§ 312, 314, or 601, the sponsor must submit the data to the IND, NDA, or BLA, respectively, and should follow the appropriate algorithm. If the FDA becomes aware of the significance of a particular PG test after evaluating results across sponsors, the Agency will notify sponsors about this determination. A review division also may consult the IPRG when pharmacogenomic data are part of a required submission to an IND, NDA, or BLA as a complete report, abbreviated report, or synopsis.

The animal and in vitro toxicology database needed to support human trials at various stages of the IND process and to support marketing of short- or long-term use drugs is well established. Any proposals for the substitution or addition of new animal safety tests will ordinarily be the

product of a public process involving the international scientific and drug development community.

Currently, as discussed above, only a few pharmacogenetic tests for certain drug metabolizing enzymes are considered valid biomarkers in humans. Considerable concern has been expressed about how the FDA will evaluate newer types of pharmacogenomic data (e.g., results that may predict increased risk of adverse events, or point to an enhanced probability of response). In fact, the FDA has considerable experience dealing with these issues in other contexts. Examples of how pharmacogenomic studies fit into this experience include the following.

- Descriptions of drug metabolizing phenotypes and discussion of their impacts on dosing are common in drug labels. Extrapolation of this information to pharmacogenetic testing is straightforward.
- There are many conditions or co-factors that may increase an individual's susceptibility to an adverse event (e.g., co-morbid conditions, metabolic susceptibilities such as renal or hepatic failure, or interacting drugs).

FDA's usual approach in such cases has been to request that information be added to the drug label that describes the possible interaction and advises on precautions. Were a sponsor to discover a new pharmacogenomic test that could possibly distinguish patients at greater risk for a serious adverse event, it is likely that both the sponsor and the Agency would have great interest in exploring the correlation in the appropriate populations. However, if the sponsor also moved forward on developing the drug in the overall indicated population, the FDA would evaluate the safety database on its merits. If the sponsor decided to develop the drug solely in populations from which certain patients were excluded based on pharmacogenomic testing, the FDA would recommend co-development of the pharmacogenomic test (as a diagnostic) and the drug because the FDA would be unable to approve a drug for which the safety profile was predicated on a pharmacogenomic test that was unavailable.

It is most likely that, in the near future, pharmacogenomic markers that predict drug toxicity will be identified and developed on a parallel path with overall drug development. In other words, the drug would be developed in a conventional manner with a parallel effort to identify appropriate predictors of toxicity. If the drug's risk-benefit profile were acceptable, the drug could be approved prior to the completion of efforts to refine and develop the relevant pharmacogenomic tests. When and if a test's predictive value were to be established and the test were to become commercially available (either as an approved device or as a service), the drug label could be changed to reflect the data.

- The FDA has similar experience with tests used to target populations likely to respond to therapy.

Several decades ago, broad indications for use were described in labels. Over time, as more exact diagnoses were developed, narrower indications were sought by sponsors, based on the clinical trials conducted. A similar evolution occurred in the field of anti-HIV therapies as drug resistance testing became available. We encourage sponsors to continue to develop pharmacogenomic tests that are predictive of subpopulations with enhanced response to therapy.

559 However, if overall drug development is pursued in the larger population, the effectiveness and
560 risk-benefit will be evaluated in that population, and approval decisions will be based on the
561 overall database.
562
563 Much of the concern about FDA actions in this area is based on the perception that
564 pharmacogenomic testing is likely to give very definitive answers about safety and effectiveness
565 in subpopulations. This may happen sometimes (e.g., in oncology) and in such cases, rapid
566 development of a diagnostic test is highly encouraged. However, this is unlikely to be the
567 ordinary case. In most instances, genotype or gene expression profile is likely to be one of a
568 number of factors, so that probability of an adverse event or a favorable response would be
569 increased, but the outcome not inevitable. For this reason, genetic markers can ordinarily be
570 handled like other predictive markers in the clinical arena.
571

GLOSSARY

The following definitions are for use in the processes outlined in this guidance, and are not intended to be broadly applicable to the entire field.

