Guidance for Industry
Pharmacogenomic Data Submissions

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)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

2003D-0497

GDL-2

Guidance for Industry
Pharmacogenomic Data Submissions

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

Office of Health and Industry Programs
Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive
Rockville, MD 20850-4307 U.S.A.
http://www.fda.gov/cdrh/ggpmain.html
Email: dsma@cdrh.fda.gov
Fax: 301.443.8818
(Tel) Manufacturers Assistance: 800.638.2041 or 301.443.6597
(Tel) International Staff Phone: 301.827.3993

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)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. SUBMISSION POLICY 3

- A. General Principles 3
- B. Specific Uses of Pharmacogenomic Data in Drug Development and Labeling 5
- C. Benefits of Voluntary Submissions to Sponsors and FDA 7

IV. SUBMISSION OF PHARMACOGENOMIC DATA 8

- A. Submission of Pharmacogenomic Data During the IND Phase 8
- B. Submission of Pharmacogenomic Data to a New NDA, BLA, or Supplement 10
- C. Submission to a Previously Approved NDA or BLA 11
- D. Compliance with 21 CFR Part 58 11
- E. Submission of Voluntary Genomic Data from Application-Independent Research 12

V. FORMAT AND CONTENT OF A VGDS 12

VI. PROCESS FOR SUBMITTING PHARMACOGENOMIC DATA 14

VII. FDA REVIEW OF VOLUNTARY GENOMIC DATA SUBMISSIONS 14

GLOSSARY 17

APPENDIX A: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO AN IND 19

APPENDIX B: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO A NEW NDA, BLA, OR SUPPLEMENT 21

APPENDIX C: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO AN APPROVED NDA, BLA, OR SUPPLEMENT 23

APPENDIX D: QUICK REFERENCE ON PHARMACOGENOMIC SUBMISSIONS 24

APPENDIX E: VOLUNTARY SUBMISSION COVER SHEET 25

Contains Nonbinding Recommendations

Guidance for Industry[1]
Pharmacogenomic Data Submissions

This guidance represents 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 drug development. 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 format and content to provide for submissions, and (3) how and when the data will be used in regulatory decision making. Key information, including examples of when pharmacogenomic data submissions would be required and when voluntary genomic data submissions (VGDSs) would be welcome are provided in a separate companion document (*Pharmacogenomic Data Submissions, Attachment: Examples of Voluntary Submissions or Submissions Required Under 21 CFR 312, 314, or 601*).

For the purposes of this guidance, the term *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 those uses at a future time. *Pharmacogenomics* also does not refer to data resulting from proteomic or metabolomic

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), in cooperation with the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* or *drug product* includes human drug and biological 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 0910-0557 (expires 12/31/2007). 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.

techniques. This document is not meant to provide guidance on pharmacoproteomics or multiplexed protein analyte based technologies. However, the voluntary submission process described in this guidance may be used to submit such data if so desired.

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 to help identify sources of inter-individual variability in drug response (both effectiveness and toxicity); this information will make it possible to 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. The Agency has heard that pharmaceutical sponsors have been reluctant to embark on programs of pharmacogenomic 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 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 effectiveness (including 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 must 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 apply to the developing field of pharmacogenomics. Because the field of pharmacogenomics is rapidly evolving, in many circumstances, the experimental results may not be well enough established scientifically 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 yet be well understood.

- 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 standards for transmission, processing, and storage of the large amounts of highly dimensional data generated from microarray technology have neither been well defined 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 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. FDA developed this guidance to facilitate the use of pharmacogenomic tests during drug development and 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 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 the submission of information on pharmacogenomic tests and a potential algorithm for deciding whether submission of such data is voluntary or required. The Science Board endorsed moving forward with both of these proposals. In November 2003, FDA published a draft version of this guidance and received public comment on the draft guidance. The Agency also has developed internal policy related to pharmacogenomics and voluntary submissions.[3]

The policies and processes outlined in this final 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 the public health.

