QTc Information in Human Prescription Drug and Biological Product Labeling

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2025
Labeling

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Contains Nonbinding Recommendations

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

I. INTRODUCTION

This guidance is intended to assist applicants with incorporating heart rate-corrected QT (QTc) interval prolongation-related information into the labeling of non-antiarrhythmic human prescription drug and biological products.[2] This guidance provides recommendations to help ensure that clinically relevant information on QTc interval prolongation[3] is included in and distributed appropriately across sections of labeling, in accordance with regulatory requirements for the content and format of human prescription drug labeling.[4]

This guidance provides illustrative examples of the content and format of QTc interval prolongation-related information in the labeling involving a fictitious subject drug (e.g., DRUG-X (drugozide) tablets).[5]

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), the Labeling Policy Team and other staff in the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drug, drugs,* or *biological products* include both human drug products and biological products regulated by CDER and CBER, unless otherwise specified.

[3] See the guidances for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) and *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers* (August 2022). 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.

[4] See 21 CFR 201.56(a) and (d) and 21 CFR 201.57.

[5] For the purposes of this guidance, the term *subject drug* refers to the drug for which the labeling is being developed.

This guidance does not address methodological considerations for evaluating or interpreting QTc interval prolongation data.[6]

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

II. BACKGROUND

An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QTc interval on the surface electrocardiogram (ECG). A delay in cardiac repolarization creates an electrophysiological environment that favors the development of torsade de pointes (TdP), which can progress to ventricular fibrillation, leading to sudden death. The risk of TdP may also be increased for patients with risk factors for QTc interval prolongation (e.g., elevated baseline QTc interval, ischemic cardiomyopathy, hypokalemia, history of long QT syndrome, genetic predisposition, or use of a concomitant drug that prolongs the QTc interval or increases exposure to the subject drug that can prolong the QTc interval).

TdP may not be reported in clinical databases, even for drugs known to have significant proarrhythmic effects. The failure to observe an episode of TdP during a drug's clinical development program is not considered sufficient grounds for dismissing the possible arrhythmogenic risks of a drug. While the degree of QTc interval prolongation is recognized as an imperfect biomarker for proarrhythmic risk, in general, there is a qualitative relationship between QTc interval prolongation and the risk of TdP, especially for drugs that cause prolongation of the QTc interval due to inhibition of the rapid delayed rectifier potassium channel.

FDA and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommend that sponsors for most non-antiarrhythmic drugs with systemic bioavailability assess the effect on cardiac repolarization early in clinical development including a clinical electrocardiographic evaluation.[7] The QTc assessment in early clinical development may inform the frequency and continuation of ECG monitoring in late phase clinical trials.

FDA recommends sponsors conduct an assessment of QTc prolongation risk, which may be through a "thorough QT/QTc" (TQT) study, early clinical trial, or an integrated nonclinical assessment. The TQT study assesses the effect of a drug on the QTc interval; this trial is typically conducted in healthy participants who may receive a placebo, a positive control, and the

[6] See footnote 3 for information on FDA guidance documents that address clinical and nonclinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for drugs.

[7] Ibid.

subject drug at therapeutic dose(s) and/or doses above the maximum recommended dose of the drug.[8] In some cases, early clinical trials (e.g., first-in-human studies, multiple-ascending dose studies) that include robust, high-quality ECGs and evaluate the QTc interval response at a sufficient multiple (commonly two times) of the high clinical exposure can be used as a substitute for a TQT study.[9] Some patient-specific or drug-specific factors may limit the ability to conduct a conventional TQT study for certain drugs; therefore, it is recommended, when appropriate, to use alternative strategies to assess the QTc interval effects for these drugs.[10]

FDA recommends that an integrated nonclinical risk assessment[11,12] be used as a substitute for a TQT study when the clinical investigation did not include sufficient multiples of the high clinical exposure for reasons of safety or tolerability (or for other reasons such as saturable absorption), or when a conventional TQT study is not feasible.

III. QTc INTERVAL PROLONGATION INFORMATION IN THE CLINICAL PHARMACOLOGY SECTION

When there is relevant clinical pharmacology-related information on effects of a drug on the QTc interval, such information should be described under a Cardiac Electrophysiology heading in the *Pharmacodynamics* subsection in the CLINICAL PHARMACOLOGY section of labeling. The studied dose(s) or observed exposure range should be included under this heading. Additionally, when available, an identified dose- or exposure-response (QTc interval prolongation response) relationship should be included under this heading. Table 1 below provides examples of how to describe the effect of a drug on the QTc interval under this heading.[13]

[8] Ibid.

