
Drug Interaction Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry

DRAFT GUIDANCE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)**

**October 2024
Labeling**

Drug Interaction Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry

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1 **Drug Interaction Information in Human Prescription Drug and**
2 **Biological Product Labeling**
3 **Guidance for Industry¹**
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6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person
9 and is not binding on FDA or the public. You can use an alternative approach if it satisfies the
10 requirements of the applicable statutes and regulations. To discuss an alternative approach,
11 contact the FDA staff responsible for this guidance as listed on the title page.
12

13
14
15
16 **I. INTRODUCTION**
17

18 This guidance is intended to assist applicants of human prescription drug and biological
19 products² in determining the appropriate placement and content of drug interaction (DI)
20 information in labeling as described in the regulations for the content and format of labeling for
21 human prescription drug and biological products.^{3,4} The purpose of this guidance is to provide
22 recommendations to help ensure that appropriate DI information is consistently placed in the
23 proper sections and subsections within labeling so that the information is clear and accessible to
24 health care practitioners (HCPs) and includes content that guides the safe and effective use of the
25 drug. Applicants should follow the recommendations in this guidance when developing this
26 section of labeling for a new drug submitted to the FDA under a new drug application under
27 section 505(b) of the FD&C Act or a biologics license application under section 351(a) of the

¹ This guidance has been prepared by the Office of Clinical Pharmacology in the Office of Translational Sciences in collaboration with the Labeling Policy Team in the Office of New Drugs, in the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

² This guidance applies to drugs, including biological products that are regulated as drugs. For the purpose of this guidance, references to *drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

³ 21 CFR 201.56(a) and (d) and 201.57(c)(8).

⁴ This is one of many guidance documents addressing labeling for human prescription drugs. For additional human prescription drug labeling guidance documents, see the FDA's Labeling Resources for Human Prescription Drugs website (available at <https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs>) and the Prescribing Information Resources website (available at <https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources>).

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28 PHS Act, and when revising existing information in the labeling for a currently approved drug in
29 a supplement to such applications.⁵

30
31 Sections III and VI of this guidance provide examples (denoted with a sawtooth line in the left
32 margin) of the content and format of DI information in the Full Prescribing Information and
33 Highlights of Prescribing Information (Highlights), respectively, involving a fictitious subject
34 drug⁶ (e.g., DRUG-X (drugozide-x)) and concomitant (i.e., other) drugs (e.g., drugofen-a,
35 drugofen-b, drugofen-c). Section IX of this guidance (the Appendix) provides additional
36 examples of the content and format of DI information throughout the Prescribing Information.

37
38 This guidance does not address methodological considerations for evaluating or interpreting DIs
39 during drug development or after drug approval. Recommendations for evaluating the DI
40 potential during drug development are included in an FDA guidance for industry.⁷

41
42 When finalized, Section VI.A. of this guidance will supersede DI labeling-specific
43 recommendations for the Highlights in the FDA guidance for industry *Labeling for Human*
44 *Prescription Drug and Biological Products – Implementing the PLR Content and Format*
45 *Requirements* (February 2013).⁸

46
47 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
48 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
49 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
50 the word *should* in Agency guidances means that something is suggested or recommended, but
51 not required.

52

53

II. BACKGROUND

54

55

56

57

Prescription drug labeling must contain a summary of the essential information necessary for
safe and effective use of the drug.⁹ Prescription drug labeling is a primary tool to communicate

⁵ See generally, 21 CFR parts 314 and 601.

⁶ For this guidance, the term *subject drug* refers to the drug for which the labeling is being developed.

⁷ See the FDA guidance for industry *M12 Drug Interaction Studies* (August 2024). 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>.

⁸ Specifically, this guidance, when finalized, will supersede the following recommendation in section V.B.7. HIGHLIGHTS, Information in Highlights, Dosage and Administration (§ 201.57(a)(7)) of the guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*, “Information under the Dosage and Administration heading [contains] ... other clinically significant clinical pharmacology information that affects dosing recommendations (e.g., dosing modifications recommended for concomitant therapy ...)”.

⁹ 21 CFR 201.56(a)(1).

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58 DI information to HCPs. Effective communication of DI information in the labeling informs
59 optimal use of the drug and the HCP’s clinical decision-making (e.g., prescribing decisions or
60 management instructions).

61
62 In this guidance, we use the term *drug interacting class* to mean a group of drugs and/or foods
63 that all share a specific characteristic that is relevant to a clinically significant DI (e.g., all
64 members of the class have in common a particular effect on drug metabolism).¹⁰ In the case of
65 drugs, the shared characteristic that identifies the drug interacting class may be unrelated to the
66 drug’s therapeutic class.¹¹

67
68 DI information in the labeling must be accurate and must be updated when new information
69 becomes available that causes the labeling to be inaccurate, false, or misleading.¹² Applicants
70 should review DI information in the labeling at least annually to ensure it is accurate and
71 contains up-to-date information.¹³

72
73

74 III. CONTENT AND FORMAT OF THE DRUG INTERACTIONS SECTION

75
76

A. Overview of the DRUG INTERACTIONS Section

77
78

78 The DRUG INTERACTIONS section must describe clinically significant DIs, either observed or
79 predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g.,
80 dietary supplements, grapefruit juice).^{14,15} The primary focus of the description of the clinically
81 significant DI and its prevention or management instructions in this section should be the subject
82 drug (i.e., how the subject drug is affected by other drugs or foods or how the subject drug
83 affects other drugs). This section:

84
85

- Must include specific practical instructions for preventing or managing clinically significant DIs¹⁶ (see section III.B.1 of this guidance)

86

¹⁰ For example, the strong cytochrome P450 3A4 (CYP3A4) inhibitor drug interacting class includes a food (grapefruit juice) as well as several drugs, including boceprevir, ceritinib, clarithromycin, and cobicistat.

¹¹ For example, fluconazole (an anti-fungal), fluoxetine (an anti-depressant), and ticlopidine (an anti-platelet drug) are all strong CYP2C19 inhibitors, a drug interacting class that is relevant to their DI, but they are in different, unrelated classes with respect to their therapeutic uses.

¹² 21 CFR 201.56(a)(2).

¹³ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

¹⁴ 21 CFR 201.57(c)(8)(i).

¹⁵ See the FDA guidance for industry *M12 Drug Interaction Studies* (August 2024).

¹⁶ 21 CFR 201.57(c)(8)(i).

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- 87
- 88 • Must briefly describe the mechanism of clinically significant DIs, if known¹⁷ (see section
- 89 III.B.2 of this guidance)
- 90
- 91 • Should include the clinical effects of clinically significant DIs¹⁸ (see section III.B.3 of
- 92 this guidance).
- 93

94 DIs that are described in the CONTRAINDICATIONS and/or WARNINGS AND

95 PRECAUTIONS sections must be discussed in more detail in the DRUG INTERACTIONS

96 section.¹⁹

97

98 Practical guidance on known interference of the drug with laboratory tests must also be included

99 in the DRUG INTERACTIONS section²⁰ (see section III.D of this guidance).

