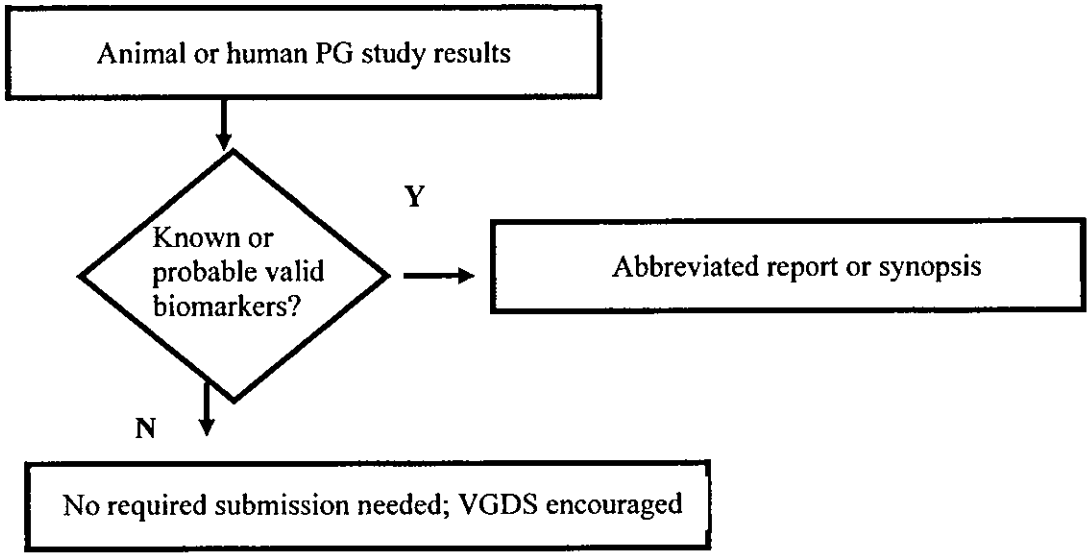
APPENDIX C: SUBMISSION OF PHARMACOGENOMIC (PG) DATA TO AN APPROVED NDA, BLA, OR SUPPLEMENT



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.

Contains Nonbinding Recommendations

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!

Attachment to

Guidance on Pharmacogenomic Data Submissions

Examples of Voluntary Submissions or Submissions Required Under 21 CFR 312, 314, or 601

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

Contains Nonbinding Recommendations

Pharmacogenomic Data Submissions
Attachment: Examples of Required or Voluntary Submissions

This attachment to the guidance *Pharmacogenomic Data Submissions* is intended to illustrate when it would be appropriate to submit a voluntary (VGDS) genomic data submission versus a pharmacogenomic data submission required under 21 CFR 312, 314, or 601 (RGDS). Please refer to the complete guidance, or contact the relevant center if you have any questions. Examples for various topic areas are provided using the following format:

Scenario
Type of Submission
Rationale

Topic Area: Metabolizing Enzymes

Scenario 1: During IND development, a sponsor conducts single- and multiple-dose pharmacokinetic studies of a new molecular entity (NME) in healthy volunteers enrolled to represent the major racial demographic groups. The NME is metabolized primarily by CYP2C19 to inactive metabolites. The sponsor assesses the CYP2C19 genotypes in the volunteers to determine the clearance phenotype with the goal of determining if drug dosing needs to be individualized based on the genotype groups.

Type of Submission:
Required in full report (IND)

Rationale:
The sponsor uses the test results to "support scientific arguments pertaining to the pharmacologic mechanism of action, the selection of drug dosing or the safety and effectiveness of a drug" (as described in Figure A2 of this document).

Scenario 2: A sponsor conducts a phase 3 clinical trial of a NME in patients with the target indication. The NME is metabolized primarily by CYP2D6 to an active metabolite equipotent to the parent molecule. The sponsor genotypes a randomly selected subset of the patients for their CYP2D6 alleles to explore the association between genotype, drug dosing, and clinical outcome. The results show minor differences in clinical outcomes among the genotypes. The information is included in the proposed labeling in the NDA submission.

Type of Submission:
Required in full report (NDA)

Rationale:
The sponsor included the test results in the drug label (as described in Figure B1 of this document).

Scenario 3: A sponsor conducts a phase 3 clinical trial of a NME in patients with the target indication. The NME is metabolized primarily by CYP2D6 to an active metabolite equipotent to the parent molecule. After the trial is completed, the sponsor genotypes a randomly selected subset of the patients for their CYP2D6 alleles to explore the association between genotype and clearance values. The sponsor will not include the results in the labeling.