Biological marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[6]

Pharmacogenetic test: An assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics) including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins

Pharmacogenomic test: An assay intended to study interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response

Valid biomarker: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results

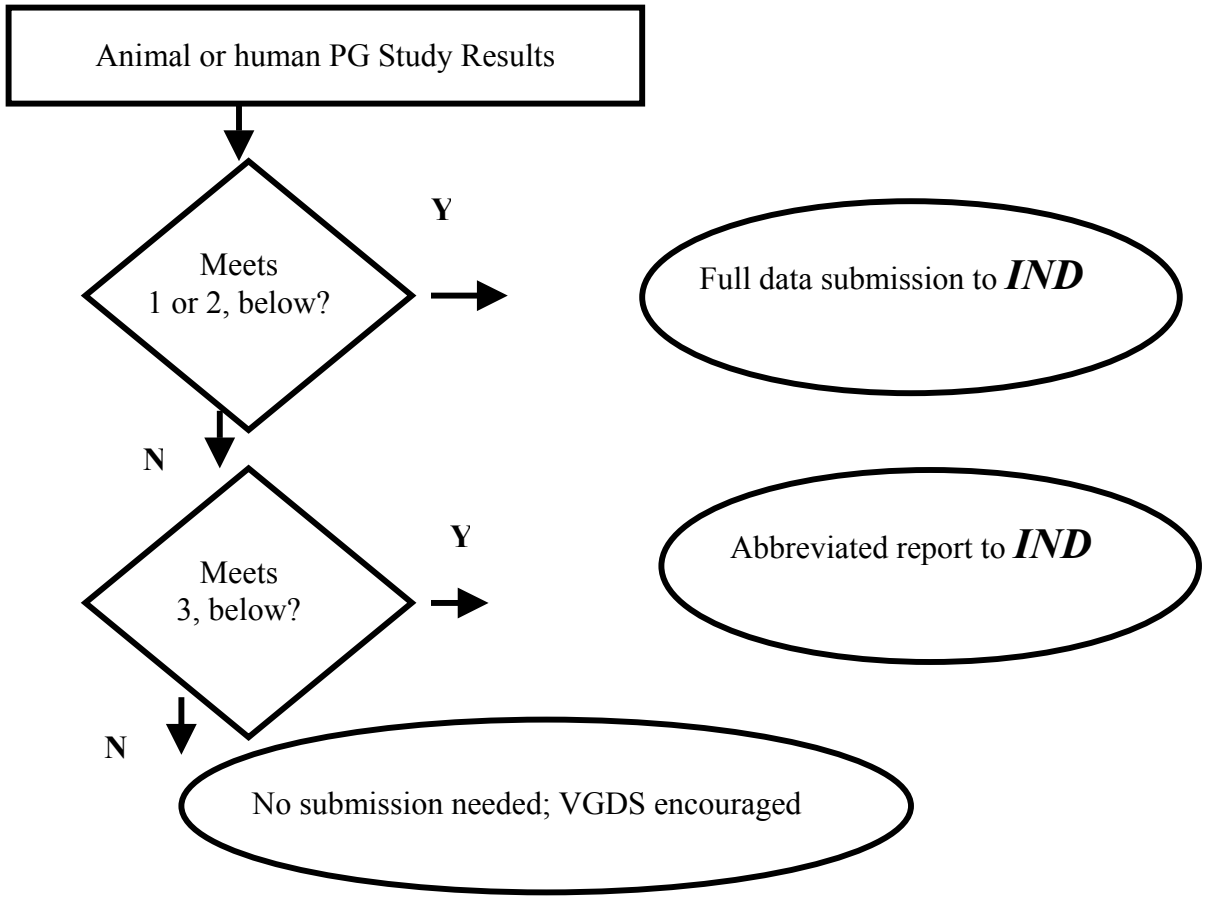
- **Known valid biomarker**: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results

- **Probable valid biomarker**: A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. A probable valid biomarker may not have reached the status of a known valid marker because, for example,
  - – The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.
  - – The data elucidating its significance, although highly suggestive, may not be conclusive.
  - – Independent replication of the results may not have occurred.

[6] Biomarkers Definitions Working Group, "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," *Clinical Pharm. & Therapeutics*, vol. 69, N. 3, March 2001.