100

101 Cross-references should be used to reduce redundancy of information if pertinent DI information

102 is presented in more than one section of labeling.²¹

103

104 The entire DRUG INTERACTIONS section or required content within this section must be

105 omitted from the Full Prescribing Information (FPI) if it is clearly inapplicable,²² such as if there

106 are no clinically significant DIs and it is not critical to communicate the absence of a clinically

107 significant DI (see section III.C. of this guidance).

108

B. Communicating a Clinically Significant DI

110

111 Information about clinically significant DIs should be communicated in the DRUG

112 INTERACTIONS section in a manner that is understandable and clinically informative to HCPs,

113 including those with limited clinical pharmacology expertise. Descriptions of DIs should

114 generally contain information presented in the following order to promote consistency, as

115 applicable: (1) instructions for preventing or managing the clinically significant DIs, (2)

116 mechanisms of the clinically significant DIs, and (3) clinical effects of the clinically significant

117 DIs. This labeling approach prioritizes the information that is most actionable and may impact

¹⁷ 21 CFR 201.57(c)(8)(i).

¹⁸ Clinical effects should be derived from the totality of evidence (e.g., clinical studies, safety analyses, exposure-response data, exposure-safety data, modeling, and simulation). See the FDA guidance for industry *M12 Drug Interaction Studies* (August 2024).

¹⁹ 21 CFR 201.57(c)(8)(i).

²⁰ 21 CFR 201.57(c)(8)(ii).

²¹ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

²² 21 CFR 201.56(d)(4). There may be situations when it is critical to communicate the absence of a clinically significant DI in this section (see section III.C. of this guidance).

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118 the HCP’s clinical decision-making.

119

120 1. Instructions for Preventing or Managing DIs

121

122 Instructions to prevent or manage clinically significant DIs in the DRUG INTERACTIONS
123 section must be accurate,²³ specific, and practical²⁴ and should be actionable for the HCP. For
124 example, a prevention or management recommendation for a clinically significant DI of the
125 subject drug with warfarin that describes a specific change in the frequency or timing of
126 international normalized ratio (INR) monitoring is more informative for HCPs than a non-
127 specific recommendation such as “monitor INR” that reflects standard clinical practice for
128 patients taking warfarin. Applicants should use specific statements rather than vague or
129 ambiguous statements (e.g., “avoid concomitant use” is preferred over “use with caution,”
130 “reduce dosage” is preferred over “adjust dosage”) and use active voice instead of passive voice.

131

132 Prevention or management instructions presented in the DRUG INTERACTIONS section may
133 include, but are not limited to, the following:

134

- 135 • **Concomitant use is contraindicated:** Contraindicate concomitant use because the risk
136 of use clearly outweighs any possible therapeutic benefits.²⁵ For example, the DRUG
137 INTERACTIONS section would state:

138

139 “Concomitant use of DRUG-X with drugofen-a is contraindicated [*see*
140 *Contraindications (4)*].”

141

- 142 • **Avoid concomitant use:** Concomitant use is generally inadvisable but does not rise to
143 the level of a contraindication. For example, the DRUG INTERACTIONS section would
144 state:

145

146 “Avoid concomitant use of DRUG-X with drugofen-a.”

147

148 When concomitant use is generally unavoidable (e.g., when the concomitant drug is
149 indicated for the treatment of a serious or life-threatening condition or disease), consider
150 providing recommendation(s), when possible, for actionable measures that can be taken
151 to prevent or manage the DI. For example, the DRUG INTERACTIONS section would
152 state:

153

154 “Avoid concomitant use of DRUG-X with drugofen-a. If concomitant use is
155 unavoidable, obtain ECGs prior to initiating, during concomitant use, and

²³ 21 CFR 201.56(a)(2).

²⁴ 21 CFR 201.57(c)(8)(i).

²⁵ 21 CFR 201.57(c)(5); also see the FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

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156 { additionally as clinically indicated.”

- 157
- 158 • **Modify dosage/administration:** Concomitant use necessitates a dosage or
- 159 administration modification (e.g., increase dosage, reduce dosing frequency, stagger
- 160 administration, temporarily discontinue one drug) of either the subject drug (i.e., DRUG-
- 161 X) or concomitant drug(s) or drugs within a drug interacting class (e.g., strong CYP3A4
- 162 inhibitors, CYP2C8 substrates).
- 163
- 164 ○ **Modify dosage/administration of the subject drug:** If there are dosage
- 165 modifications for the subject drug for DIs, the:
- 166
- 167 ▪ DOSAGE AND ADMINISTRATION section must include this information, as
- 168 appropriate.²⁶ More specifically, when there is sufficient information to support
- 169 specific recommendations to modify the dosage or administration of the subject
- 170 drug to reduce the risk of a DI, these recommendations should be included in the
- 171 DOSAGE AND ADMINISTRATION section and cross-reference to the DRUG
- 172 INTERACTIONS section.²⁷
- 173
- 174 ▪ DRUG INTERACTIONS section should identify when a dosage or administration
- 175 modification for the subject drug is recommended and cross-reference to the
- 176 details regarding the dosage or administration modification in the DOSAGE AND
- 177 ADMINISTRATION section.
- 178

179 For example:

180

181 { **2 DOSAGE AND ADMINISTRATION**

182 { ...

183 { Reduce the dosage of DRUG-X from 200 mg once daily to 100 mg once

184 { daily when used concomitantly with a strong CYP3A inhibitor [*see Drug*

185 { *Interactions (7.x)*].

186

187 { **7 DRUG INTERACTIONS**

188 { ...

189 { Reduce the dosage of DRUG-X when used concomitantly with a strong

190 { CYP3A inhibitor [*see Dosage and Administration (2.x)*].

- 191
- 192 ○ **Modify dosage/administration of the concomitant drug:** The DRUG
- 193 INTERACTIONS section should identify when a dosage or administration
- 194 modification for the concomitant drug is recommended, if applicable, and may
- 195 reference the concomitant drug’s labeling for the relevant DI. For example, this
- 196 section would state:

²⁶ 21 CFR 201.57(c)(3)(i)(H).

²⁷ See the FDA draft guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2023). When final, this guidance will represent the Agency’s current thinking on this topic.

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197
198 ~ “Reduce the dosage of drugofen-a when used concomitantly with DRUG-X (see
199 ~ drugofen-a’s Prescribing Information).”

200
201 In this situation, no cross-reference to the DOSAGE AND ADMINISTRATION
202 section is needed because the DOSAGE AND ADMINISTRATION section should
203 not include the dosage or administration modification for the concomitant drug.
204

- 205 • **Monitor:** Concomitant use necessitates additional or increased frequency of monitoring
206 of specific clinical parameters. For example, the DRUG INTERACTIONS section would
207 state:

208
209 ~ “Monitor liver enzymes weekly for the first four weeks and then monthly when
210 ~ DRUG-X is used concomitantly with drugofen-a [*see Warnings and Precautions*
211 ~ (5.x)].”