Type of Submission:
Required in abbreviated report (IND or NDA/BLA)

Rationale:
Although the test results were not used in decision-making or scientific arguments (such as described in Figure A1 or A2) or in the drug label or as part of the scientific database (such as described in Figure B1), CYP2D6 is a

known valid biomarker. Therefore, the test results must be submitted as an abbreviated report (as described in Figure A3, Figure B2 of this document).

Scenario 4: A sponsor conducts a drug interaction study in healthy volunteers of their NME, a CYP3A substrate, co-administered with ketoconazole as an enzyme inhibitor. Subsequent to the study, the subjects are genotyped for their CYP3A5 alleles to determine the relative contribution of this polymorphism to inter-individual variability in AUC.

Type of Submission:
For submissions under an IND, these data could be submitted as a VGDS. For submissions under NDA/BLA, these data would be required to be submitted as a synopsis, and a VGDS of the data is encouraged.

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2) or in the drug label or as part of the scientific database (such as described in Figure B1). In addition, polymorphism of CYP3A5 is not widely studied and is therefore neither a probable or known valid biomarker (such as described in Figure A3, B2, or B3). The information on this genotype is considered to be exploratory (as described in Figure A4 or B4 of this document).

Topic Area: Transporters

Scenario 1: A sponsor conducts a phase 1 bioavailability study in human volunteers. The NME is a substrate of ABCB1. After the completion of the study, the sponsor genotypes the subjects for their alleles. The data may be used to explore causes of inter-individual variability in AUC.

Type of Submission:
For submissions under IND, these data could be submitted as a VGDS. For submissions under NDA/BLA, these data would be required to be submitted as a synopsis, and a VGDS of the data is encouraged.

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2) or in the drug label or as part of the scientific database (such as described in Figure B1). In addition, polymorphism of ABCB1 is not well established. Conflicting data on the P-gp activities of various SNPs differ in published reports and is therefore neither a probable or known valid biomarker (such as described in Figures A3, B2, or B3). The information on this genotype is considered to be exploratory (as described in Figure A4 or B4 of this document).

Scenario 2: During IND development, a sponsor conducts a phase 3 clinical trial of a NME in patients with the target indication. The NME is a substrate of ABCB1. The sponsor genotypes patients for their ABCB1 alleles prior to therapy and uses two different treatment regimens based on genotypes.

Type of Submission:
Required in full report (IND)

Rationale:
The test results are used in clinical decision making (affecting dose selection) (as described in Figure A1 of this document).

Topic Area: Receptors

Scenario 1: During the IND stage of development, a sponsor reported that, based on a retrospective analysis, 5-HT1A Ser22 allele was associated with poor response to an SSRI anti-depressant. In the next clinical trial, the sponsor excludes patients with this marker genotype from the trial to enhance the drug's efficacy profile.

Contains Nonbinding Recommendations

Type of Submission:
Required in full report (IND)

Rationale:
Data will be used in clinical decision making (entry criteria) (as described in Figure A1).

Topic Area: Clinical Outcomes- Efficacy

Scenario 1: During the IND stage of development, a 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. The sponsor excludes patients with this marker genotype from the trial to enhance the drug's efficacy profile.

Type of Submission:
Required in full report (IND)
The sponsor is encouraged to develop a pharmacogenomic diagnostic test (unless it is already available), if it to be reflected in label.

Rationale:
Data will be used in clinical decision making (entry criteria) (as described in Figure A2).

Topic Area: Clinical Outcomes- Safety and Efficacy

Scenario 1: In a clinical trial, psoriatic lesions are biopsied for gene expression profiling of 160 known disease-associated genes and 140 genes potentially predictive of response for the purpose of comparing gene profiles in responders and nonresponders treated with 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 the sponsor does not intend to incorporate the genetic information into labeling

Type of Submission:
For submissions under IND, these data could be submitted as a VGDS. For submissions under NDA/BLA, these data would be required as a synopsis, and a VGDS of the data is encouraged.

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2). In addition, these are research data and are therefore neither a probable or known valid biomarker (such as described in Figure A3, B2, or B3). The data are considered to be exploratory (as described in Figure A4 of this document).

Scenario 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.

Type of Submission:
These data could be submitted as a VGDS.

Rationale:

The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2). In addition, these are research data and are therefore neither a probable or known valid biomarker (such as described in Figure A3). The data are considered to be exploratory (as described in Figure A4 of this document).

