# Pharmacogenomic Data Submissions

## Guidance for Industry

***DRAFT GUIDANCE***

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For questions regarding this draft document, contact CDER_OCP_GPT@fda.hhs.gov.

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**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**National Center for Toxicological Research (NCTR)**

**March 2023**
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# Pharmacogenomic Data Submissions Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

This guidance is intended to facilitate progress in the field of pharmacogenomics and the use of pharmacogenomic data in drug[2] development. This document is intended to clarify the contexts in which pharmacogenomic study findings and data must be included in submissions related to investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) based on the FDA's regulations. In addition, this document provides recommendations to sponsors and applicants on the format and content of the pharmacogenomic data submissions.

For the purposes of this guidance, the term *pharmacogenomics* is defined as the study of variations of DNA and RNA characteristics as related to drug response;[3] DNA or RNA variations can be germline, somatic, or microbial. *Pharmacogenomics* does not refer to data resulting from proteomic, metabolomic, or other *-omic* studies, although similar considerations in this guidance could be applicable for determining whether to submit findings and data from such studies.

In 2005, FDA issued a final guidance for industry, *Pharmacogenomic Data Submissions*. When finalized, this guidance will replace the 2005 guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration as well as the National Center for Toxicological Research.

[2] For the purposes of this guidance, the terms *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs.

[3] For more information, see the FDA guidance entitled *E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories* (April 2008). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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

Pharmacogenomic studies have the potential to help identify sources of interindividual variability in drug exposure or response (both effectiveness and toxicity), making it possible to optimize therapy for individuals. Currently, several pharmacogenomic biomarkers with well-accepted mechanistic and clinical significance are being integrated into drug development (e.g., enriched clinical trial designs) and clinical practice.

Sponsors and applicants submitting or holding INDs, NDAs, or BLAs are subject to FDA requirements for submitting data to the FDA that are relevant to drug safety and effectiveness.[4] However, the regulations were developed before the advent of widespread animal or human genetic testing (e.g., high-throughput DNA sequencing) or gene expression testing and do not specifically describe the submission requirements for such data as a separate category.[5]

This guidance, when final, will constitute the FDA's current thinking about pharmacogenomic study results and the associated data required to be submitted in IND, NDA, or BLA submissions, as well as the FDA's recommendations as to the level of detail and format for reporting. Discussions of when and how to submit pharmacogenomic study results and the associated data in an investigational device exemption (IDE) application or other device submission to the FDA are excluded from the scope of this document.[6] This guidance is intended to facilitate the generation and use of pharmacogenomic data during drug development. The policies outlined in this guidance are intended to advance the field in a manner that will benefit both drug development programs and public health.

## III. SUBMISSION POLICY

The FDA's regulations establish requirements for the submission of information in INDs, NDAs, and BLAs.[7] Consistent with these regulations, the sections below summarize the contexts in which pharmacogenomic study results and data must be reported in IND, NDA, and BLA submissions.[8]

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[4] 21 CFR parts 312, 314, and 601 (including 21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12).

[5] 21 CFR parts 312, 314, and 601.

[6] 21 CFR part 812.

[7] 21 CFR parts 312, 314, and 601.

[8] 21 CFR parts 312, 314, and 601 (including 21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12).

Table 1 also summarizes the FDA's recommendations on the amount and level of detail to report for each context in which pharmacogenomic study results and data are reported to the FDA. The amount and level of detail to report to the FDA should vary depending on the context of how the genomic biomarkers are utilized and the potential risks associated with the biomarker. For example, data related to exploratory safety studies should be supplied in a brief synopsis, whereas data supporting statements in FDA labeling should be supplied in submission of subject-level data from clinical trials. Genomic data that fit multiple contexts should be submitted at the more detailed reporting level. For example, genomic biomarker studies that are related to pharmacokinetics (e.g., drug metabolizing enzyme gene variants) are recommended to be submitted as a synopsis. However, if those same genomic data are also the basis for patient dosing, subject-level data, and a full report rather than only a synopsis should be submitted. More detailed reports and data can be submitted where synopses are recommended. Furthermore, the FDA may request additional data (e.g., detailed reports, subject level data) as needed for the review of IND submissions as well as NDAs or BLAs as outlined in 21 CFR parts 312, 314, and 601.

Sections III.A and III.B provide additional information regarding the submission of pharmacogenomic data under IND regulations and NDA and BLA regulations, respectively. For additional information on data submission and report formats, see section IV.

