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# Guidance for Industry Pharmacogenomic Data Submissions

## *DRAFT GUIDANCE*

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)**

**November 2003  
Procedural**

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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

# Guidance for Industry Pharmacogenomic Data Submissions

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**U.S. Department of Health and Human Services  
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**Guidance for Industry<sup>1</sup>  
Pharmacogenomic Data Submissions**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**I. INTRODUCTION**

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

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

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, the term *drug* or *drug product* includes human drug and biological drug products.

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

40

### **II. BACKGROUND**

41

42  
43 The promise of pharmacogenomics lies in its potential ability to identify sources of inter-  
44 individual variability in drug response (both efficacy and toxicity); this will help individualize  
45 therapy with the intent of maximizing effectiveness and minimizing risk. However, the field of  
46 pharmacogenomics is currently in early developmental stages, and such promise has not yet been  
47 realized. Pharmaceutical sponsors have been reluctant to embark on programs of  
48 pharmacogenomic testing during the FDA-regulated phases of drug development because of  
49 uncertainties in how the data will be used by the FDA in the drug application review process.  
50 This guidance is intended to help clarify FDA policy in this area.

51

52 Sponsors submitting or holding INDs, NDAs, or BLAs are subject to FDA requirements for  
53 submitting to the Agency data relevant to drug safety and efficacy (21 CFR 312.22, 312.23,  
54 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12). Because these regulations were developed  
55 before the advent of widespread animal or human genetic or gene expression testing, they do not  
56 specifically address when such data should be submitted. The FDA has received numerous  
57 inquiries about what these regulations require of sponsors who are conducting such testing.

58

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

61

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

64

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

69

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

72

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

75

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

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

81  
82 It is important for the FDA to have a role in the evaluation of pharmacogenomic tests, both to  
83 ensure that evolving FDA policies are based on the best science and to provide public confidence  
84 in the field. It is also important that FDA policy facilitate, not impede, the use of  
85 pharmacogenomic tests during drug development and, to the extent possible, encourage open and  
86 public sharing of data and information on pharmacogenomic test results.

87  
88 To this end, the Agency has undertaken a process for obtaining input on these issues from the  
89 scientific community and the public. On May 16 and 17, 2002, the Agency held a workshop,  
90 cosponsored by pharmaceutical industry groups, to identify key issues associated with the  
91 application of pharmacogenetics and pharmacogenomics to drug development. Subsequently,  
92 on April 8, 2003, a public presentation was made to the FDA Science Board. This presentation  
93 contained a proposal for developing guidance on submission of information on  
94 pharmacogenomic tests and a potential algorithm for deciding whether a submission of such data  
95 is needed. The Science Board endorsed moving forward with both of these proposals.

96  
97 The policies and processes outlined in this draft guidance are intended to take the above factors  
98 into account and to assist in advancing the field in a manner that will benefit both drug  
99 development programs and public health.

100

101

### **102 III. SUBMISSION POLICY**

103

#### **104 A. General Principles**

105

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

120

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<sup>3</sup> 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.

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

127  
128 For the purposes of this guidance, a pharmacogenomic test result may be considered a *valid*  
129 *biomarker* if (1) it is measured in an analytical test system with well established performance  
130 characteristics and (2) there is an established scientific framework or body of evidence that  
131 elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.  
132 For example, the consequences for drug metabolism of genetic variation in the human enzymes  
133 CYP450 2D6 and thiopurine methyltransferase are well understood in the scientific community  
134 and are reflected in certain approved drug labels. The results of genetic tests that distinguish  
135 allelic variants of these enzymes are considered valid biomarkers. The guidance makes an  
136 additional distinction between known valid biomarkers that have been accepted in the broad  
137 scientific community and probable valid biomarkers that appear to have predictive value for  
138 clinical outcomes, but may not yet be widely accepted or have been independently replicated  
139 (see Glossary). When a sponsor generates, or possesses, data sufficient to establish a significant  
140 association between a pharmacogenomic test result and clinical outcomes, the test result  
141 represents a probable valid biomarker. The algorithms described below for IND, NDA, and BLA  
142 holders describe when to submit to FDA data on known valid biomarkers. Data on probable  
143 valid biomarkers need not be submitted to the IND if they are not used by the sponsor in decision  
144 making. However, we recommend that sponsors or applicants submit reports on probable valid  
145 biomarkers to unapproved NDAs or BLAs according to the algorithm in section IV.B.