2. *Mechanism of the Clinically Significant DI*

212
213 The mechanism of the clinically significant DI, if known, must be briefly described in the DRUG
214 INTERACTIONS section.²⁸ A clinically significant DI can be the result of pharmacokinetic
215 (PK) and/or pharmacodynamic (PD) changes.
216
217

- 218
219 • For PK metabolism- (e.g., cytochrome P450) and transporter-based interactions, the
220 subject drug should be identified as an inhibitor, inducer, or substrate. Additionally, the
221 change in drug exposure²⁹ should be briefly summarized (e.g., increases drugozide-x
222 exposure, decreases drugozide-x exposure), with a cross-reference to the supporting DI
223 information in the *Pharmacokinetics* subsection in the CLINICAL PHARMACOLOGY
224 section. For example, the DRUG INTERACTIONS section would state:

225
226 ~ “Drugozide-x is a CYP3A substrate. Strong CYP3A inhibitors increase
227 ~ drugozide-x exposure [*see Clinical Pharmacology (12.3)*].”

- 228
229 • For PD-based interactions, the nature of the PD effects should be described. For example,
230 the DRUG INTERACTIONS section would state:

231
232 ~ “Both drugozide-x and non-selective MAO inhibitors inhibit catecholamine
233 ~ metabolism.”

3. *Clinical Effects of the Clinically Significant DI*

234
235 The clinical effects of a clinically significant DI should be stated in the DRUG INTERACTIONS
236 section. Describing the changes in PD and PK parameters alone is generally insufficient to
237
238

²⁸ 21 CFR 201.57(c)(8)(i).

²⁹ Exposure includes drug concentration, C_{max}, and AUC, as applicable.

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239 communicate the clinical effects of a DI on the safety or effectiveness of the drug. For example,
240 with a PK-based DI, an exposure change for one drug may result in a different clinical effect,
241 based on its exposure-response relationship, compared to another drug with the same exposure
242 change. The following approaches to communicate clinical effects are recommended in this
243 section:

244

- 245 • When data are sufficient to support a clinical effect statement in specific terms, the
246 description of the clinical effects should be specific. For example, the DRUG
247 INTERACTIONS section would state:

248

249 “*The concomitant use of DRUG-X with drugofen-a may increase the risk of*
250 *bleeding [see Clinical Pharmacology (12.2)].*”

251

- 252 • When data are not sufficient to support a clinical effect statement in specific terms, the
253 clinical effects should generally be described in broad terms. For example, the DRUG
254 INTERACTIONS section would state:

255

256 “*The concomitant use of DRUG-X with drugofen-a may increase the risk of*
257 *DRUG-X-associated adverse reactions*”

258

259 or

260

261 “*The concomitant use of DRUG-X with drugofen-b may reduce effectiveness of*
262 *DRUG-X.*”

263

264 4. *Drug Interacting Classes and Examples of Drugs Within Drug Interacting* 265 *Classes*

266

267 When there are clinically significant DIs of the subject drug with all drugs within a drug
268 interacting class,³⁰ the FDA recommends that applicants identify only the drug interacting class
269 and avoid naming the drugs within the drug interacting class in the DRUG INTERACTIONS
270 section.³¹ In this situation, reasons that the FDA generally recommends not naming examples of
271 drugs within the drug interacting class in this section include the following:

272

- 273 • If examples of individual drugs within a drug interacting class are included in labeling,
274 those examples may become less relevant over time (e.g., new drugs in the drug
275 interacting class may be approved, or selected examples of drugs in the drug interacting
276 class may no longer be commonly used in clinical practice or may no longer be available
277 because they have been withdrawn from the market).

³⁰ An example of this situation is when a clinical study demonstrates a clinically significant DI of DRUG-X with one member of a drug interacting class, and the results of the study can be applied to all the other drugs in the drug interacting class.

³¹ If a food (e.g., dietary supplements, grapefruit juice) is in a drug interacting class, the food must be listed separately, in addition to the drug interacting class in the DRUG INTERACTIONS section. See 21 CFR 201.57(c)(8)(i).

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- 278 • HCPs can reference publicly available resources to determine which drugs are within a
279 drug interacting class.

280

281 The FDA generally recommends that applicants identify only the drug interacting class in the
282 DRUG INTERACTIONS section. However, this section should name the drugs within the drug
283 interacting class if concomitant use of the subject drug with drugs within the drug interacting
284 class (e.g., drugofen-a, drugofen-b, drugofen-c) has different clinical effects or prevention and
285 management instructions (e.g., “concomitant use of DRUG-X with drugofen-a is
286 contraindicated,” “avoid concomitant use of DRUG-X with drugofen-b,” “reduce the DRUG-X
287 dosage when used concomitantly with drugofen-c”). In these situations, this section should list
288 the individual interacting drugs with their different clinical effects or their respective prevention
289 and management instructions, respectively.

290

291 If some, but not all, of the drugs in a drug interacting class have a clinically significant
292 interaction with the subject drug, then only individual drugs with the clinically significant
293 interaction should be identified in this section. In this situation, the class of drugs and the drugs
294 without the clinically significant interaction should not be named in this section.

295

296 When there are clinically significant DIs of the subject drug with all drugs within a drug
297 interacting class (with the same prevention and management instructions and the same clinical
298 effects), but the applicant believes that it is essential to identify specific drugs within a drug
299 interacting class in this section, the FDA recommends that the applicant provide justification and
300 consult the corresponding review division.

301

302 Clinically significant DIs involving CYP- or transporter system-based drug interacting classes
303 are very common. One resource that HCPs can reference regarding these drug interacting classes
304 is an FDA website that lists examples of clinical substrates, inhibitors, and inducers of CYP
305 enzymes and substrates and inhibitors of transporters.³² This FDA website allows HCPs to view
306 which drugs or foods are within a specific CYP- or transporter-based drug interacting class.
307 When there are clinically significant DIs of the subject drug with all drugs in a CYP- or
308 transporter-based drug interacting class, the FDA recommends that in addition to identifying the
309 drug interacting class and avoiding naming individual drugs within the drug interacting class,
310 applicants consider referring to the FDA’s website with examples of drugs and foods within the
311 CYP- and transporter-based drug interacting class.

312

313 5. *Therapeutic Proteins That Reduce Proinflammatory Cytokines in Diseases or* 314 *Conditions Associated With Elevated Cytokine Levels*

315

316 Certain diseases or conditions are associated with elevated cytokine levels leading to reduced
317 CYP enzyme expression. Therapeutic proteins that reduce the level of pro-inflammatory

³² The FDA website www.fda.gov/CYPandTransporterInteractingDrugs provides examples of interacting drugs and foods within CYP-based metabolic- and transporter system-based drug interacting classes, and is evaluated, compiled, and routinely updated by the FDA. The field of metabolic and transporter pharmacology is evolving; thus, the examples on this website are a guide and not considered a comprehensive list of all possible drugs and foods that fit these CYP- and transporter system-based drug interacting classes.

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318 cytokines in these situations can increase expression of these CYP enzymes.³³ This increased
319 expression results in a decreased CYP substrate exposure, which may reduce effectiveness of
320 CYP substrates.³⁴ Therefore, the FDA recommends that the DRUG INTERACTIONS section for
321 these therapeutic proteins include the following language or similar language under the heading
322 Certain CYP Substrates.