**Table 1. Contexts for When Pharmacogenomic Data Submissions Are Required and Recommended Reporting Levels**

| **Context of Genomic Biomarker Study Results** (§§ 312.23, 312.32, 312.33, 314.50, 314.81, 601.2, 601.12) | **Reporting Level** | |
|---|---|---|
| | **IND** | **NDA/BLA** |
| Proposed for inclusion in labeling | -- | Detailed Report, Subject-Level Data |
| Justifies the use of a genomic biomarker in the design, conduct, or analysis of planned clinical trials intended to support approval* | Detailed Report | -- |
| Results from the integral use of a genomic biomarker in the design, conduct, or analysis of completed clinical trials* | Synopsis | Detailed Report, Subject-Level Data |
| Indicates substantial differences in responses related to efficacy across subgroups† | Synopsis | Detailed Report |
| Indicates a significant risk in a subset of individuals† | Synopsis | Detailed Report |
| Relates to pharmacokinetics (i.e., drug metabolism or transport) | Synopsis | Synopsis |
| Relates directly to the drug's target or mechanism of action or informs pharmacodynamic effects | Synopsis | Synopsis |
| Relates to safety but does not indicate a significant risk or a potential safety issue | -- | Synopsis |

* In effect, the genomic biomarker is used for the inclusion or exclusion of study subjects, treatment allocation (e.g., stratified randomization), subgroup hypothesis testing, or altered dosing or monitoring.

† For example, a genetic marker reaches genome-wide significance in a genome-wide association study for a response related to efficacy or a significant risk, whether based on the analysis of an individual study or multiple studies.

### A. Submission of Pharmacogenomic Data Under IND Regulations

- 21 CFR part 312 describes reporting requirements for IND sponsors. Sponsors are required to submit certain information related to an IND for which they are responsible in

order to comply with the regulation's requirements.[9] The contexts in which pharmacogenomic data must be submitted and the FDA's recommendations for the extent of and mechanism for reporting are as follows:

- Pharmacogenomic study findings supporting the use of a genomic biomarker in the design, conduct, or analysis[10] of planned clinical trials are required to be reported to the FDA with detailed information about such findings.[11] Detailed reports should be submitted in this context to facilitate the review of the biomarker's clinical validity and ensure that trials making use of the biomarker are expected to meet stated objectives.[12] Detailed reports should be submitted in the IND under the Previous Human Experience section, in meeting packages, or in clinical study protocols/reports, as appropriate.

- Pharmacogenomic study results from completed clinical trials where the biomarker was integral to the design, conduct, or analysis "[are] pertinent to the understanding of the drug's actions" and must be described in Annual Reports.[13]

- Pharmacogenomic study findings derived from animal or in vitro studies must be submitted when intended primarily to support the safety of the proposed clinical investigation.[14]

- The FDA recognizes that many pharmacogenomic studies are exploratory and might not have been replicated. However, pharmacogenomic studies that identify significant predictors of treatment response must be reported in Annual Reports because they pertain to understanding the drug's actions.[15] Significant predictors of treatment response include substantial differences in treatment response across biomarker-defined subgroups or statistically significant relationships between the biomarker and primary study endpoints in the context of the study. In addition, all pharmacogenomic studies generating data related to the effect of variation in the drug target or other genes related to the mechanism of action on efficacy or safety endpoints, as well as pharmacodynamic studies that make use of genomic biomarkers as an endpoint (e.g., gene expression), must also be reported in

[9] See 312.23, 312.32, 312.33.

[10] In effect, the genomic biomarker is used for the inclusion or exclusion of study subjects, treatment allocation (e.g., stratified randomization), subgroup hypothesis testing, altered dosing, or monitoring.

[11] 21 CFR 312.23(a)(9)(i).

[12] 21 CFR 312.23(a)(9)(i) for information on the detailed information that must be submitted to the FDA.

[13] 21 CFR 312.33(b)(5).

[14] 21 CFR 312.23(a)(8)(ii).

[15] 21 CFR 312.33(b)(5).

Annual Reports because they pertain to understanding the drug's actions.[16] These pharmacogenomic studies should be reported as synopses and should also be included in meeting packages and/or in clinical study protocols/reports, as appropriate. A study could be an analysis of an individual study or a pooled analysis of multiple trials. Statistical significance should be considered in the context of applying conventional multiplicity corrections.