146  
147 Many pharmacogenomic testing programs currently carried out by pharmaceutical sponsors or  
148 by scientific organizations are intended to develop the knowledge base necessary to establish the  
149 validity of new genomic biomarkers. During such a period of scientific exploration, test results  
150 are not useful in making regulatory judgments pertaining to the safety or effectiveness of a drug  
151 and are not considered known or probable valid biomarkers. However, scientific development of  
152 this sort is highly desirable for advancing understanding of relationships between genotype or  
153 gene expression and responses to drugs and, therefore, should be encouraged and facilitated. For  
154 these reasons, although submission of exploratory pharmacogenomic data is not required under  
155 the regulations, the FDA is encouraging *voluntary submission* of such data, as described below.

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

156  
157  
158  
159 As the field of pharmacogenomics advances, it is likely (and desirable) that sponsors will begin  
160 to use pharmacogenomic tests to support drug development and/or to guide therapy. Sponsors  
161 may choose to submit pharmacogenomic data that have not achieved the status of a valid  
162 biomarker to an IND, NDA, or BLA to support scientific contentions related to dosing, safety, or  
163 efficacy. For example, a sponsor may wish to provide supportive data demonstrating that  
164 changes in drug-induced gene expression differ between species that have different toxicologic  
165 responses to a drug, thus correlating changes in certain gene expression patterns with a specific

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

168  
169 When pharmacogenomic results are to be used in decision making in an animal safety trial, or  
170 during clinical development in a human trial as part of the protocol, the submission algorithms  
171 described below suggest that full information on the test system should be submitted to the IND.  
172 In contrast, results from earlier feasibility studies done under the same IND (or outside the IND)  
173 to establish the potential usefulness of the pharmacogenomic test (e.g., from samples taken  
174 during a dose-response study) should not normally be submitted unless they provide support for  
175 the use of the test in clinical decision making.<sup>4</sup>

176  
177 If a pharmacogenomic test shows promise for enhancing the dose selection, safety, or  
178 effectiveness of a drug, a sponsor may wish to fully integrate pharmacogenomic data into the  
179 drug development program. This could occur in two ways:

180  
181 1. The pharmacogenomic data are intended to be included in the drug label in an  
182 informational manner.

183  
184 For example, such data might be used to describe the potential for dose adjustment by  
185 drug metabolism genotype or to mention the possibility of a side effect of greater severity  
186 or frequency in individuals of a certain genotype or gene expression profile. In such  
187 cases, the pharmacogenomic test result may or may not be considered a valid biomarker,  
188 and an FDA-approved or widely used commercial pharmacogenomic test may not be  
189 available. Given this level of complexity, at the current time, sponsors should consult the  
190 relevant FDA review division for advice on how to proceed in a specific case. However,  
191 in all such cases, when a sponsor intends to include pharmacogenomic data in the drug  
192 label, we expect that complete information on the test and results would be submitted to  
193 the Agency as envisioned under §§ 314.50 and 601.2.

194  
195 2. Dose selection, safety, or efficacy of a drug as described in its label will be contingent  
196 upon the performance of a pharmacogenomic test or tests. For example:

- 197  
198 • In the later phases of clinical drug development, patients will be tested for drug  
199 metabolism genotype and dosed according to the test results.
- 200 • Patients will be selected for efficacy trial entry based on genotype (of patient or  
201 tumor) or gene expression profile.
- 202 • Patients will be excluded from the trial based on genotype or gene expression profile  
203 (e.g., marker for adverse event).