323

324 The following fictitious labeling example is for the therapeutic protein DRUG-X (drugimab-
325 abxd):³⁵

326

327 **7.x Effects of DRUG-X on Other Drugs**

328

...

329 Certain CYP Substrates

330 For CYP substrates where minimal:

331

- 332 • Decreases in the concentration may reduce CYP substrate effectiveness,
333 monitor for reduced effectiveness of the CYP substrate upon DRUG-X
334 initiation.
- 335 • Increases in the concentration may increase CYP substrate adverse reactions,
336 monitor for increased adverse reactions of the CYP substrate after DRUG-X
337 discontinuation.

338

339 Increased concentrations of cytokines (e.g., IL-1, IL-6, IL-10, TNF α , IFN) during
340 chronic inflammation associated with certain diseases including *[insert diseases or*
341 *conditions that the drug is approved to treat in which this statement applies]* may
342 suppress the formation of CYP enzymes. Therapeutic proteins, including drugimab-
343 abxd, that decrease the concentrations of these pro-inflammatory cytokines may
344 increase the formation of CYP enzymes resulting in decreased CYP substrate exposure.

345

346 If the potential for a clinically significant DI with the use of a therapeutic protein is low, an
347 applicant can propose to revise or exclude such language in this section of labeling.³⁶

348

349 **C. Communicating the Absence of a Clinically Significant DI**

350

351 Generally, the FDA does not recommend that the DRUG INTERACTIONS section describe the
352 absence of a DI. However, in the situations as described below, it may be critical to
353 communicate the absence of a clinically significant DI. If an applicant proposes to include
354 information on the absence of a clinically significant DI in this section, the FDA recommends the

³³ See the FDA guidance for industry *Drug-Drug Interaction Assessment for Therapeutic Proteins* (June 2023).

³⁴ See the FDA guidance for industry *Drug-Drug Interaction Assessment for Therapeutic Proteins* (June 2023).

³⁵ If there are sufficient data demonstrating that the concentrations of only a few cytokines are increased during chronic inflammation associated with the diseases/conditions that the drug is approved to treat, only such cytokines should be listed.

³⁶ See the FDA guidance for industry *Drug-Drug Interaction Assessment for Therapeutic Proteins* (June 2023).

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355 applicant provide a justification.

356

357 The FDA recommends communicating the absence of a clinically significant DI in the DRUG
358 INTERACTIONS section in the following two situations.

359

- 360 • If DRUG-X has clinically significant DIs with all drugs in a drug interacting class (e.g.,
361 strong CYP3A inhibitors) except for one drug (e.g., drugofen-a) in this class, this
362 exception should be described in this section of labeling. For example:

363

364 7.x Effects of Other Drugs on DRUG-X

365

...

366

366 Strong CYP3A Inhibitors

367

367 Reduce the DRUG-X dosage when used concomitantly with strong CYP3A
368 inhibitors [see *Dosage and Administration (2.x)*], except with drugofen-a. No
369 dosage modification is recommended for DRUG-X when used concomitantly with
370 drugofen-a.

371

372 Drugozide-x is a CYP3A substrate. Strong CYP3A inhibitors increase drugozide-x
373 exposure, which may increase the risk of DRUG-X-associated adverse reactions.

374

374 Although drugofen-a is a strong CYP3A inhibitor, the interaction with DRUG-X is
375 not clinically significant [see *Clinical Pharmacology (12.3)*].

376

- 377 • If a drug class (e.g., tyrosine kinase inhibitors) is known to have a clinically significant
378 interaction with a drug (e.g., drugofen-b); however, the subject drug (e.g., DRUG-X), a
379 member of that class, does not interact with that concomitant drug (e.g., drugofen-b), this
380 exception should be described in this section of labeling. For example:

381

382 7.x Absence of Clinically Significant Interaction with Drugofen-b

383

...

384

384 No dosage modification is recommended for DRUG-X when used concomitantly
385 with drugofen-b. Although it is a tyrosine kinase inhibitor, DRUG-X does not have a
386 clinically significant interaction with drugofen-b [see *Clinical Pharmacology*
387 (12.3)].

388

389 D. Communicating a Drug Interference with Laboratory Tests

390

391 The DRUG INTERACTIONS section must contain practical guidance on known interference of
392 the drug with laboratory tests.³⁷ When the drug interferes with a laboratory test, it can cause an
393 inaccurate test result. A clinically significant drug-test interference should be included in this
394 section when an erroneous test result would negatively affect clinical decision-making (e.g., false

³⁷ 21 CFR 201.57(c)(8)(ii).

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395 positive hemocult test, false negative HIV test).³⁸ Accurate test results reflecting changes in a
396 PD parameter caused by the drug are not considered a laboratory test interference and should not
397 be included in the DRUG INTERACTIONS section.³⁹

398

399 This section should provide instructions to prevent or manage the interference and the clinical
400 effect(s) of the interference, if feasible. Additionally, the WARNINGS AND PRECAUTIONS
401 section must briefly describe the drug interference with laboratory tests and cross-reference to
402 the DRUG INTERACTIONS section for more details.⁴⁰ For example:

403

404

7.x Interference of DRUG-X with Platelet Tests

405 When performing platelet tests in DRUG-X-treated patients, run blood samples within 4
406 hours of blood collection or collect blood samples in tubes containing citrate.

407

408 Drugozide-x interferes with automated platelet counts (platelet clumping), in particular
409 when blood samples are collected in tubes containing ethylenediaminetetraacetic acid
410 (EDTA), which may lead to unevaluable or falsely decreased platelet counts [*see*
411 *Warnings and Precautions (5.x)*].

412

413 If there is drug interference with two or more laboratory tests, the FDA generally recommends
414 including these drug interferences with laboratory tests under one subsection entitled **7.x**
415 **Interference of DRUG-X with Laboratory Tests** in the DRUG INTERACTIONS section with
416 appropriate headings (e.g., Interference of DRUG-X with Lab Test-A, Interference of DRUG-X
417 with Lab Test-B).

418

E. Organization and Formatting of the DRUG INTERACTIONS Section

420

421 Information in the DRUG INTERACTIONS section should generally be placed into subsections
422 to enhance the organization, presentation, and accessibility of information (e.g., **7.1 Effects of**
423 **Other Drugs on DRUG-X**).⁴¹ Subsections should be ordered to reflect the content's importance
424 and relative public health significance. Subsection headings should accurately reflect the content
425 of the subsection. The FDA recommends placing all information under subsections instead of
426 inserting information between the section heading and first subsection heading (i.e., capture
427 information under numbered subsections instead of between the section 7 heading and subsection
428 7.1). Floating content will not be associated with a specific subsection heading in Full

³⁸ See section II.B.1. in the FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

³⁹ Changes in PD parameters are included in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY).

⁴⁰ 21 CFR 201.57(c)(6)(iv).

⁴¹ See 21 CFR 201.56(d)(2).