III. SUBMISSION POLICY

A. General Principles

FDA recognizes that its pharmacogenomic data submission policies must be consistent with the relevant codified regulatory submission requirements for investigational and marketing application submitters and holders. At present, many pharmacogenomic results are not well enough established

[3] A charter has been developed outlining the organization, principles, and function of the inter-center Interdisciplinary Pharmacogenomics Review Group (IPRG) (MaPP 4180.2). In addition, policy has been developed for Agency staff, explaining how voluntary genomic data submissions (VGDSs) will be received and reviewed in the Agency (MaPP 4180.3; SOPP 8114).

scientifically to be appropriate for regulatory decision making.[4] This guidance 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. In some cases, complete reports of pharmacogenomic studies suffice, while in others, an abbreviated report or synopsis should or must be submitted.[5]

Because FDA regulations establish different requirements for investigational applications, unapproved marketing applications, and approved marketing applications, this guidance sets out different submission algorithms for each of these categories. The guidance also clarifies how the Agency 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.

This guidance also makes a distinction between pharmacogenomic tests that may be considered either probable or known *valid biomarkers,* which may be appropriate for regulatory decision making, and other less well-developed tests that are either observational or exploratory biomarkers that, alone, are insufficient for making regulatory decisions. 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. Throughout the development of these tests, as appropriate, FDA will continue to seek public comment as we evaluate whether a biomarker is a *valid biomarker* (e.g., via discussions at Advisory Committee meetings).

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 CYP2D6 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 to be well established and, therefore, valid biomarkers.

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 (see Glossary). When a sponsor generates, or

---

[4] For purposes of this document, the term *regulatory decision making*, as defined here, applies to decisions that FDA may make in the evaluation of pharmacogenomic information used to establish the dosing, safety, or effectiveness of a drug or biological product. FDA regulatory decisions occur throughout the investigational stages of product development, during premarket review, and during postmarket regulation.

[5] 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.

possesses, data sufficient to establish a significant association between a pharmacogenomic test result and clinical outcomes, the test result represents a probable valid biomarker. It would be expected that this biomarker would meet criteria (1) and (2) above, and its association with a meaningful outcome would have been demonstrated in more than one experiment.

The algorithms described below for investigational and marketing application holders describe when to submit to FDA data on known valid biomarkers. Data on probable valid biomarkers need not be submitted to the IND unless they are used by a sponsor to make decisions regarding specific animal safety studies or clinical trials (e.g., using biomarker data as inclusion or exclusion criteria, assessment of treatment-related prognosis, or stratifying patients by dose) or are a probable valid biomarker in human safety studies (see section IV.A).[6] However, we recommend that sponsors or applicants submit reports on all probable valid biomarkers to new (i.e., unapproved) NDAs or BLAs according to the algorithm in section IV.B.

Many pharmacogenomic testing programs implemented 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 the 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, 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 investigational or marketing application to support scientific contentions related to dosing and dosing schedule, safety, or effectiveness. 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. Or, a pharmacogenomic test result might also be used to stratify patients in a clinical trial or to identify patients at higher risk for an adverse event to correlate test results with clinical outcome.

When pharmacogenomic results affect the design of a specific animal safety trial, or human safety or efficacy trial, the submission algorithms described below suggest that full information on the test system must be submitted to the IND (§§ 312.30(b) and 312.31). 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) are not a required submission, but would be encouraged as a voluntary

[6] For the purposes of this guidance, the phrase *decision making by the sponsor*, as defined here, refers to study- or trial-specific decisions that a sponsor might make in the development of a drug, but not to overall strategies related to drug development or portfolio management.

submission. However, a plan to perform any invasive test, including phlebotomy, with the possible intent to conduct pharmacogenomic testing on a sample, must be noted both in the protocol and the informed consent document (§§ 312.23(a)(6), 312.30(b), and 50.25).

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 integration could occur in two ways:

1. The pharmacogenomic data may be intended to be included in the drug labeling in an informational manner.

   For example, such data might be used to describe the potential for dose adjustment by drug metabolism genotype (e.g., CYP2D6*5) 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 would be considered a known valid biomarker. However, an FDA-approved pharmacogenomic test may not be available or required to be available, or a commercial pharmacogenomic test may not be widely 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, whenever a sponsor intends to include pharmacogenomic data in the drug label, complete information on the test and results must be submitted to the Agency as described under §§ 314.50 and 601.2.