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

Type of Submission:
Required in full report (IND)

Rationale:
The 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 (as described in Figure A2.)

Topic Area: Nonclinical Safety

Scenario 1: Vasculitis is a major drug-related nonclinical safety signal and the underlying mechanism of toxicity is unknown. It is normally confirmed by histopathology. A sponsor uses new rat gene chip micro array technology to profile 8000 known genes to investigate the mechanism of toxicity and possibly see a pattern of genetic biomarkers in treated rats that is different from controls.

Type of Submission:
For submissions under IND, these data could be submitted as a VGDS. For submissions under NDA/BLA, these data would be required as a synopsis, and a VGDS of the data is encouraged.

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2). In addition, these are research data and are therefore neither a probable or known valid biomarker (such as described in Figure A3, B2, or B3). The data are considered to be exploratory (as described in Figure A4 of this document).

Scenario 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.

Type of Submission:
Required in full report (IND).

Rationale:
The 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 (as described in Figure A2)

Scenario 3: During the IND stage of development, 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.

Type of Submission:

These data could be submitted as a VGDS (IND).

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2). In addition, these are research data and are therefore neither a probable or known valid biomarker (such as described in Figure A3). The data are considered to be exploratory (as described in Figure A4 of this document).

Scenario 4: During the IND stage of development, 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. The sponsor succeeds 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.

Type of Submission:
Required as full report (IND).

Rationale:
The 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 (as described in Figure A2).

Scenario 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 indicates that the dose-limiting effect of their drug candidate will probably injure 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.

Type of Submission:
For submissions under IND, these data could be submitted as a VGDS. For submissions under NDA/BLA, these data would be required as a synopsis, and a VGDS of the data is encouraged.

Rationale:
The test results are not being used in decision-making or scientific arguments (such as described in Figure A1 or A2). In addition, these are research data and are therefore neither a probable or known valid biomarker (such as described in Figure A3, B2, or B3). The data are considered to be exploratory (as described in Figure A4 or B4 of this document).

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.[1]

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

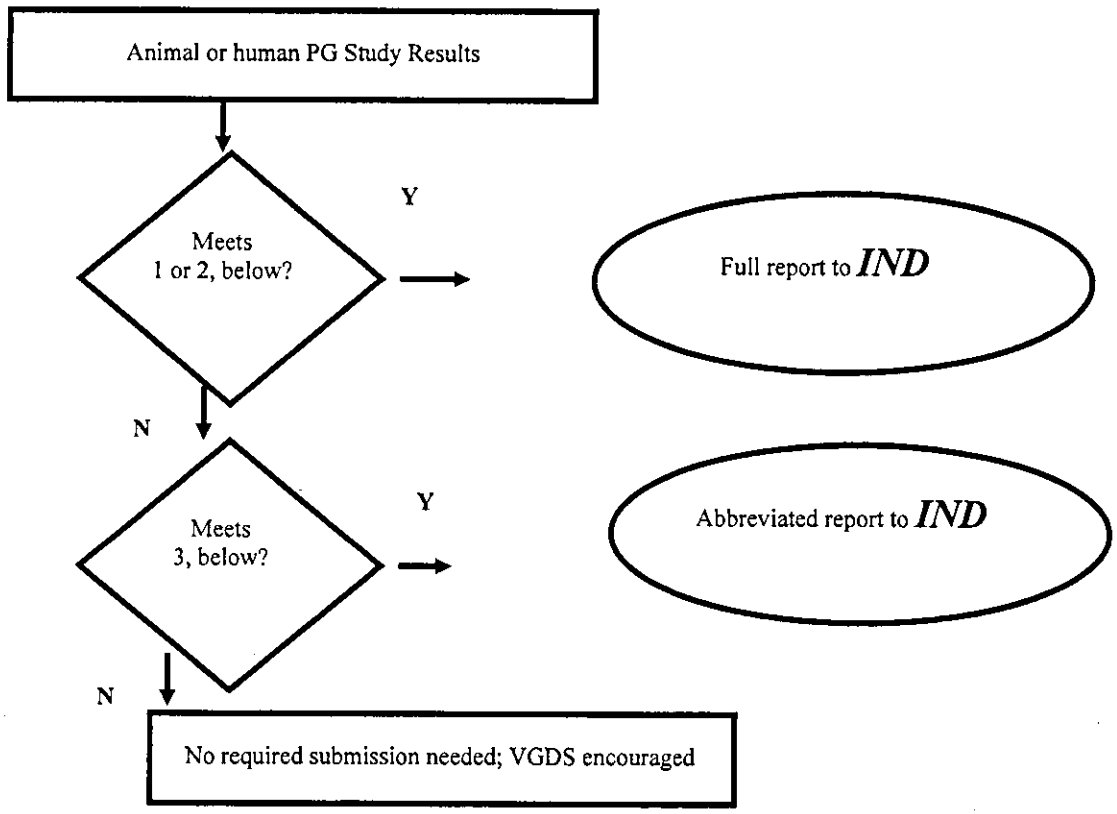
- **Probable valid biomarker:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance 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.
  - 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.