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

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



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

209  
210 If a new pharmacogenomic test will be used in therapeutic decision making (choosing or dosing  
211 of drugs), we recommend that sponsors consider obtaining premarket review by the Center for  
212 Devices and Radiological Health (CDRH) in conjunction with their drug development program.  
213 By studying or considering diagnostic issues in conjunction with the introduction of new drugs,  
214 or changes to existing therapeutic claims, it is often possible to provide simpler and more  
215 consolidated studies.

216  
217 The Office of In Vitro Diagnostics in CDRH is willing to meet with sponsors to discuss both  
218 scientific and regulatory issues with regard to new pharmacogenomic diagnostics and has both  
219 formal (IDE) and informal (pre-IDE) processes for helping to evaluate protocols.

220

### **C. Voluntary Submission of Exploratory Pharmacogenomic Research Data**

222

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

228

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

235

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

243

244

### **IV. SUBMISSION OF PHARMACOGENOMIC DATA**

246

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

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### 251           **A.       Submission of Pharmacogenomic Data During the IND Phase**

252  
253 Section 312.23 outlines information submission requirements for an IND, including for data  
254 generated or available during the IND phase. Section 312.23(a)(8) lays out the requirements for  
255 pharmacology and toxicology information: “Adequate information about pharmacologic and  
256 toxicological studies of the drug involving laboratory animals or in vitro, *on the basis of which*  
257 the sponsor has concluded that it is reasonably safe to conduct the proposed clinical  
258 investigations” (emphasis added). The in vitro and animal studies needed to establish a basis for  
259 proceeding with human trials of various types are well established internationally. Therefore,  
260 pharmacogenomic data relevant to, or derived from, animal or in vitro studies should ordinarily  
261 be submitted under § 312.23(a)(8) when the sponsor wishes to use these data to make a scientific  
262 case, or when the test is well established as a predictive biomarker (i.e., is a known valid  
263 biomarker).

264  
265 Section 312.23(a)(9) sets forth the requirements for submission of previous human experience  
266 with the investigational drug. A summary is required on trials or human experience relevant to  
267 an evaluation of the safety or effectiveness of the drug. Therefore, sponsors must submit human  
268 data of known relevance (e.g., known valid pharmacogenomic biomarkers). In addition,  
269 sponsors or applicants must submit “any other information that would aid evaluation of the  
270 proposed clinical investigations with respect to their safety or their design and potential as  
271 controlled clinical trials to support the marketing of the drug” (312.23(a)(10)(iv)) and “if  
272 requested by the FDA, any other relevant information needed for review of the application”  
273 (312.23 (a)(11)). Human pharmacogenomic data intended to be used in decision making in the  
274 drug development process is such data. In cases when the validity of the test is not well  
275 established, such data will be viewed by the FDA as supportive only for the purposes of  
276 regulatory decision making.

277  
278 Sponsors holding INDs who generate or possess pharmacogenomic data related to an  
279 investigational drug can comply with FDA requirements using the following algorithm:

280  
281           ***Pharmacogenomic data must be submitted to the IND under § 312.23 if ANY of the***  
282           ***following apply:***

- 283  
284           1. The test results will be used for decision making in any clinical trial, or in an animal  
285           trial used to support safety. (For example, the results will affect dose selection, entry  
286           criteria, safety monitoring, or subject stratification.)
- 287           2. The sponsor is using the test results to support scientific arguments pertaining to, for  
288           example, the safety, effectiveness, dosing and pharmacology of the drug.
- 289           3. The test results constitute a known valid biomarker for physiologic, pathophysiologic,  
290           pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known  
291           valid biomarker for a safety outcome in animal studies. If the information on the  
292           biomarker (example, human P450 2D6 status) is **not** being used for purposes 1 or 2  
293           above, the information can be submitted to the IND as an abbreviated report.