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429 Prescribing Information: Contents⁴² and may therefore be less accessible.⁴³

430

431 A typical approach to including PK-based DIs in this section is to incorporate such information
432 into one of two subsections: **7.1 Effects of Other Drugs on DRUG-X** or **7.2 Effects of DRUG-
433 X on Other Drugs**. For complex PK-based DI scenarios (e.g., DRUG-X is affected by and has
434 an effect on the concomitant drug), DI information should be included under both subsections
435 (e.g., **7.1 Effects of Other Drugs on DRUG-X** and **7.2 Effects of DRUG-X on Other Drugs**) in
436 order to accurately describe both DIs. PD-related DIs should generally be presented in separate
437 subsection(s) with a title specific to the interacting drug or drug interacting class, as applicable.
438 If there are clinically significant DIs with the subject drug that combine two or more
439 mechanisms, the FDA recommends that the heading that describes such information in the
440 DRUG INTERACTIONS section include all the mechanisms (e.g., Combined P-gp and
441 Moderate CYP3A Inhibitors). This approach should also be used for scenarios involving one or
442 more DI mechanisms in a specific population (e.g., Combined P-gp and Moderate CYP3A
443 Inhibitors in Patients with Renal Impairment).

444

445 The FDA recommends that applicants select a format that will most effectively communicate DI
446 information in this section. Different formats could be warranted depending on the number,
447 complexity, and type of clinically significant DIs included in this section. For example, complex
448 or extensive information (e.g., three or more DIs) could be more effectively conveyed in a table
449 rather than in text. When referring to tables in this section, a statement preceding the table should
450 be included that describes the content in the table. For example:

451

452 ~ “Table X describes clinically significant DIs where concomitant use of another drug
453 ~ affects DRUG-X.”

454

455 Refer to the Appendix for an example of the content and format of DI information in the
456 Highlights and the content and format of the DRUG INTERACTIONS section, as well as other
457 sections of the FPI (i.e., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,
458 WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY, PATIENT
459 COUNSELING INFORMATION) that may contain DI information.

460

461

IV. CONTENT NOT INCLUDED IN THE DRUG INTERACTIONS SECTION

462

463
464 Generally, the DRUG INTERACTIONS section should not describe DIs that are not clinically
465 significant, unless it is important to communicate the absence of a clinically significant DI (see
466 Section III.C of this guidance).

467

468 In vitro and/or animal data alone should not be included in this section because they are
469 generally insufficient to justify the presence of a clinically significant DI. If necessary, applicants
470 should consult with the FDA regarding the inclusion of DIs based only on in vitro and/or animal

⁴² See 21 CFR 201.57(b).

⁴³ If labeling has floating content between the section 7 heading and subsection 7.1, the FDA recommends that applicants move the floating content to the appropriate subsection(s) in the DRUG INTERACTIONS section.

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471 data in this section.

472
473 To minimize redundancy, the DRUG INTERACTIONS section must not repeat details of DI PK
474 studies (e.g., magnitude of exposure change) that are included in the CLINICAL
475 PHARMACOLOGY section.⁴⁴ Instead, a cross-reference to the CLINICAL
476 PHARMACOLOGY section should be provided.

477
478 If there is a recommendation to modify the dosage or administration of the subject drug, to
479 minimize redundancy, the FDA recommends that detailed instructions of the dosage or
480 administration modification for the subject drug be included in the DOSAGE AND
481 ADMINISTRATION section and not in the DRUG INTERACTIONS section (see Section
482 III.B.1 of this guidance).

483
484 The reduction of immunological response to a vaccine by an immunosuppressive drug is not
485 considered a true DI; therefore, this type of vaccine information should generally be included in
486 the WARNINGS AND PRECAUTIONS section (as well as the *Pharmacodynamics* subsection
487 in the CLINICAL PHARMACOLOGY section, as appropriate) instead of the DRUG
488 INTERACTIONS section.

489
490 Drug incompatibilities (e.g., unwanted physical and chemical reactions that occur between two
491 or more drugs or between a drug and a diluent when combined in the same container) are not
492 considered DIs. Therefore, this information should not appear in the DRUG INTERACTIONS
493 section.⁴⁵

494

495

V. DI CONTENT IN OTHER SECTIONS OF THE FULL PRESCRIBING INFORMATION

498

499 In addition to the DRUG INTERACTIONS section, required and recommended DI information
500 is included in other sections of the FPI, as applicable.

501

- 502 • **BOXED WARNING:** The FDA may require a boxed warning for certain
503 contraindications or serious warnings, particularly those that may lead to death or serious
504 injury, resulting from a DI.⁴⁶
- 505 • **DOSAGE AND ADMINISTRATION:** This section must describe dosage modifications
- 506

⁴⁴ 21 CFR 201.57(c)(8)(i); see also the FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

⁴⁵ The DOSAGE AND ADMINISTRATION section must contain “essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents.” 21 CFR 201.57(c)(3)(iv).

⁴⁶ 21 CFR 201.57(c)(1).

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507 needed because of DIs.⁴⁷ More specifically, when there is sufficient information to
508 support specific recommendations to modify the dosage or administration of the subject
509 drug to reduce the risk of a DI, the specific recommendations should be included in this
510 section. The DOSAGE AND ADMINISTRATION section should also describe
511 administration modifications for the subject drug due to DIs (e.g., alteration of the timing
512 of a dose of the subject drug relative to dosing of the concomitant drug) and cross-
513 reference the DRUG INTERACTIONS section for more detailed DI information (see
514 sections III.A. and III.B. in this guidance). When there is not enough information to
515 support a specific dosage or administration modification for the subject drug, the DI
516 should ordinarily not be discussed in the DOSAGE AND ADMINISTRATION
517 section.⁴⁸

518

519 • **CONTRAINDICATIONS:** This section must list drugs that are contraindicated because
520 the risk from concomitant use with the subject drug clearly outweighs any possible
521 therapeutic benefit.⁴⁹ The CONTRAINDICATIONS section should cross-reference to
522 more detailed DI information in the DRUG INTERACTIONS section and other sections
523 of the labeling as appropriate (e.g., WARNINGS AND PRECAUTIONS).⁵⁰

524

525 • **WARNINGS AND PRECAUTIONS:** This section must describe clinically significant
526 adverse reactions or other potential safety hazards resulting from a DI.⁵¹ Rather than
527 repeating the DIs from the DRUG INTERACTIONS section in the WARNINGS AND
528 PRECAUTIONS section, generally only the most clinically significant DIs (e.g., those
529 that lead to treatment failure, drug resistance, serious safety issues), if any, should be
530 included in the WARNINGS AND PRECAUTIONS section. The WARNINGS AND
531 PRECAUTIONS section should include additional details about the clinical effects of
532 those clinically significant DIs (e.g., severity, outcomes), and should include a brief
533 description of the prevention or management instructions with a cross-reference to more
534 detailed DI information elsewhere in the labeling⁵² (e.g., DOSAGE AND
535 ADMINISTRATION, DRUG INTERACTIONS, CLINICAL PHARMACOLOGY
536 sections). The WARNINGS AND PRECAUTIONS section must also briefly note

⁴⁷ 21 CFR 201.57(c)(3)(i)(H).