2. The pharmacogenomic data and resulting test or tests may be intended to be included in the drug labeling to choose a dose and dose schedule, to identify patients at risk, or to identify patient responders. Inclusion of a pharmacogenomic test in the labeling would be contingent upon its performance characteristics. For example:

   - Patients will be tested for drug metabolism genotype and dosed according to the test results.
   - Patients will be selected as potential responders for an efficacy trial (or deselected because of a high risk) based on genotype (e.g., of either the patient or the patient's tumor) or gene expression profile.
   - Patients will be excluded from a clinical trial based on genotype or gene expression profile (e.g., biomarker for risk of an adverse event).

   In all of these cases, FDA recommends co-development of the drug and the pharmacogenomic tests, if they are not currently available, and submission of complete information on the test/drug combination to the Agency. The FDA plans to issue further guidance on co-development of pharmacogenomic tests and drugs.

   The Office of In Vitro Diagnostics in CDRH, appropriate review divisions in CBER, and the Clinical and Clinical Pharmacology Review divisions in CBER or CDER are willing to meet jointly with sponsors to discuss both scientific and regulatory issues with regard to new pharmacogenomic tests. The CDRH has both formal (IDE) and informal (pre-IDE) processes to evaluate protocols for pharmacogenomic test development.

C. Benefits of Voluntary Submissions to Sponsors and FDA

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, voluntary submissions can benefit both the industry and the FDA in a general way by providing a means for sponsors to ensure that regulatory scientists are familiar with and prepared to appropriately evaluate future genomic submissions. FDA and industry scientists alike would benefit from an enhanced 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
- The scientific rationale for standardizing naming and characterization of the genes used on different genomic analysis platforms and for developing bioinformatics software programs used to evaluate pharmacogenomic data
- Facilitate identification of predictors of safety, effectiveness, or toxicity

A greater understanding of the issues surrounding the use of pharmacogenomic data may prevent delays in reviews of future submissions where genomics are an integral part of specific studies in a drug development program.

Therefore, FDA is requesting that sponsors conducting such programs consider providing pharmacogenomic data to the Agency ***voluntarily***, when such data are not otherwise required under the regulations. To facilitate VGDSs, FDA has established a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDSs, to work on policy development, and, upon request, to advise review divisions on interpretation and evaluation of pharmacogenomic data.

For sponsors, voluntary submission of genomic data offers a number of specific potential benefits:

- Meet *informally* with FDA and receive peer review assessments of scientific data from pharmacogenomic experts at the Agency
- Obtain insight into the evolving regulatory decision making process as it relates to genetic and genomic information
- Familiarize FDA scientists with novel pharmacogenomic experiments, data analysis, and interpretation approaches at an early stage

- Conserve time and resources by obtaining feedback from FDA on a VGDS that might highlight unaddressed issues that could prove time consuming or costly later during product development
- Identify new opportunities for drug development (e.g., feedback from FDA might help reach new strategic decisions). For example, a shelved product may be continued when new tools such as genotyping assays become available to demonstrate effectiveness in a subpopulation.
- Make a contribution to the VGDS data repository to facilitate advancement of pharmacogenomics and development of rational, data-based policies and guidances

IV. SUBMISSION OF PHARMACOGENOMIC DATA

FDA regulations establish different requirements for INDs, new (i.e., 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 describes information submission requirements for an IND, including data generated or available during the IND phase. Section 312.23(a)(8) contains 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 must ordinarily be submitted according to § 312.23(a)(8) when the sponsor wishes to use these data to make a scientific case, or when the pharmacogenomic test is a known valid biomarker.

Section 312.23(a)(9) sets forth the requirements for submitting previous human experience with an investigational drug. The application must include a summary of trials or human experience relevant to an evaluation of the safety or effectiveness of a 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)). Sponsors may possess human data that suggest that a particular biomarker is a probable valid biomarker for evaluating the safety of the drug being evaluated. In these cases, information on the biomarker must be submitted to the IND because it could potentially aid in evaluation of the safety of the investigations per the regulations.