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

- 298           4. Information is from exploratory studies or is research data, such as from general gene  
299           expression analyses in cells/animals/humans, or single-nucleotide polymorphism  
300           (SNP) analysis of trial participants.
- 301           5. Information consists of results from test systems where the validity of the biomarker  
302           is not established.

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

306

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

310

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

315

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

316

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

326

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

331

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

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

342

343 1. Provide reports on pharmacogenomic investigations intended by the sponsor to be used in  
344 the drug label or as part of the scientific database being used to support approval as  
345 complete submissions (not in the form of an abbreviated report, synopsis, or VGDS),  
346 including information about test procedures and complete data, in the relevant sections of  
347 the NDA or BLA. If the pharmacogenomic test is already approved by the FDA or is the  
348 subject of an application filed with the Agency, information on the test itself can be  
349 provided by cross reference.

350 The following examples would fit this category.

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

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

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

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

376

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

379

380 **C. Submission to an Approved NDA or BLA**

381

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

382 The requirements for submitting new scientific information to an approved NDA or BLA are  
383 outlined in §§ 314.81(b)(2) and 601.12. Results of nonclinical or clinical pharmacogenomic  
384 investigations on known or probable valid biomarkers must be submitted in the annual report as  
385 synopses or abbreviated reports (21 CFR 314.81(b)(2)).

386  
387 Pharmacogenomic study results of other types do not meet the submission requirements outlined  
388 in the regulations (§ 314.81(b)(2)). However, such reports can be voluntarily submitted to the  
389 NDA or BLA as a VGDS.

390

### **D. Compliance with 21 CFR Part 58**

392

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

401

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

406

407

### **V. FORMAT AND CONTENT OF A VGDS**

409

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

418

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

426

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

- 435
- 436 • An article submitted to a peer-reviewed scientific journal
- 437 • An evolving public standard for specific types of experiments, such as the Minimum Information  
438 About a Microarray Experiment (MIAME) standard for microarray expression data.<sup>5</sup> An  
439 analogous approach could be used for formatting a VGDS containing genotyping or other  
440 genomic data derived from technology platforms other than nucleic acid hybridization arrays.
- 441 • A report on a gene expression microarray experiment containing the following:
  - 442 Title page
  - 443 Background and scientific rationale
  - 444 Primary and secondary study goals
  - 445 Synopses and summary of findings
  - 446 Study design and sample collection
  - 447 Array design and description
  - 448 Quality control tests performed on arrays
  - 449 Sample processing and preparation
  - 450 Demonstration of quality of RNA or DNA
  - 451 Hybridization procedures and parameters
  - 452 Measures of performance of hybridization such as spike-in control
  - 453 Measurements and quantification
  - 454 Normalization controls
  - 455 Number of repeats (array hybridized), number of biological assays performed
  - 456 Statistical analysis
  - 457 Bioinformatics tools and software used. Source of gene annotation
  - 458 Validation of gene expression by conventional assays such as Northern blot, real time  
459 PCR (polymerase chain reaction), RT-PCR (reverse transcriptase-PCR),  
460 immunohistochemistry, or Western blot, if reagents available
  - 461 Validation of SNP by SSCP (single-strand conformation polymorphism) or other assays
  - 462 Submission of electronic file containing raw images, raw data, scatter plots for all  
463 experiments reaching the conclusion, as well as an electronic data file of the  
464 background-corrected gene expression data (spot intensities) from microarray  
465 experiments that were used for analysis
  - 466 Results and conclusions
  - 467 References
  - 468

---

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

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

471

472

### **VI. PROCESS FOR SUBMITTING PHARMACOGENOMIC DATA**

474

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

477

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

480

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

485

486

### **VII. FDA REVIEW OF PHARMACOGENOMIC DATA**

488

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

497

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

510

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

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

516  
517 Currently, as discussed above, only a few pharmacogenetic tests for certain drug metabolizing  
518 enzymes are considered valid biomarkers in humans. Considerable concern has been expressed  
519 about how the FDA will evaluate newer types of pharmacogenomic data (e.g., results that may  
520 predict increased risk of adverse events, or point to an enhanced probability of response). In fact,  
521 the FDA has considerable experience dealing with these issues in other contexts. Examples of  
522 how pharmacogenomic studies fit into this experience include the following.