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

Figure 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 a 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).

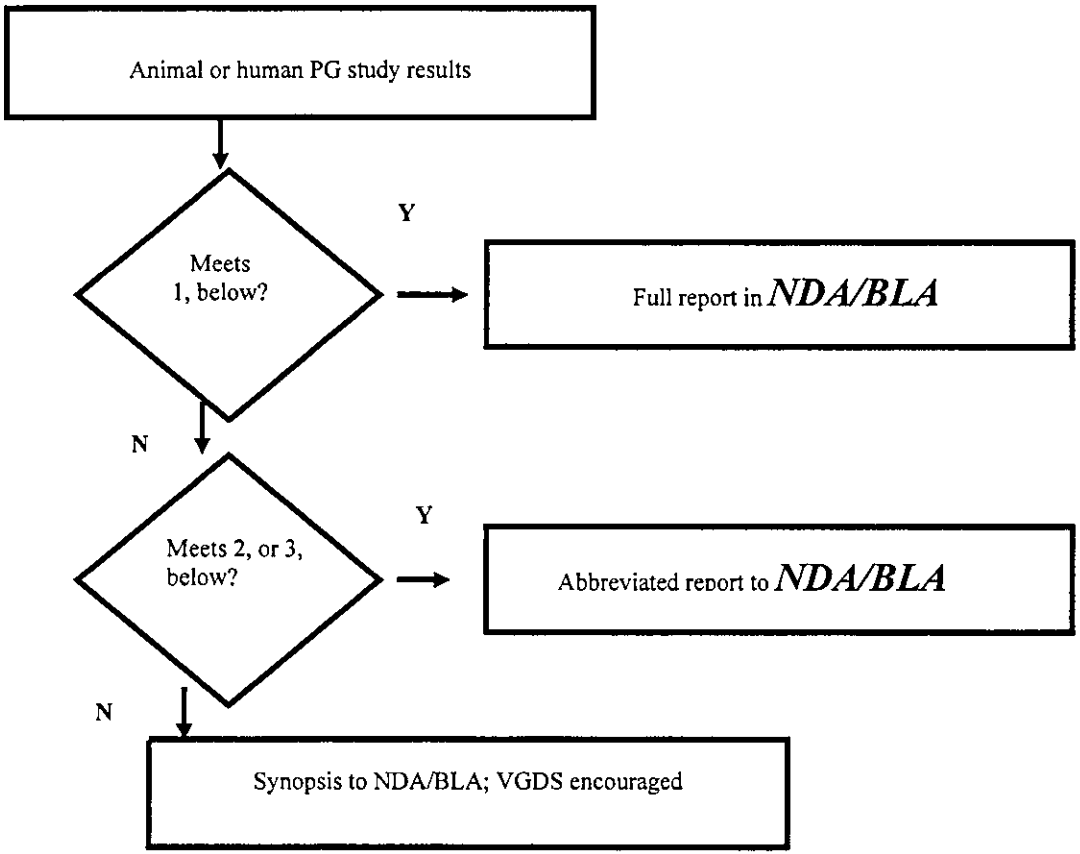
2. A sponsor is using the test results to support scientific arguments pertaining to the pharmacologic mechanism of action, the selection of drug dosing or the safety and effectiveness of a drug.
3. The test results constitute a known, valid biomarker for physiologic, pathophysiologic, pharmacologic, 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 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.

Figure 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 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.