In addition, section 312.23(a)(11) states that a sponsor must submit "if requested by FDA, any other relevant information needed for review of the application." Therefore, during the IND review, FDA may request pharmacogenomic information the Agency considers relevant (e.g., information related to the mechanism of action of the drug).

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 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 (example, human CYP2D6 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 required, 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 concerning a product under an IND will not be used for regulatory decision making. However, after the sponsor submits a VGDS, if additional information becomes available that triggers the requirements for submission under §§ 312, 314, or 601, the sponsor must submit the data to the relevant application 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 must provide reports of certain pharmacogenomic investigations in their NDAs, and to permit a thorough analysis of a biologics application, a sponsor must 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 submission 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 generally 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. Like NDA sponsors, BLA sponsors must provide reports of certain 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 describing what kind of report to submit:

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

   The following examples would fit this category.

   - Pharmacogenomic test results from clinical trials used to support scientific arguments made by the sponsor about selecting drug doses, assessing safety, selecting patients for treatment, or monitoring the beneficial responses
   - Pharmacogenomic test results that the sponsor proposes to describe in the drug labeling
   - Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug labeling

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 such studies as germane in determining the safety or effectiveness of a product, 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 such a study in a VGDS.

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

C. Submission to a Previously Approved NDA or BLA

The requirements for submitting new scientific information to a previously 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 (§ 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.

Pharmacogenomic data collected in pharmacoepidemiologic and observational studies can be submitted as a VGDS by the applicant in accordance with the recommendations in this guidance (see Section VI).

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 using 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. If full compliance with 21 CFR Part 58 cannot be met, a sponsor must clearly indicate in the study report the areas in which such data do not comply with Part 58 (§§ 312.23(a)(8)(iii) and 314.50(d)(2)(v)). Any studies eligible to be submitted in an abbreviated report, synopsis, or VGDS under the algorithms discussed above do not fall under part 58.

The FDA recognizes that it may not be feasible to conduct separate, long-term, non-GLP preclinical studies. For this reason, FDA encourages sampling of tissues from GLP studies for investigational purposes. Removal of tissue samples and the reason for removal (e.g., exploratory, mechanistic study, tissue banking) should be specified in the protocol. Removal of specimens for investigational purposes from a study does not invalidate the GLP status of the main toxicology study, if otherwise acceptable. If the tissue samples are subsequently analyzed, the results should be reported to the NDA as a synopsis. FDA would also be interested in receiving these data in a VGDS. If findings from these studies are considered by the sponsor to be relevant to the safety of the compound under study (e.g., related to a known valid biomarker), the findings must be reported to the application, as is necessary for any other relevant nonclinical study findings 312.23(a)(8), 312.32(c)(1)(i)(B), 314.50(d)(2)).

E. Submission of Voluntary Genomic Data from Application-Independent Research

FDA will also accept pharmacogenomic data from investigators who may not have an active IND, NDA, or BLA , but who wish to provide the information voluntarily to the FDA, according to the process described in Section VI of this guidance.

We recommend that all VGDSs be prominently marked as **VGDS**, or **VOLUNTARY SUBMISSIONS**, on the cover letter that accompanies the submission (see Appendix E).

V. FORMAT AND CONTENT OF A 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, but not specific claims pertaining to drug dosing, safety assessments, or effectiveness evaluations. 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 data format for the VGDS.

We recommend that, to achieve the goals of the VGDS process as delineated in Section III(C), the content of 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 the submission of a VGDS to be overly burdensome and time-consuming for sponsors. Therefore, VGDS could be submitted in a number of forms:

- As an article submitted to a peer-reviewed scientific journal with raw or processed data submitted electronically
- As an evolving public standard for specific types of experiments, such as the Minimum Information About a Microarray Experiment (MIAME) standard for microarray expression data.[7] Using an approach similar in content to MIAME one can format a VGDS containing genotyping or other genomic data derived from technology platforms other than nucleic acid hybridization arrays.
- As a full report on a gene expression microarray experiment, the content could contain the following analytical, preclinical and/or clinical information, for example:
  - Title page
  - Table of contents
  - Background and scientific rationale
  - Primary and secondary study goals
  - Synopses and summary of findings
  - Study design and sample collection
  - Array design and description
    - 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
  - Data Analysis
    - Statistical analysis
    - Bioinformatics tools and software used. Source of gene annotation
  - Results and conclusions, including, for example, data visualization (e.g., scatter plots, principle component analysis (PCA), hierarchical clustering (heat maps)), correlation between expression profiles and outcomes, and appropriate information about relevant co-factors
  - References
- Additional Study Information related to mircroarray studies might include the following:
  - Confirmation of SNP analysis by sequencing or other assays