- 523
- 524 • Descriptions of drug metabolizing phenotypes and discussion of their impacts on dosing  
525 are common in drug labels. Extrapolation of this information to pharmacogenetic testing  
526 is straightforward.
  - 527 • There are many conditions or co-factors that may increase an individual's susceptibility  
528 to an adverse event (e.g., co-morbid conditions, metabolic susceptibilities such as renal or  
529 hepatic failure, or interacting drugs).

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

541  
542 It is most likely that, in the near future, pharmacogenomic markers that predict drug toxicity will  
543 be identified and developed on a parallel path with overall drug development. In other words,  
544 the drug would be developed in a conventional manner with a parallel effort to identify  
545 appropriate predictors of toxicity. If the drug's risk-benefit profile were acceptable, the drug  
546 could be approved prior to the completion of efforts to refine and develop the relevant  
547 pharmacogenomic tests. When and if a test's predictive value were to be established and the test  
548 were to become commercially available (either as an approved device or as a service), the drug  
549 label could be changed to reflect the data.

- 550
- 551 • The FDA has similar experience with tests used to target populations likely to respond to  
552 therapy.

553  
554 Several decades ago, broad indications for use were described in labels. Over time, as more  
555 exact diagnoses were developed, narrower indications were sought by sponsors, based on the  
556 clinical trials conducted. A similar evolution occurred in the field of anti-HIV therapies as drug  
557 resistance testing became available. We encourage sponsors to continue to develop  
558 pharmacogenomic tests that are predictive of subpopulations with enhanced response to therapy.



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

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

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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<sup>6</sup>

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

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

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

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

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

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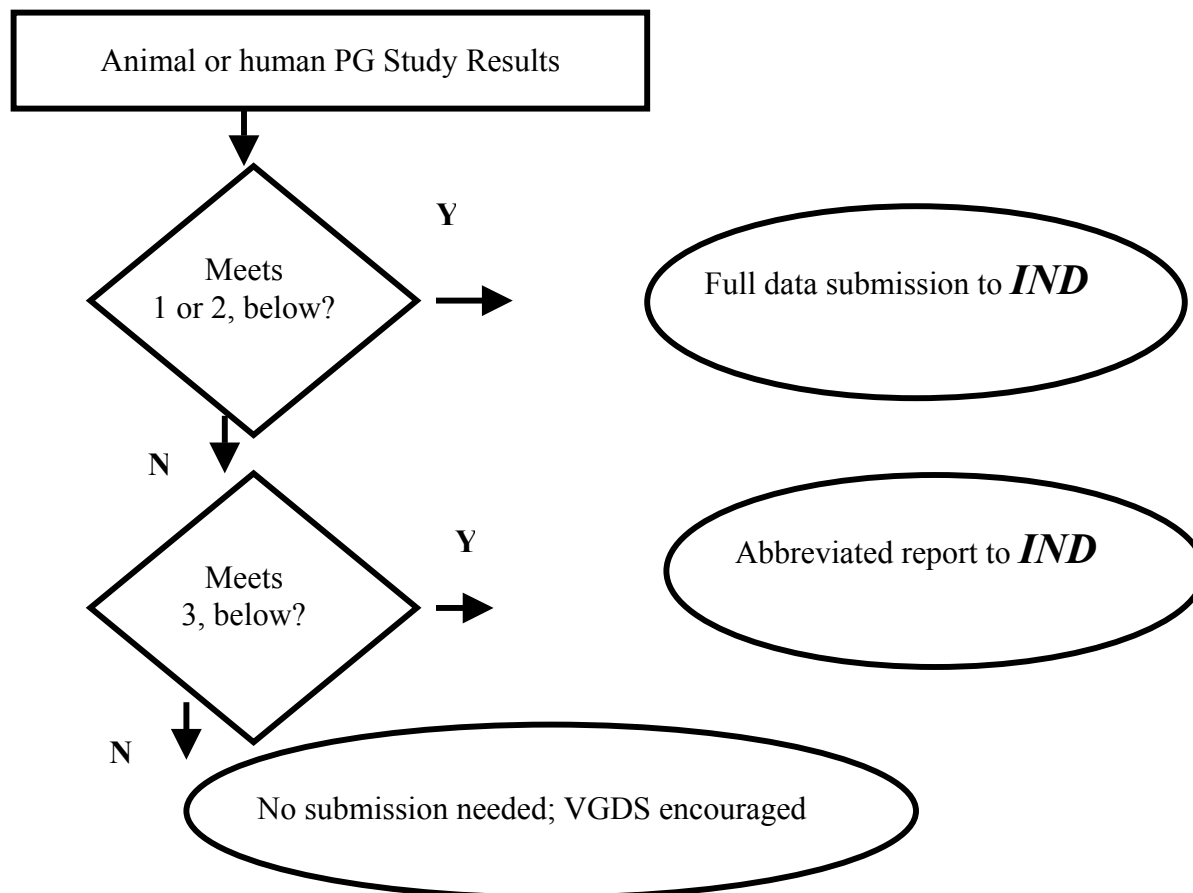
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613 **Voluntary genomic data submission (VGDS):** The designation for pharmacogenomic data  
614 submitted voluntarily to the FDA