- Pharmacogenomic study findings related to safety endpoints must be reported in IND Safety Reports because they pertain to the drug's safety[17] or in Annual Reports because they pertain to understanding the drug's actions.[18] These pharmacogenomic studies should be reported as synopses and should also be included in meeting packages and/or in clinical study protocols/reports, as appropriate. Pharmacogenomic findings that identify predictors of adverse events which may pose significant risks to study subjects, or otherwise indicate a significant risk, must be submitted in an IND Safety Report.[19]

- Other studies related to safety endpoints or that use gene expression as an endpoint to identify safety signals but do not identify any significant relationships must be described in Annual Reports.[20] Pertinent negative findings must be explicitly reported (e.g., absence of HLA involvement in immune-related adverse events, or absence ADME-related effects where an exposure-response relationship for safety has been documented).[21]

- Study findings related to pharmacokinetics must be reported in Annual Reports because they pertain to the drug's bioavailability and/or dose-response relationship.[22] This can include pharmacokinetic studies where enrollment is prospectively based on drug metabolizing enzyme or transporter genotype, or retrospective studies on efficacy, safety, or pharmacokinetic endpoints (e.g., drug metabolizing enzyme and transporter panels). These studies should be reported as synopses and should also be included in meeting packages and/or in clinical study protocols/reports, as appropriate.

- FDA regulations require inclusion of a summary of relevant data related to

[16] 21 CFR 312.33(b)(5).

[17] 21 CFR 312.32(c)(1)(ii).

[18] 21 CFR 312.33(b)(5).

[19] 21 CFR 312.32(c)(1)(ii).

[20] 21 CFR 312.33(b)(5).

[21] 21 CFR 312.33(b)(5).

[22] 21 CFR 312.33(b)(5).

pharmacogenomic associations with pharmacokinetics, effectiveness, or safety in Investigator Brochures.[23]

- Pharmacogenomic studies that are not required to be submitted under 21 CFR part 312 can be voluntarily reported.

- 21 CFR 312.23(a)(11) states that a sponsor shall submit "[i]f requested by FDA, any other relevant information needed for review of the application." Therefore, during the IND review, the FDA might request additional pharmacogenomic information it considers relevant.

### B. Submission of Pharmacogenomic Reports and Data Under NDA and BLA Regulations

- 21 CFR 314.50 outlines the NDA submission requirements. As the introduction to 21 CFR 314.50 states, "[t]he NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source." Information that is pertinent to an evaluation of the application includes information related to each controlled clinical study pertinent to a proposed use of the drug, a description and analysis of "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product," and "[a] summary and updates of safety information."[24] The pharmacogenomic studies required to be submitted to the FDA for an IND are generally relevant to the FDA's evaluation of the safety and effectiveness of a drug product. Therefore, to comply with these regulations, sponsors must provide reports of certain pharmacogenomic studies in their NDAs as outlined in Table 1.[25] Table 1 also specifies the recommended reporting level for each type of pharmacogenomic study reported in NDAs. Sponsors can discuss submission of pharmacogenomic reports and data in NDA submissions at pre-NDA meetings.

- 21 CFR 601.2 generally outlines the BLA submission requirements. 21 CFR 601.2 states that the BLA manufacturer "shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency..." The pharmacogenomic studies required to be submitted to the FDA for an IND are generally relevant to the FDA's evaluation of the safety, purity, and potency of a biological product. Therefore, like NDA sponsors, BLA sponsors must provide reports of certain pharmacogenomic studies in their BLAs as outlined in Table 1.[26] Table 1 also specifies the recommended reporting level for each

[23] 21 CFR 312.23(a)(5)(iii) and 21 CFR 312.23(a)(5)(iv).

[24] 21 CFR 314.50(d)(5)(iv) and (vi); 21 CFR 314.50(d)(5)(vi) also identifies the specific types of information that constitute the "summary and updates of safety information."

[25] 21 CFR 312 and 314.

[26] 21 CFR 312 and 601.

type of pharmacogenomic study reported in BLAs. Sponsors can discuss submission of pharmacogenomic reports and data in BLA submissions at pre-BLA meetings.

- In addition, if a sponsor intends for pharmacogenomic study data to be used in the drug labeling or as part of the scientific database being relied upon to support approval, then data must be submitted from such studies to the NDA or BLA.[27] Such data should be submitted as subject-level data in a detailed report. This includes data pertaining to pharmacogenomic biomarkers that inform labeling, because the data pertain to selecting patients for clinical trials (whether enrollment is limited to or stratified by the biomarkers), determining dosing and administration, or informing drug-drug interactions (or lack thereof). Also, information not tied to specific clinical recommendations must be submitted if it relates to any narrative about the drug's pharmacokinetic disposition or clinical trial populations in labeling.[28]

- 21 CFR 314.81(b)(2) and 601.12 outline the requirements for submitting to a previously approved NDA or BLA, new scientific information that might affect the safety, effectiveness, or labeling of a drug. Pharmacogenomic studies outlined in Table 1, and as further described in section III.A, must be submitted in Annual Reports[29] and should also be submitted, as appropriate, in meeting packages and/or clinical study protocols/reports.