⁴⁸ See the FDA draft guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2023). When final, this guidance will represent the Agency’s current thinking on this topic.

⁴⁹ 21 CFR 201.57(c)(5). See also the FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

⁵⁰ See the FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

⁵¹ 21 CFR 201.57(c)(6).

⁵² See the FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

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- 537 information on any known interference by the drug with laboratory tests and cross-
538 reference the DRUG INTERACTIONS section⁵³ (see section III.D of this guidance).
539
- 540 • CLINICAL PHARMACOLOGY: This section must include information relating to the
541 human clinical pharmacology and actions of the drug.⁵⁴ It should also include relevant
542 details about study results from DI studies if essential to understand dosing or DI
543 information presented in other sections of the labeling (e.g., DOSAGE AND
544 ADMINISTRATION, DRUG INTERACTIONS sections).⁵⁵ Both positive and pertinent
545 negative results from clinical studies conducted to evaluate DIs should be included under
546 the Drug Interaction Studies heading in the *Pharmacokinetics* subsection in the
547 CLINICAL PHARMACOLOGY section.⁵⁶ If clinical DI studies have not been
548 conducted or are inconclusive, then pertinent negative and/or positive results from in
549 vitro DI studies should be included under the Drug Interaction Studies heading. In
550 addition, specific details regarding the mechanism of the DI (e.g., time dependent
551 inhibition) should also be provided, when pertinent. The CLINICAL
552 PHARMACOLOGY section should not include instructions to prevent or manage a
553 clinically significant DI.⁵⁷ If positive findings are discussed under the Drug Interaction
554 Studies heading but the:⁵⁸
 - 555 ○ Findings are not clinically significant, then an additional statement about the lack of
556 clinical significance of the findings should be included under this heading
557
 - 558 ○ Clinical significance of these findings is unknown, then an additional statement that
559 the clinical significance of the findings is unknown should be included under this
560 heading
561
 - 562 • PATIENT COUNSELING INFORMATION: DI information for HCPs to convey to
563 patients (or caregivers) should be included in this section if it concerns an important risk
564 (e.g., the DI is mentioned in the BOXED WARNING, CONTRAINDICATIONS, or
565

⁵³ 21 CFR 201.57(c)(6)(iv).

⁵⁴ 21 CFR 201.57(c)(13)(i).

⁵⁵ See the FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

⁵⁶ See the FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

⁵⁷ See the FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

⁵⁸ See the FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

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566 WARNINGS AND PRECAUTIONS sections).⁵⁹ Additionally, DI information for HCPs
567 to convey to patients (or caregivers) should be included in this section if concomitant use
568 could be initiated by the patient (e.g., an interaction with a nonprescription drug or
569 food).⁵⁹⁶⁰ A complete listing of known DIs should typically not be included in this
570 section because the decision to concomitantly use two prescription drugs generally rests
571 with the HCP at the time of prescribing.⁵⁹⁶¹

572
573

574 VI. DRUG INTERACTION CONTENT IN THE HIGHLIGHTS OF PRESCRIBING 575 INFORMATION

576

577 The Drug Interactions heading in the Highlights must include a concise summary of the
578 information required under the DRUG INTERACTIONS section of the FPI.⁶² This concise
579 summary of information should typically include,⁶³ but is not limited to, a listing of the most
580 clinically significant DIs and the practical instructions for preventing or managing those
581 clinically significant DIs. For example:

582

583 -----**DRUG INTERACTIONS**-----

584

585 ...

- 586 • *Strong CYP3A Inhibitors*: Avoid concomitant use with DRUG-X (7.x).
- 587 • *Moderate CYP3A Inhibitors*: Reduce DRUG-X dosage to 50 mg once daily (2.x, 7.x).
- 588 • *Hepatotoxic Drugs*: In patients with (7.x):
 - 589 ○ Hepatic impairment: Avoid concomitant use with DRUG-X.
 - 590 ○ Normal hepatic function: Monitor liver enzymes weekly for the first four weeks
591 and then monthly during concomitant use with DRUG-X.

591 ...

592

593 When space in Highlights permits (e.g., when additional information does not cause Highlights
594 to be greater than one-half page in length),⁶⁴ the Drug Interactions heading in Highlights should
595 also include the effects of the clinically significant DI concerning potential safety hazards not

⁵⁹ See the FDA guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format* (December 2014).

⁶⁰ See the FDA guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format* (December 2014).

⁶¹ See the FDA guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format* (December 2014).

⁶² 21 CFR 201.57(a)(12).

⁶³ See section VI.B of this guidance for situations when a drug has numerous clinically significant DIs, and it is not possible to concisely summarize each clinically significant DI and their prevention or management instructions under the Drug Interactions heading in Highlights.

⁶⁴ 21 CFR 201.57(d)(8) and also see the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

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596 captured elsewhere in Highlights. For example:

- 597
- 598 -----**DRUG INTERACTIONS**-----
- 599 ...
- 600 • *Strong CYP3A Inhibitors*: Avoid concomitant use with DRUG-X. Concomitant use
- 601 with DRUG-X may increase the risk of hypotension and syncope (7.x).
- 602 • *Moderate CYP3A Inhibitors*: Reduce DRUG-X dosage to 50 mg once daily.
- 603 Concomitant use with DRUG-X may increase the risk of hypotension (2.x, 7.x).
- 604 • *Hepatotoxic Drugs*: Concomitant use with DRUG-X may increase the risk of
- 605 hepatotoxicity. In patients with (7.x):
- 606 ○ Hepatic impairment: Avoid concomitant use with DRUG-X.
- 607 ○ Normal hepatic function: Monitor liver enzymes weekly for the first four weeks and
- 608 then monthly during concomitant use with DRUG-X.
- 609 ...
- 610

611 If there is more than one clinically significant DI that is appropriate to include under the Drug

612 Interactions heading in Highlights, the order of these DIs should be consistent with the ordering

613 of these DIs in the DRUG INTERACTIONS section of the FPI.⁶⁵ If there are no clinically

614 significant DIs, the Drug Interactions heading should be omitted from Highlights.⁶⁶ Generally,

615 the FDA recommends that Highlights not include statements about the absence of a clinically

616 significant DI.