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



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

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

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

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

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

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659  
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***Submission to an IND is NOT needed, but voluntary submission is encouraged (i.e., information does not meet the criteria of § 312.23) if***

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662

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.

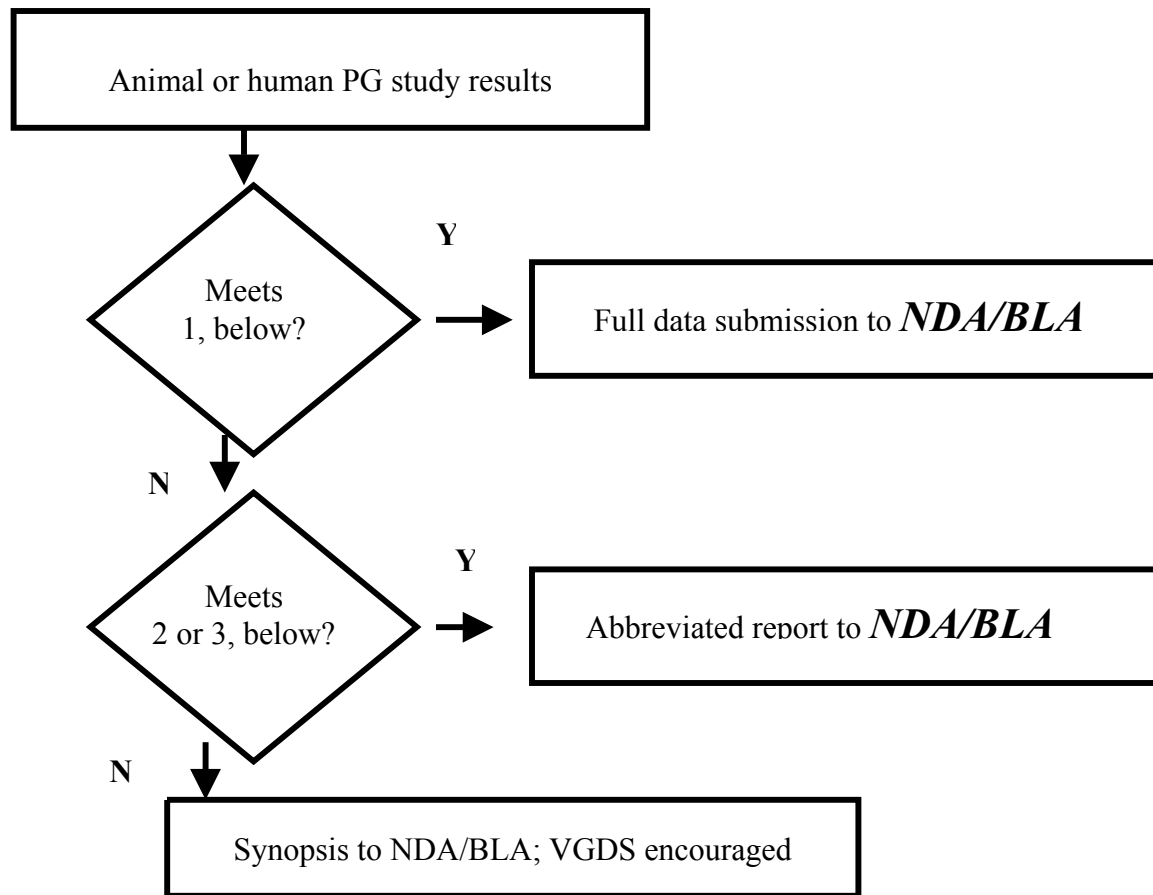
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5. Information consists of results from test systems where the validity of the biomarker is not established.