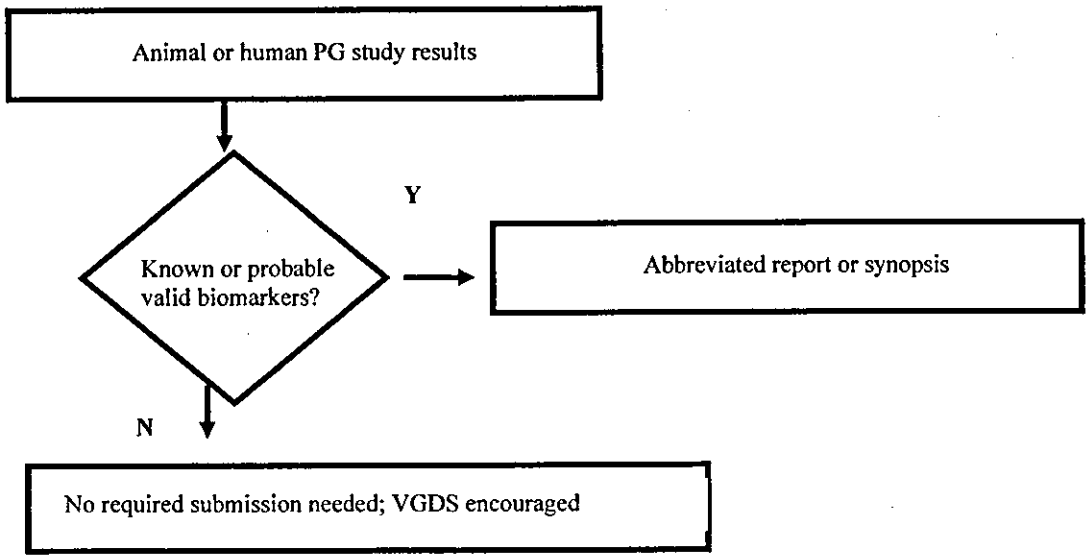
   - Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection, or effectiveness
   - Pharmacogenomic test results that the sponsor proposes to describe in the drug label
   - Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label

2. 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.

Figure C: Submission of Pharmacogenomic (PG) Data to an Approved NDA, BLA, or Supplement



OFFICE OF THE CENTER DIRECTOR

Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG)

CONTENTS

PURPOSE
BACKGROUND
REFERENCES
DEFINITIONS
GENERAL POLICY
RESPONSIBILITIES
EFFECTIVE DATE

Attachment: IPRG Organization

PURPOSE

This MAPP describes

- The role and responsibilities of the Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Procedures to be used in designating members to serve on the IPRG
- The structure and function of the IPRG within the FDA

BACKGROUND

At present, most pharmacogenomic data are of an exploratory or research nature, and FDA regulations do not require that these data be submitted to an investigational new drug application, or that complete reports be submitted to a new drug application or biologics licensing application. However, to be prepared to appropriately evaluate anticipated future submissions, FDA scientists need to develop an understanding of relevant scientific issues, such as:

- 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 and to clinical outcomes
- The ability to transmit, store, and process large amounts of complex pharmacogenomic data streams with retention of fidelity

As described in the guidance for industry on *Pharmacogenomic Data Submissions*, the FDA is asking sponsors conducting such programs to consider providing pharmacogenomic data to the Agency voluntarily, when such data are not otherwise required by regulation. The guidance also announced the formation of a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review voluntary pharmacogenomic data submissions (VGDSs) and communicate with sponsors, provide

guidance to the reviewing divisions on required submissions; and work on ongoing pharmacogenomic data submission policy development. This MAPP provides the charter for the IPRG.

REFERENCES

- Guidance for industry, *Pharmacogenomic Data Submissions*
- CDER MAPP 4180.3, Processing and Reviewing Voluntary Genomic Data Submissions
- CBER SOPP 8204, Processing of Voluntary Genomic Data Submissions
- CBER SOPP 8114, Administrative Processing of Documents Received Prior to Submitting Investigational or Marketable Submissions (Pre-Submissions).

DEFINITIONS

IPRG: Designation for Interdisciplinary Pharmacogenomic Review Group. The IPRG will oversee the review of all VGDSs submitted to the Agency and consult, on request, on the GDSs.

GDS: Designation for Genomic Data Submission

Voluntary GDS (VGDS): Designation for Voluntary Genomic Data Submission

Stand alone VGDS: The designation for a voluntary GDS that is not associated with an existing application. Such voluntary submissions will be handled as submissions to a new pre-IND application.

Associated VGDS: The designation for a voluntary GDS that is submitted to an existing application (e.g., investigational new drug application (IND), new drug application (NDA), biologics licensing application (BLA), or supplement). Such information will be submitted to the existing application, but will not be used by FDA in the regulatory decision making process.

Required GDS: The designation for a GDS that is required (per the relevant regulations) to be submitted to, or as part of, an existing application (e.g., IND, NDA, BLA, or supplement) and that will be used during the regulatory decision making process. This MAPP does not address required GDS submissions which will be processed according to standard processing for routine application submissions.