613 **Voluntary genomic data submission (VGDS):** The designation for pharmacogenomic data
614 submitted voluntarily to the FDA

APPENDIX A: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO AN IND



Reports of pharmacogenomic investigations should be submitted to the NDA in the following formats:

Pharmacogenomic data must be submitted to the IND under § 312.23 if ANY of the following apply:

1. The test results will be used for decision making in any clinical trial, or in an animal trial used to support safety. (For example, the results will affect dose selection, entry criteria, safety monitoring, or subject stratification.)

2. The sponsor is using the test results to support scientific arguments pertaining to, for example, the safety, effectiveness, dosing and pharmacology of the drug.

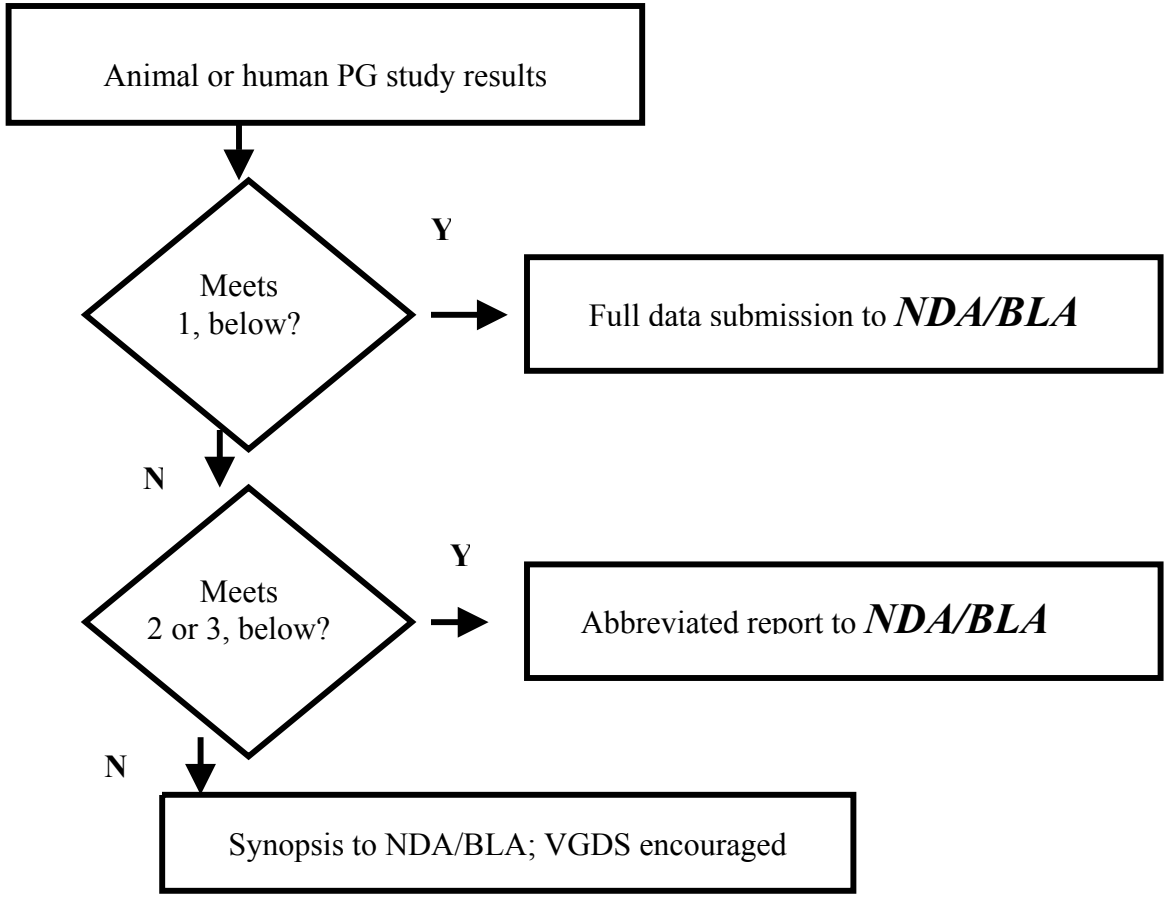
3. The test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known valid biomarker for a safety outcome in animal studies. If the information on the biomarker (example, human P450 2D6 status) is ***not*** being used for purposes 1 or 2 above, the information can be submitted to the IND as an abbreviated report.