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



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

1. Provide reports on pharmacogenomic investigations intended by the sponsor to be used in the drug label or as part of the scientific database being used to support approval as complete submissions (not in the form of an abbreviated report, synopsis, or VGDS), including information about test procedures and complete data, in the relevant sections of the NDA or BLA. If the pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

The following examples would fit this category.

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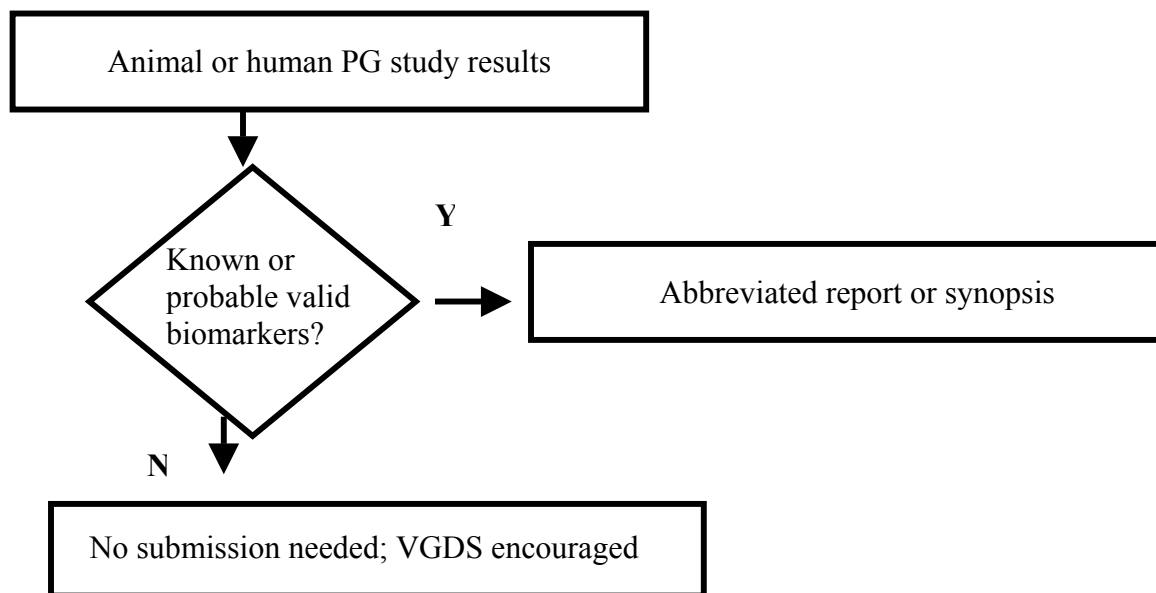
- 704                   – Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection,  
705                   or effectiveness
- 706                   – Pharmacogenomic test results that the sponsor proposes to describe in the drug label
- 707                   – Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label
- 708           2.   Submit reports of pharmacogenomic test results that constitute known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic,  
709           or clinical states or outcomes in the relevant species, but that the sponsor is not relying on or mentioning in the label, to the Agency as an abbreviated  
710           report (not in the form of a synopsis or VGDS). (If a pharmacogenomic test of this type was conducted as part of a larger overall study, the reporting of  
711           the pharmacogenomic test results can be incorporated into the larger study report.)
- 712           3.   Submit reports of pharmacogenomic tests that represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or  
713           clinical states or outcomes in the relevant species to the NDA or BLA as an abbreviated report. (If the pharmacogenomic testing of this type was  
714           conducted as part of a larger study, the abbreviated report can be appended to the report of the overall study.)
- 715           4.   There is no need to submit detailed reports of general exploratory or research information, such as broad gene expression screening, collection of sera or  
716           tissue samples, or results of pharmacogenomic tests that are not known or probable valid biomarkers to the NDA or BLA. Because the Agency does not  
717           view these studies as germane in determining the safety or effectiveness of a drug, the submission requirements in §§ 314.50 or 601.2 will be satisfied  
718           by the submission of a synopsis of the study. However, the Agency encourages the voluntary submission of the data from the study in a VGDS  
719           submitted to the NDA or BLA.