GENERAL POLICY

- The FDA will not use information submitted through the voluntary process for regulatory decision making on investigational and marketing/licensing applications.
- The IPRG will review all VGDSs.
- The reviewing divisions can request a consult with the IPRG on ***required*** GDS submissions.
- Required GDSs will be part of the associated application.
- VGDSs will be received by the Agency, processed, and sent directly to the IPRG.

- The IPRG will be the primary contact (internal and external) for all voluntary submissions, coordinating the communication with sponsors and the FDA regarding all VGDS-related issues.
- When an exploratory biomarker appears to be a probable or known biomarker, the IPRG will initiate a meeting of the Pharmacogenomic Advisory Subcommittee to allow public assessment of the related issues.

ORGANIZATION (See graphic depiction in the Attachment)

- **Oversight** – A senior manager appointed by the FDA Commissioner (***the OC Representative***) and the ***Center Directors of CDER, CBER, and CDRH*** will oversee the IPRG.

- **Location** – Although an interdisciplinary group, the IPRG is located in CDER in the immediate Office of Clinical Pharmacology and Biopharmaceutics.

- **IPRG Members** –
  - ***Chair***, appointed by the OC representative
  - ***CDER, CBER, and CDRH representatives***, appointed by the Center Directors of CDER, CBER, and CDRH. Five representatives are appointed from each center.
  - ***Executive secretary/project manager***, reporting to the Chair

- **Center Experts** – Reviewers, appointed by the CBER, CDER, and CDRH representatives. Experts serve on a temporary basis and are appointed "ad-hoc" depending on the subject matter of the GDS to be reviewed.

- **Advisory Subcommittee** – Advisors to the IPRG will be appointed to a subcommittee (***IPRG Advisory Subcommittee***) under the Drug Safety and Risk Management Advisory Committee. Advisors will be experts in the field and are critical to ensure state-of-the-art scientific evaluation of VGDSs.

RESPONSIBILITIES

The IPRG is the body responsible for reviewing VGDSs. In addition, the IPRG has several responsibilities related to the implementation of genomic review practice within the Agency. In particular, the IPRG will:

General Responsibilities

- Review and evaluate VGDSs
- Meet with sponsors upon request before or after submitting a VGDS (see MAPP 4180.3)
- Consult upon request with review staff on required submissions containing genomic data
- Integrate pharmacogenomics into the regulatory review process and help develop future guidance and review standards
- Harmonize review practices and quality review systems for GDS applications
- Coordinate development of the optimal format for VGDSs, including coordinating electronic formats

- Coordinate among disciplines and organizations in FDA, in particular CBER, CDER, Office of Combination Products (OCP), and CDRH to guarantee the efficient, accurate, and transparent review of genomic data
- Coordinate public discussions and set agendas for advisory committee meetings with regard to "lessons learned" from VGDS review
  - Define key issues to advance the use of rational pharmacogenomic principles in drug development, in particular issues pertaining to the regulatory review process
  - Facilitate FDA internal education regarding pharmacogenomic data, including seminars and printed materials
  - Meet once every month to discuss data submissions and other organizational or policy issues
  - Establish and maintain related policies
  - Establish working groups to facilitate goals of IPRG
  - Bring topics to Drug Safety and Risk Management Advisory Committee

Specific Responsibilities

- OC Representative
  - Appoints Chair of IPRG
  - Updates Office of the Commissioner on IPRG activities

- Center Directors (CDER, CBER, CDRH)
  - Appoint center representatives (max. five representatives per center)

- Chair
  - Coordinates IPRG activities
  - Communicates with sponsors, HHS, industry, and academia
  - Signs off on final reviews of VGDSs
  - Updates OC representative on IPRG activities

- Project Manager/Executive Secretary
  - Track and distribute submissions
  - Set up meetings
  - Document internal and external meetings (meeting minutes)

- Reviewers
  - Provide expertise in highly specialized areas
  - Update center representatives on review activities
  - Review VGDS
  - Request consults
  - Prepare questions for sponsors
  - Recommend new or improved policies
  - Consult with the review divisions upon request for required GDSs
  - Draft VGDS review and/or report

- CDER, CBER, CDRH Representatives
  - Appoint CDER, CBER, CDRH reviewers
  - Disseminate information (submissions, reports, meetings) via appropriate channels within their centers
  - Update Center Directors on IPRG activities

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment

Overview IPRG Organization