- Pharmacogenomic studies that are exploratory in nature, such as initial studies to discover predictors of drug response, pharmacoepidemiologic, or observational studies, and that are not described in Table 1 or sections III.A or III.B, are not required to be reported.

## IV. FORMAT AND CONTENT OF SUBMISSIONS

### A. Reports

The FDA recommends that synopses of pharmacogenomic studies should include a brief summary of the following:

- Study design, and if a substudy, a description of the clinical studies from which specimens for genomic analyses were acquired

- Methods, including assay method/platform and patient inclusion/exclusion criteria

- Statistical analysis plan, including prespecified endpoints, the analysis population, multiplicity corrections, and models utilized

[27] 21 CFR 314.50(c)(2)(i), 314.50(d)(5)(ii), (iv), (v), and (vi), and 601.2.

[28] 21 CFR 314.50(c)(2)(i), 314.50(d)(5)(ii), (iv), and (v), and 601.2.

[29] 21 CFR 314.81(b)(2) and 601.12.

- Topline results, including sample size and findings that meet study-level significance or for key prespecified endpoints

The FDA recommends that detailed reports of pharmacogenomic studies include the following:

- Synopsis
- Introduction, including the rationale for the study
- Objectives, including the objectives and prespecified endpoints of both the pharmacogenomic study and, if a substudy, the clinical studies from which specimens for genomic analyses were acquired
- Methods
    - Clinical trial/study methods, including study design, treatment regimens, inclusion/exclusion criteria for the primary study and substudy (as applicable), key prespecified endpoints
    - Genetic study methods, including study designs, data-generation platform, specific allele selection, sample handling and isolation, assay quality control, genotype/phenotype relationships, source and version of genomic references, and databases utilized
    - Statistical methods, including model or algorithm for analyses, the prespecified analysis population, corrections for multiplicity, tools, versions, and parameters used at each stage of the analyses, adjustments for race/ethnicity, computational environment and resources used to process data, and handling of missing data[30]
- Results, including demographics of the overall and genotyped populations, genotype/haplotype distributions, association results, appropriate graphical or table-based summaries (e.g., box plots, Kaplan-Meier plots)
- Discussion and Conclusions
- Pharmacogenomic study reports, submitted using the "pharmacogenomics" file-tag in eCTD backbone files and study tagging files, as appropriate

### B. Subject-Level Data Submissions

- Study data contained in NDAs, certain BLAs, and certain INDs must be in an electronic format that the Agency can process, review, and archive, unless such submission is

[30] For more information on the FDA's expectations for and recommendations on use of a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials, see the FDA guidance entitled *Collection of Race and Ethnicity Data in Clinical Trials* (October 2016).

exempt from the electronic submission requirements, or if the FDA has granted a waiver.[31] For more information on electronic submissions, please see *Providing Regulatory Submissions in Electronic Format - Standardized Study Data, Providing Regulatory Submissions in Electronic Format - IND Safety Reports,* and the *Study Data Technical Conformance Guide.*[32]

- Relevant data obtained from high-throughput analysis platforms can be extracted at the sponsor's discretion. If such data are contained in NDAs, certain BLAs, and certain INDs, the data must be in an electronic format that the Agency can process, review, and archive, unless such submission is exempt from the electronic submission requirements, or if the FDA has granted a waiver.[33]

- If pharmacogenomic study data are not able to be linked to primary clinical trial datasets based on the informed consent (e.g., genetic data are anonymized), relevant clinical trial data should be included in separate analysis datasets.

### C. Location[34]

- Synopses and detailed reports submitted to the IND should be referenced in relevant sections of a submission, such as Safety Reports or in Annual Reports, as appropriate. The FDA also encourages reporting of these results in meeting packages, clinical study reports, or other submissions to the FDA, as appropriate.

- Synopses or detailed reports and associated data submitted to NDAs or BLAs should be referenced in relevant sections of a submission. Analyses for a single study should be incorporated within the clinical study reports and clinical trial datasets for that single study; analyses and datasets from multiple studies should be submitted as a separate report under *Reports of analyses of data from more than one study*, section 5.3.5.3 of the eCTD. The FDA encourages summarizing these data in relevant submission summaries such as the Integrated Summary of Safety or the Integrated Summary of Effectiveness, as appropriate.

[31] Section 745A(a) of the FD&C Act.

[32] Available at http://www.fda.gov/eStudyResources.

[33] Section 745A(a) of the FD&C Act.

[34] The eCTD Submission Standards, which include a *Comprehensive Table of Contents of Headings and Hierarchy* and *eCTD Specifications*, can be found at the following link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd. Detailed reports of pharmacogenomic studies should be reported using the *pharmacogenomics* file-tag.