617

618 When information about a DI appears in more than one section of the FPI, the information

619 should typically be presented only once in Highlights.⁶⁷ DIs that are summarized elsewhere in

620 Highlights (e.g., Boxed Warning, Contraindications heading, Warnings and Precautions heading)

621 need not be repeated under the Drug Interactions heading in Highlights.⁶⁸

622

623 **A. Streamlining Information Under the Dosage and Administration Heading**

624 **and the Drug Interactions Heading in the Highlights**

625

626 To minimize redundancy and fragmentation of DI information between the Dosage and

627 Administration and the Drug Interactions headings in Highlights, dosage modifications due to

628 DIs should be included under the Drug Interactions heading instead of the Dosage and

629 Administration heading in Highlights. The Drug Interactions heading should include

630 modifications for the subject drug and for drugs affected by the subject drug. For example:

⁶⁵ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

⁶⁶ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

⁶⁷ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

⁶⁸ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

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- 631
632 -----**DRUG INTERACTIONS**-----
633 • *Strong CYP1A2 Inhibitors*: Avoid concomitant use with DRUG-X. If concomitant use
634 is unavoidable, reduce DRUG-X dosage to 50 mg once daily (2.x, 7.x).
635 • *Drugofen-a*: Reduce DRUG-X dosage to 50 mg once daily (2.x, 7.x).
636

637 In addition to the information required for the Dosage and Administration heading in
638 Highlights,⁶⁹ a reference under this heading should be included to the DI-related dosage
639 modifications for the subject drug in the DOSAGE AND ADMINISTRATION section of the
640 FPI. For example:

- 641 -----**DOSAGE AND ADMINISTRATION**-----
642 ...
643 See full prescribing information for DRUG-X dosage modifications due to drug
644 interactions (2.x).
645 ...
646

B. When There Are Numerous Clinically Significant DIs to Summarize

647
648
649 When a drug has numerous clinically significant DIs, it may not be possible to concisely
650 summarize each clinically significant DI and their prevention or management instructions under
651 the Drug Interactions heading in Highlights due to the half-page length requirement.⁷⁰ In these
652 instances, information under the Drug Interactions heading should include: (1) DIs that are most
653 critical to the safe and effective use of the drug; and (2) a statement to alert the HCP to the
654 presence of additional DI information in the DRUG INTERACTIONS section of the FPI.⁷¹ For
655 example:
656

- 657 -----**DRUG INTERACTIONS**-----
658
659 • QT-prolonging Drugs: Avoid concomitant use with DRUG-X (7.x).
660 • Hormonal Contraceptives: Avoid concomitant use with DRUG-X. Use alternative
661 nonhormonal contraceptive methods during concomitant use and for 28 days after
662 discontinuation of DRUG-X (7.x).
663 • Other Antiretroviral Drugs: Because DRUG-X is a complete regimen for the
664 treatment of HIV, concomitant use is not recommended (7.x).
665 • See full prescribing information for additional clinically significant drug interactions

⁶⁹ A concise summary of the information required under the DOSAGE AND ADMINISTRATION section of the FPI, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information must be included under the Dosage and Administration heading in Highlights. See 21 CFR 201.57(a)(7).

⁷⁰ 21 CFR 201.57(d)(8) and also see the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

⁷¹ See the FDA guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

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and recommended dosage modifications due to drug interactions (2.x, 7.x).

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667 **VII. ABBREVIATIONS**

668

AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
CFR	Code of Federal Regulations
CNS	Central nervous system
CYP	Cytochrome P450
DI	Drug interaction
EDTA	Ethylenediaminetetraacetic acid
FPI	Full Prescribing Information
HIV	Human immunodeficiency virus
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
MAO	Monoamine oxidase
MATE	Multidrug And Toxic Compound Extrusion
OAT1	Organic anion transporter
OATP	Organic anion transporter protein
OCT	Organic cation transporter
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PLR	Physician Labeling Rule
QT	QT-interval
TNF	Tumor necrosis factor
UDP	Uridine 5'-diphosphate
UGT	Uridine 5'-diphospho-glucuronosyltransferase
URL	Uniform Resource Locator

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671 **VIII. DEFINITIONS**

672

Moderate inhibitor	Drug that increases the AUC of sensitive index substrates of a given metabolic enzyme by ≥ 2 - to < 5 -fold.
Strong inducer	Drug that decreases the AUC of sensitive index substrates of a given metabolic enzyme by ≥ 80 percent.
Strong inhibitor	Drug that increases the AUC of sensitive index substrates of a given metabolic enzyme ≥ 5 -fold.
Substrate	Drug whose exposure changes due to inhibition or induction of an enzyme or transporter.

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674 IX. APPENDIX

675
676 The following fictitious labeling example for DRUG-X (drugozide-x) includes excerpts from its
677 Highlights of Prescribing Information and Full Prescribing Information that illustrate the content
678 and format of drug interaction (DI) information throughout the Prescribing Information. Various
679 formatting techniques (e.g., headings, a table, white space) are used to enhance communication
680 of DI information in this fictitious labeling example. The content and format used in this
681 example are meant to be illustrative only and are not intended to limit the use of other possible
682 formats and approaches to convey DI information in the labeling.

683 HIGHLIGHTS OF PRESCRIBING INFORMATION

684 ...

685 -----DOSAGE AND ADMINISTRATION-----

686 ...

- 687 • See full prescribing information for DRUG-X dosage modifications with
688 concomitant use of moderate CYP3A inhibitors (2.4).

689 ...

690 -----CONTRAINDICATIONS-----

- 691 • Concomitant use with strong CYP1A2 inhibitors (4, 5.1).

692 ...

693 -----WARNINGS AND PRECAUTIONS-----

- 694 • *Sedation and Respiratory Depression:* Closely monitor for signs of
695 sedation and respiratory depression with concomitant use of DRUG-X
696 with CNS depressants (5.2).

697 ...

698 -----DRUG INTERACTIONS-----

699 ...

- 700 • *Strong CYP3A Inhibitors:* Avoid concomitant use with DRUG-X (7.1).
- 701 • *Moderate CYP3A Inhibitors:* Reduce DRUG-X dosage to 100 mg once
702 daily (2.4, 7.1).
- 703 • *Strong CYP3A Inducers:* Avoid concomitant use with DRUG-X (7.1).
- 704 • *CYP3A Substrates:* Avoid concomitant use unless otherwise
705 recommended in the Prescribing Information for CYP3A substrates
706 where minimal concentration changes may lead to serious adverse
707 reactions (7.2).

708 ...

709 FULL PRESCRIBING INFORMATION

710 ...

711 2 DOSAGE AND ADMINISTRATION

712 ...

713 2.4 Dosage Modifications for CYP3A Inhibitors

714 Avoid concomitant use of DRUG-X with strong CYP3A inhibitors. Reduce the DRUG-X
715 dosage to 100 mg once daily when used concomitantly with moderate CYP3A inhibitors
716
717
718

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[see Drug Interactions (7.1)].

...

4 CONTRAINDICATIONS

DRUG-X is contraindicated in patients taking strong CYP1A2 inhibitors [see Warnings and Precautions (5.1) and Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Hypotension and Syncope with Concomitant Strong CYP1A2 Inhibitors

The concomitant use of DRUG-X with strong CYP1A2 inhibitors is contraindicated [see Drugs Interactions (7.1)]. In Studies 1 and 2, severe hypotension or syncope requiring medical intervention occurred in 20% of patients treated concomitantly with DRUG-X and a strong CYP1A2 inhibitor [see Adverse Reactions (6.1)].

5.2 Sedation and Respiratory Depression

Closely monitor for signs of sedation and respiratory depression with concomitant use of DRUG-X with CNS depressants. In Studies 1 and 2, sedation, somnolence, and reduced psychomotor function that required dosage interruption or reduction occurred in 19% of DRUG-X-treated patients compared to 0% of placebo-treated patients [see Adverse Reactions (6.1)].