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

- Confirmation of gene expression by other conventional assays (e.g., Northern blot, RT-PCR (real time polymerase chain reaction)). As much as possible, all genes of importance should be confirmed with secondary assays. However, if the genomic profile is of importance, it may be appropriate to sample a selected subpopulation of affected genes
- Alternative approaches that examine endpoints other than gene expression changes may also be appropriate under certain circumstances (e.g., immunohistochemistry or Western blot, if reagents available).

VI. PROCESS FOR SUBMITTING PHARMACOGENOMIC DATA

Using the decision trees (see Appendices A-C), sponsors should submit genomic data according to the following recommendations.

- For required submissions, complete reports, abbreviated reports, or synopses of pharmacogenomic studies should be submitted to INDs, NDAs, or BLAs in the usual manner.
- For candidate drugs or stand alone voluntary submissions (submissions not related to any application), sponsors should submit the package ***clearly labeled as*** **VOLUNTARY GENOMIC DATA SUBMISSION *(VGDS)*.** A voluntary submission cover sheet that can be used is included in Appendix E. For VGDSs related to an existing IND, NDA, or BLA, please include the reference number on the voluntary submission cover sheet.

VII. FDA REVIEW OF VOLUNTARY GENOMIC DATA SUBMISSIONS

The FDA has received many questions about the use of pharmacogenomic data in the application review process. 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 experts in interpretation of such data.

FDA will not use genomic information submitted through the voluntary process for regulatory decision making on INDs, BLAs, or NDAs.

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 §§ 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. Also, a review division may consult the IPRG when pharmacogenomic data are submitted as part of an IND, NDA, or BLA.

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 genomic safety tests will ordinarily be the product of a public process involving the international scientific and drug development communities. If FDA becomes aware that a particular pharmacogenomic test has taken on great significance based upon cumulative experience (e.g., from evaluating results across submissions, and/or obtaining input from Advisory Committees), the Agency will notify sponsors about its findings.

Currently, as discussed above, only a few pharmacogenetic tests for certain drug metabolizing enzymes are considered known valid biomarkers in humans. Considerable concern has been expressed about how 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 effectiveness response). 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 effects 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 hepatic failure, or concomitant drug therapies) or the probability of a beneficial response.

FDA's usual approach in such cases has been to request that information be added to the drug labeling that describes the possible interaction and relevant co-factors and advises on precautions. If a sponsor discovers 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, 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, FDA would recommend co-development of the pharmacogenomic test (as a diagnostic) and the drug because FDA would be unable to approve a drug for which the risk or benefit was predicated on a pharmacogenomic test that was unavailable.

It is most likely that, in the near future, pharmacogenomic biomarkers that predict drug toxicity will be identified and developed on a path parallel with overall drug development. In other words, a 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 in the entire target population, 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 values 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.

- 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. However, if overall drug development is pursued in the larger population, the effectiveness and risk-benefit will be evaluated in that population, and approval decisions will be based on the overall database.

Much of the concern about FDA actions in this area is based on the perception that pharmacogenomic testing is likely to give definitive answers about the probability of safety and effectiveness in subpopulations. Such specificity may occur occasionally (e.g., where a product is designed to inhibit a specific molecular target), and in such cases, rapid development of a diagnostic test is highly encouraged. However, this is unlikely to be the ordinary case. In most instances, a genotype or particular gene expression profile is likely to be one of a number of factors that affects the probability of an adverse event or a favorable response. For this reason, pharmacogenomic biomarkers can ordinarily be handled like other non-genomic predictive markers in the clinical arena.

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.[8]

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, or alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response. In some cases, the *pattern or profile of change* is the relevant biomarker, rather than changes in individual markers.