Submission to an IND is NOT needed, but voluntary submission is encouraged (i.e., information does not meet the criteria of § 312.23) if

4. 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.

5. Information consists of results from test systems where the validity of the biomarker is not established.

APPENDIX B: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO A NEW NDA, BLA, OR SUPPLEMENT



Reports of pharmacogenomic investigations should be submitted to the NDA in the following formats:

1. Provide 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 pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

   The following examples would fit this category.

704 – Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection,
705 or effectiveness

706 – Pharmacogenomic test results that the sponsor proposes to describe in the drug label

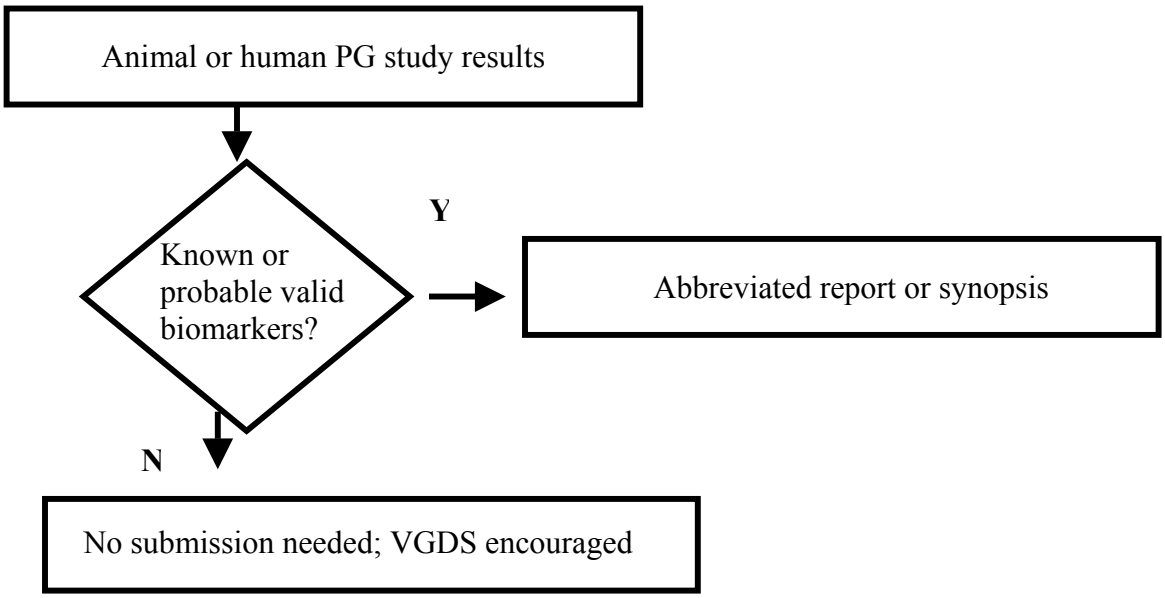
707 – Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label

708 2. Submit reports of pharmacogenomic test results that constitute known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic,
709 or clinical states or outcomes in the relevant species, but that the sponsor is not relying on or mentioning in the label, to the Agency as an abbreviated
710 report (not in the form of a synopsis or VGDS). (If a pharmacogenomic test of this type was conducted as part of a larger overall study, the reporting of
711 the pharmacogenomic test results can be incorporated into the larger study report.)

712 3. Submit reports of pharmacogenomic tests that represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or
713 clinical states or outcomes in the relevant species to the NDA or BLA as an abbreviated report. (If the pharmacogenomic testing of this type was
714 conducted as part of a larger study, the abbreviated report can be appended to the report of the overall study.)

715 4. There is no need to submit detailed reports of general exploratory or research information, such as broad gene expression screening, collection of sera or
716 tissue samples, or results of pharmacogenomic tests that are not known or probable valid biomarkers to the NDA or BLA. Because the Agency does not
717 view these studies as germane in determining the safety or effectiveness of a drug, the submission requirements in §§ 314.50 or 601.2 will be satisfied
718 by the submission of a synopsis of the study. However, the Agency encourages the voluntary submission of the data from the study in a VGDS
719 submitted to the NDA or BLA.