Concomitant use of DRUG-X with opioids, benzodiazepines, or other CNS depressants may increase the risk of sedation and respiratory depression [see Drug Interactions (7.3) and Clinical Pharmacology (12.2)].

...

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on DRUG-X

Table X describes drug interactions where concomitant use of another drug affects DRUG-X.

Table X. Drug Interactions: Concomitant Use of Other Drugs Affect the Use of DRUG-X

Strong CYP1A2 Inhibitors¹	
<i>Prevention or Management</i>	Concomitant use of DRUG-X with strong CYP1A2 inhibitors is contraindicated.
<i>Mechanism and Clinical Effect(s)</i>	Drugozide-x is a CYP1A2 substrate. Strong CYP1A2 inhibitors increase drugozide-x exposure [see Clinical Pharmacology (12.3)], which may cause severe hypotension and syncope [see Warnings and Precautions (5.1)].
Strong and Moderate CYP3A Inhibitors¹	
<i>Prevention or Management</i>	Strong CYP3A Inhibitors: Avoid concomitant use.
	Moderate CYP3A Inhibitors: Reduce the DRUG-X dosage [see

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	<i>Dosage and Administration (2.4)].</i>
<i>Mechanism and Clinical Effect(s)</i>	Drugozide-x is a CYP3A substrate. Strong or moderate CYP3A inhibitors increase drugozide-x exposure [see <i>Clinical Pharmacology (12.3)</i>], which may increase the risk of DRUG-X adverse reactions.
Strong CYP3A Inducers¹	
<i>Prevention or Management</i>	Avoid concomitant use of DRUG-X with strong CYP3A inducers.
<i>Mechanism and Clinical Effect(s)</i>	Drugozide-x is a CYP3A substrate. Strong CYP3A inducers decrease drugozide-x exposure [see <i>Clinical Pharmacology (12.3)</i>], which may reduce the effectiveness of DRUG-X.

¹ See www.fda.gov/CYPandTransporterInteractingDrugs for examples of strong CYP1A2 inhibitors, strong and moderate CYP3A inhibitors, and strong CYP3A inducers.

7.2 Effects of DRUG-X on Other Drugs

CYP3A Substrates

Avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. See www.fda.gov/CYPandTransporterInteractingDrugs for examples of CYP3A substrates.

Drugozide-x is a CYP3A inhibitor. Drugozide-x increases exposure of CYP3A substrates [see *Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions related to these substrates.

...

7.3 CNS Depressants

Closely monitor for signs of sedation and respiratory depression with concomitant use of DRUG-X with CNS depressants.

Due to the additive pharmacologic effect, concomitant use of DRUG-X with CNS depressants (e.g., opioids, benzodiazepines) may increase the risk of sedation and respiratory depression [see *Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)*].

...

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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Drug Interaction Studies

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Benzodiazepines: Measures of sedation increased, and psychomotor performance decreased in approximately 63% of DRUG-X-treated patients who received concomitant

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785 diazepam compared to 23% of those who received DRUG-X alone [see Warnings and
786 Precautions (5.2) and Drug Interactions (7.3)].

787 ...

788 **12.3 Pharmacokinetics**

789 ...

790 Drug Interaction Studies

791 *Clinical Studies and Model-Informed Approaches:* There is no clinically significant drug
792 interaction with proton pump inhibitors, histamine-2 receptor antagonists, or antacids.
793

794
795 Strong CYP1A2 Inhibitors: Fluvoxamine (strong CYP1A2 inhibitor) increased the
796 mean (min-max) ratio of drugozide-x AUC 6.5-fold (5.5-7.8) and C_{max} 2-fold (1.6-
797 2.6) [see Drug Interactions (7.1)].

798
799 Strong and Moderate CYP3A Inhibitors: Ketoconazole (strong CYP3A inhibitor)
800 increased mean drugozide-x AUC by 3.9-fold (2.9-5.2) with no changes to C_{max}.
801 Fluconazole (moderate CYP3A inhibitor) increased drugozide-x AUC 2.1-fold (1.8-
802 2.4) [see Drug Interactions (7.1)].

803
804 Strong CYP3A Inducers: Rifampin (strong CYP3A inducer) decreased mean
805 drugozide-x AUC by 78% and C_{max} by 54% [see Drug Interactions (7.1)].
806

807 Sensitive CYP3A Substrates: Drugozide-x increased midazolam (sensitive CYP3A
808 substrate) AUC 2.3-fold (1.5-3.1) and C_{max} 1.8-fold (1.3-2.2) [see Drug Interactions
809 (7.2)].

810 *In Vitro Drug Interaction Studies*

811
812
813 Cytochrome P450 (CYP450) Enzymes: Drugozide-x does not inhibit or induce CYP
814 isozymes 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. Drugozide-x is not a substrate of
815 CYP isozymes 2B6, 2C8, 2C9, 2C19, and 2D6.

816
817 UDP-Glucuronosyltransferase (UGT): Drugozide-x does not inhibit and is not a
818 substrate of UGTs 1A1, 1A3, 1A6, and 1A9.

819
820 Transporter systems: Drugozide-x does not inhibit and is not a substrate of P-gp,
821 BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2-K.
822

823 [Instead of including information on in vitro DI studies in text as exemplified above, such
824 information may be presented in a table (see below) as an alternative.]

825
826 *In Vitro Drug Interaction Studies:* Table X presents metabolic enzymes and transporter
827 systems that showed no effect on or by drugozide-x in vitro.

828
829 **Table X: Metabolic Enzymes and Transporter Systems that Showed No Effect**
830 **on or by Drugozide-x in Vitro**

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System	Inhibition	Induction	Substrate
Cytochrome P450 (CYP)	1A2 2B6 2C8 2C9 2C19 2D6	1A2 2B6 2C8 2C9 C19	2B6 2C8 2C9 2C19 2D6
UDP- Glucuronosyltransferase (UGT):	1A1 1A3 1A6 1A9		1A1 1A3 1A6 1A9
Transporter systems	P-gp BCRP OAT1 OAT3 OATP1B1 OATP1B3 OCT2 MATE1 MATE2-K		P-gp BCRP OAT1 OAT3 OATP1B1 OATP1B3 OCT2 MATE1 MATE2-K

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...
17 PATIENT COUNSELING INFORMATION⁷²
 ...
Sedation and Respiratory Depression
 Advise patients or their caregivers of the increased risk of sedation, somnolence, and reduced psychomotor function with concomitant use of DRUG-X and CNS depressants, and to monitor for signs of sedation and respiratory depression when using DRUG-X concomitantly with CNS depressants [see Warnings and Precautions (5.2)].

⁷² In this fictitious example, the concomitant use of DRUG-X with strong CYP1A2 inhibitors is contraindicated because of the risks of severe hypotension and syncope. According to the FDA guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format*, “[a]lthough contraindications are essential for informing prescribing decisions, most [contraindications] are typically not appropriate for a patient counseling discussion that occurs once a prescribing decision has been made.” Therefore, in this example the risk of severe hypotension and syncope with concomitant strong CYP1A2 inhibitors was not discussed in the PATIENT COUNSELING INFORMATION section.