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. The classification of biomarkers is context specific. Likewise, validation of a biomarker is context-specific and the criteria for validation will vary with the intended use of the biomarker. The clinical utility (e.g., predict toxicity, effectiveness or dosing) and use of epidemiology/population data (e.g., strength of genotype-phenotype associations) are examples of approaches that can be used to determine the specific context and the necessary criteria for validation.

- **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, of any one of the following reasons:
  - The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.

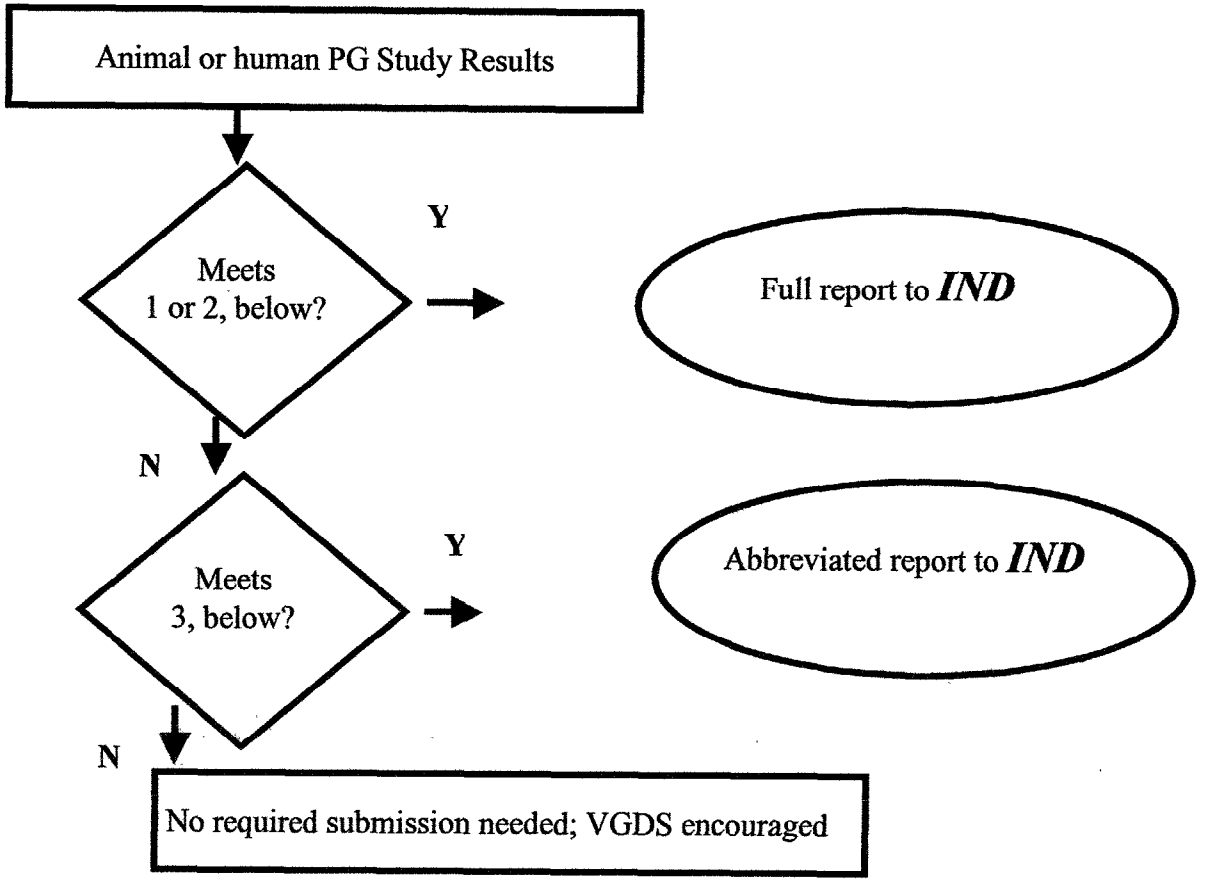
[8] Biomarkers Definitions Working Group, "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," *Clinical Pharm. & Therapeutics*, vol. 69, N. 3, March 2001.