APPENDIX C: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO AN APPROVED NDA, BLA, OR SUPPLEMENT



APPENDIX D: EXAMPLES OF PHARMACOGENOMIC DATA SUBMISSIONS

Some examples of when to provide required pharmacogenomic data submissions versus voluntary (VGDS) genomic data submissions are discussed below.

Metabolizing Enzymes

1. Genotyping CYP2D6 activity in phase 1 human volunteers of various racial and ethnic groups for a new drug where CYP2D6 is the major pathway of metabolism. The PG data may be used to define potential ethnic differences and population-specific dosage regimens.

- CYP2D6 polymorphism is well established as a valid biomarker for drug metabolism enzyme activity
- See section IV.A.2 (complete report) and B.1 (complete report)

2. Genotyping CYP2C19 activity in phase 3 clinical trial patients for a new drug where CYP2C19 is one of the pathways of metabolism. The sponsor may use the information in the labeling.

- CYP2C19 polymorphism is well established as a valid biomarker for drug metabolism enzyme activity.
- See section IV.A.2 (complete report) and B.1 (complete report)

3. Genotyping of CYP3A5 activity in healthy volunteers in a clinical study evaluating the interaction of ketoconazole with a new drug, which is a CYP3A substrate. The data may be used to estimate the relative contribution of the polymorphism to inter-individual variability in AUC.

- CYP3A5 polymorphism is currently not established as a valid biomarker.
- See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged)

Transporters

1. Genotyping the MDR1 gene encoding P-gp in phase 1 human volunteers following the completion of a bioavailability study. The data may be used to explore causes of inter-individual variability in AUC.

- These are research data.
- See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged).

2. Genotyping MDR1 gene encoding P-gp in a phase 3 trial. The sponsor proposes to use two different treatment regimens based on genotypes.

- Data will be used in clinical decision making (affect dose selection).

- See section IV.A.1 (complete report)

Receptors

1. The sponsor reported that 5-HT1A Ser22 allele is found to be associated with poor response to an SSRI anti-depressant. Individuals with the marker genotype are excluded from the trial to enhance the drug's efficacy profile in a phase 2 proof of efficacy study

- Data will be used in clinical decision making (entry criteria).
- See section IV.A.1. (complete report)

CLINICAL OUTCOMES

Efficacy

1. The sponsor of a monoclonal antibody for treatment of an autoimmune disease has discovered MHC genetic markers predictive of hypersensitivity reactions upon intravenous infusion of the product. The sponsor has also determined that serum concentrations of the antibody 4 weeks after infusion are significantly lower among patients who developed initial infusion reactions. The sponsor genotypes the MHC markers predictive of *infusion* reactions in every patient of a prospective clinical study. It is determined that patients with the genotypes predictive of infusion hypersensitivity (regardless of whether an infusion reaction developed or not) evidence a statistically significantly reduced response to the antibody. The sponsor proposed to highlight the improved efficacy demonstration with genetic stratification in the description of the effects of the drug.

- Data could be used in clinical decision making
- See section IV.A.2 (complete report)
- The sponsor is encouraged to develop a pharmacogenomic diagnostic test (unless it is already available), if it to be reflected in labeling

Safety and Efficacy

1. In a clinical trial, psoriatic lesions are biopsied for gene expression profiling of 160 known disease-associated genes and 140 genes that seemed to correlate with response for the purpose of comparing responders and non-responders to an investigational new drug. Traditional, core clinical measurements are also made to provide evidence of efficacy and safety. The investigation is intended to identify specific gene expression patterns that could possibly be used to correlate with, and predict, efficacy or an adverse event, but at present they do not intend to incorporate the genetic information into labeling.

- These are research data
- See section IV.A.4 (VGDS encouraged).

2. A sponsor filed an IND 3 years ago. During clinical trials, there was lack of efficacy and so the development of the drug was abandoned. Nevertheless the drug had some interesting pharmacological actions that warranted further investigation by the sponsor. The sponsor runs a series of genomic studies in rats and dogs with the drug and discovers a novel pharmacological profile that leads to plans to develop the drug for a different indication.