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

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### **744 APPENDIX D: EXAMPLES OF PHARMACOGENOMIC DATA SUBMISSIONS**

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746

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

749

750

#### ***751 Metabolizing Enzymes***

752

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

756

757 • CYP2D6 polymorphism is well established as a valid biomarker for drug metabolism enzyme  
758 activity

759 • See section IV.A.2 (complete report) and B.1 (complete report)

760

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

764

765 • CYP2C19 polymorphism is well established as a valid biomarker for drug metabolism  
766 enzyme activity.

767 • See section IV.A.2 (complete report) and B.1 (complete report)

768

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

772

773 • CYP3A5 polymorphism is currently not established as a valid biomarker.

774 • See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged)

775

776

#### ***777 Transporters***

778

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

782

783 • These are research data.

784 • See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged).

785

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

788

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

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

791

792

### ***Receptors***

794

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

798

- 799 • Data will be used in clinical decision making (entry criteria).

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

801

802

## **CLINICAL OUTCOMES**

804

### ***Efficacy***

806

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

817

- 818 • Data could be used in clinical decision making

- 819 • See section IV.A.2 (complete report)

- 820 • The sponsor is encouraged to develop a pharmacogenomic diagnostic test (unless it is already  
821 available), if it to be reflected in labeling

822

823

### ***Safety and Efficacy***

825

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

833

- 834 • These are research data

- 835 • See section IV.A.4 (VGDS encouraged).

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836

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

842

843 • These are research data.

844 • See section IV.A.4 (VGDS encouraged) and B.4 (synopsis; VGDS encouraged)

845

846 2.1 Based on the results of the rat and dog pharmacogenomic studies, the sponsor elects to  
847 assess a subset of 25 genes in later clinical trials that may be relevant to the safety or efficacy  
848 of the compound

849

850 • These are supportive data

851 • See section IV.B.2 (complete report).

852

853

### ***Safety***

854

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

860

861 • These are research data

862 • See section IV.A.4 (VGDS encouraged)

863

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

869

870 • These are supportive data

871 • See section IV.A.2 (complete report)

872

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

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

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

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

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

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

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

**APPENDIX E: QUICK REFERENCE ON PHARMACOGENOMIC SUBMISSIONS**

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