– The data elucidating its significance, although highly suggestive, may not be conclusive.
– Independent verification of the results may not have occurred.

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

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

Reports of pharmacogenomic investigations should be submitted to the IND in accordance with the decision tree below and in the formats indicated here or in the body of the guidance:



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

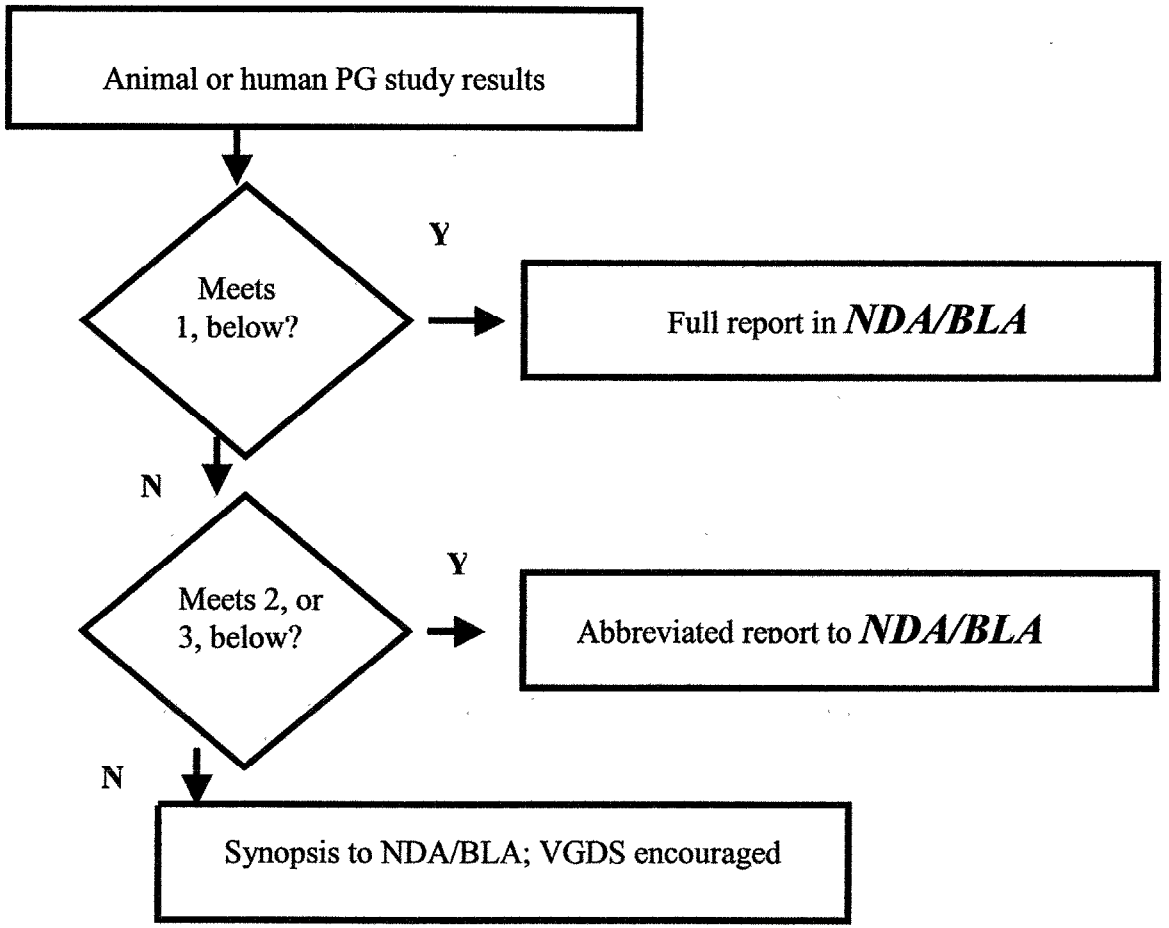
1. The test results are used for making decisions pertaining to a specific clinical trial, or in an animal trial used to support safety (e.g., the results will affect dose selection, entry criteria into a clinical trial safety monitoring, or subject stratification).
2. A sponsor is using the test results to support scientific arguments pertaining to, for example, the pharmacologic mechanism of action, the selection of drug dosing or the safety and effectiveness of a 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 or a probable valid biomarker in human safety studies. If the information on the biomarker (example, human CYP2D6 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 required, 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 accordance with the decision tree below and in the formats indicated here or in the body of the guidance:



1. The sponsor will use the test results in the drug labeling 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

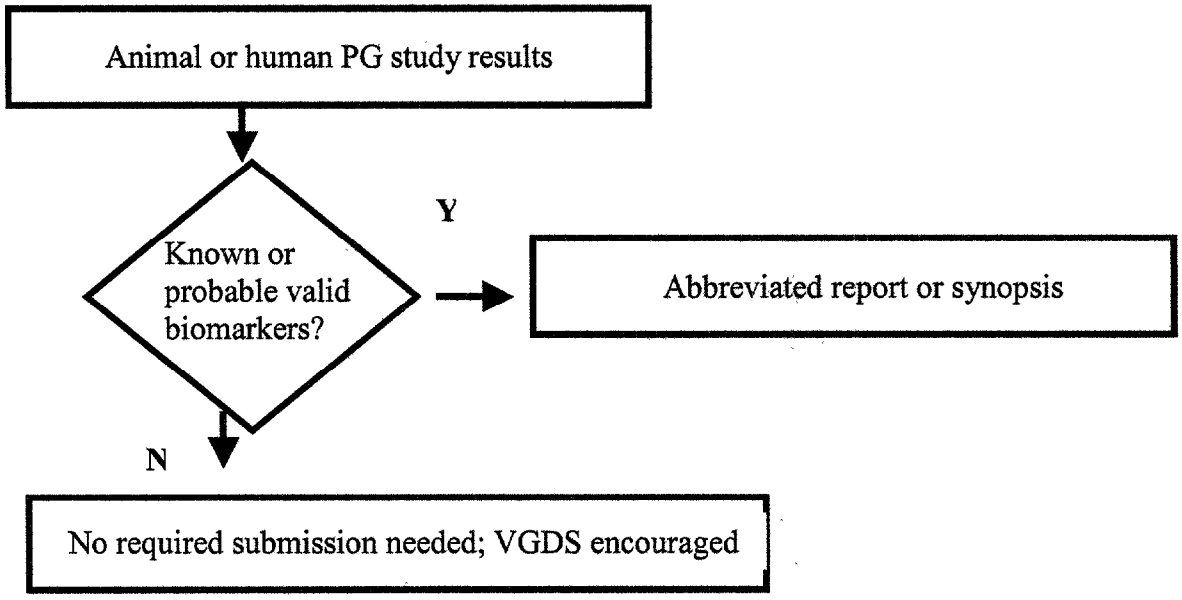
NDA or BLA. If the pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

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. The test results are known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species, but the sponsor is not relying on or mentioning this in the label. Submit to the Agency as an abbreviated report (not as 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. The test results represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species. Submit to the Agency 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. Information from general exploratory or research studies, 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 are not required to be submitted. 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.

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



APPENDIX D: QUICK REFERENCE ON PHARMACOGENOMIC SUBMISSIONS

Submitting data to an:	IND	New (Unapproved) NDA, BLA, or Supplement	Previously Approved NDA or BLA
Known Valid Biomarker	Must be submitted, pursuant to 21 CFR 312.23 (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	Does not need to be submitted.[9] 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. The FDA welcomes voluntary submission of such data in a VGDS.	The FDA welcomes voluntary submission of such data in a VGDS.

[9] Except if used in human safety studies.

APPENDIX E: VOLUNTARY SUBMISSION COVER SHEET

Send all CDER voluntary genomic data submissions to the following address accompanied by this coversheet:
FDA/CDER
Central Document Room (CDR)
5901-B Ammendale Road
Beltswille, MD 20705-1266

Attention!

This is a

Voluntary
Genomic Data Submission

Application number _____ (leave blank if this is the first submission for a stand-alone VGDS)

_____Initial Submission

_____Subsequent Submission

Please route directly to the IPRG (HFD-850) After processing in the CDR!