- These are research data.
- See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged)

2.1 Based on the results of the rat and dog pharmacogenomic studies, the sponsor elects to assess a subset of 25 genes in later clinical trials that may be relevant to the safety or efficacy of the compound

- These are supportive data
- See section IV.B.2 (complete report).

Safety

1. Vasculitis is a major drug-related nonclinical safety signal and the basic mechanism of toxicity is unknown. It is normally confirmed by histopathology. A sponsor can use new rat gene chip microarray technology for expression profiling of 8000 known sequenced genes to investigate the mechanism of toxicity and possibly see a pattern of genetic biomarkers in treated rats that is different from controls.

- These are research data
- See section IV.A.4 (VGDS encouraged)

2. A sponsor filed an IND 12 months ago. During the course of subchronic toxicity testing to support longer clinical trial designs, the sponsor finds that rats develop cataracts. This finding represents a safety concern and the sponsor elects to run toxicogenomic studies to define the mechanism of the toxicity. The sponsor discovers that the mechanism is not relevant to humans and uses the data to make their argument about human safety and the absence of cataract risk.

- These are supportive data
- See section IV.A.2 (complete report)

3. A sponsor is investigating a new drug class and seeks to select for clinical development the best of 20 drugs showing some promise in their efficacy screen. No IND has yet been filed. The sponsor elects to assess differences in gene expression profiles to help with prioritization. The data may be generated from animal studies or from cell culture studies. The sponsor feels that the comparative profiles of gene expression alterations between the 20 drugs may help to select the most effective agent with least potential for toxicity. The data are generated to assist with compound selection and are not intended to support the safety of a proposed clinical investigation.

- These are research data
- See section IV.A.4 (VGDS encouraged)

4. A sponsor completes a 2-year carcinogenicity assay in rats and finds that there is an ambiguous tumor signal generated in the kidney, a site that is generally resistant to tumor induction. The sponsor elects to prove that the event was a spontaneous event that was not drug related by dosing the same strain of rats with drug and they succeed in showing that there is no effect of the drug on gene expression in the kidney. A positive control shows a gene expression profile that is very consistent with known pathways of carcinogenesis. The data are used to argue to regulatory authorities that the drug is safe and does not present a tumorigenic risk to humans.

- These are supportive data.
- See section IV.A.2. (complete report)

5. A sponsor conducts global gene expression analyses to assess the relationship between dose and target organ effect. Their drug is a novel acting antipsychotic agent. The sponsor has experience that leads them to suspect that the dose-limiting effect of their drug candidate will be injury to the kidneys - an insidious chronic progressive nephropathy. Using pharmacogenomic analyses, the sponsor finds that reliable and reproducible effects on kidney gene expression occur in both rats and dogs at a dose that is 20-fold lower than the doses in 30-day studies causing a demonstrable histopathology lesion or changes in serum markers for renal toxicity. Insufficient information is currently available to definitively link the more sensitive dose-response changes in gene expression patterns to future changes in renal function or histopathologic lesions.

- These are research data
- See section IV.A.4 (VGDS encouraged)

APPENDIX E: QUICK REFERENCE ON PHARMACOGENOMIC SUBMISSIONS

Submitting data to an:	IND	New (Unapproved) NDA, BLA, or Supplement	Approved NDA or BLA
Known Valid Biomarker	Must be submitted, pursuant to 21 CFR 312 (a) (8), (9), (10) (iv) or (11)	Must be submitted, pursuant to 21 CFR 314.50 and 601.2. See section IV.B. of the guidance	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports
Probable Valid Biomarker	Do not need to be submitted if not used by the sponsor in decision making. However, the FDA welcomes voluntary submission of such data in a VGDS	The FDA recommends submission, using algorithm in section IV.B. of the guidance	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports
Exploratory or Research Pharmaco-genomic Data	The FDA welcomes voluntary submission of such data in a VGDS	The FDA recommends submission, using algorithm in section IV.B. of the guidance FDA welcomes voluntary submission of such data in a VGDS	The FDA welcomes voluntary submission of such data in a VGDS