[9] Ibid.

[10] Ibid.

[11] See Questions 17 (1.1) and 18 (1.2) in the guidance for industry *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers* (August 2022).

[12] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[13] The recommendations in this section of the guidance supersede QTc labeling-specific recommendations for the *Pharmacodynamics* subsection in Section IV.B of the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

Table 1: Examples of Recommended Statements to Describe the Effects of a Drug on the QTc Interval Under the Cardiac Electrophysiology Heading

QTc Assessment Results	Examples of Recommended Statements Based on the QTc Assessment Results
TQT study (or substitute) excludes a mean 10-millisecond (ms) increase in the QTc interval; or, when clinical studies are supported by an integrated nonclinical risk assessment that concludes low risk.[a]	• At the maximum recommended drugozide dose, clinically significant QTc interval prolongation was not observed. • At X times the maximum recommended drugozide dose, clinically significant QTc interval prolongation was not observed.
Alternative QTc clinical assessment without a positive control excludes a mean 10-ms increase in the QTc interval.[b]	• At the maximum recommended drugozide dose, a mean increase in the QTc interval >20 ms is unlikely. • At a drugozide dose of *[insert dose]* (X times the maximum recommended dose), a mean increase in the QTc interval >20 ms is unlikely.
An integrated nonclinical assessment concludes a low risk,[c] alternative QTc clinical assessment excludes a mean 10-ms increase in QTc interval,[b] and clinical cardiac safety database does not show imbalance in proarrhythmic adverse events.	Drugozide has a low likelihood of proarrhythmic effects due to delayed repolarization based upon integrated nonclinical and clinical cardiac event risk assessments.
For a drug for which a QTc assessment is recommended,[14] the effect on the QTc interval has not been characterized or insufficient data are available to characterize the effect.[a]	There is insufficient information to characterize the effect of drugozide on the QTc interval.
Clinically significant QTc interval prolongation detected.	The largest mean increase in QTc interval was X ms (upper confidence interval = X ms) after administration of *[insert dose]* of drugozide (X times the maximum recommended dose) in patients with [*insert study population].* The increase in the QTc interval was *(was not)* concentration-dependent *[see Warnings and Precautions (5.x)].* [May use the following alternative second sentence, as appropriate: "The increase in the QTc interval was *(was not)* dose-dependent *[see Warnings and Precautions (5.x)].*"]

[14] See the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005).

[a] No clinically significant QTc interval prolongation is concluded when the upper one-sided 95% confidence limit of the mean difference in placebo corrected QTc interval change from baseline (ΔΔQTc) is less than 10 ms in a conventional TQT study[15], substitute study or when the integrated nonclinical risk assessments are used. [see Question 12 (5.1) of the *ICH E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers* (August 2022)].
[b] If the upper bound of the one-sided 95% confidence interval around the estimated maximal effect on ΔQTc is less than 10 ms but no positive control was included in the alternative QTc study, the treatment is unlikely to have an actual mean effect as large as 20 ms [see Question 13 (6.1) of the *ICH E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers* (August 2022)].
[c] See Question 17 (1.1) in the guidance for industry *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers* (August 2022).

For drugs that do not need a QTc interval assessment (e.g., drugs with highly localized distribution; drugs not absorbed systemically; large proteins and monoclonal antibodies), the Cardiac Electrophysiology heading and related information may be omitted from the *Pharmacodynamics* subsection.[16]

IV. QTc INTERVAL PROLONGATION INFORMATION IN THE DRUG INTERACTIONS SECTION

If there are clinically significant drug interactions of the subject drug with other prescription or nonprescription drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice) that result in, or that increase risk of QTc interval prolongation, this information must be included in the DRUG INTERACTIONS section.[17] If drug interactions related to QTc interval prolongation are described in CONTRAINDICATIONS or in the WARNINGS AND PRECAUTIONS section(s), then these interactions must be discussed in more detail in the DRUG INTERACTIONS section.[18]

The DRUG INTERACTIONS section must briefly describe the mechanism of these clinically significant drug interactions (if known) and must include specific practical instructions for preventing or managing these clinically significant interactions.[19] The DRUG INTERACTIONS section should include the observed or predicted clinical effect(s) of these clinically significant interactions.[20]

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[15] Ibid.

[16] Under 21 CFR 201.56(d)(4), "[o]mit clearly inapplicable sections, subsections, or specific information." For additional information on omitting information in labeling, see the guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

[17] See 21 CFR 201.57(c)(8)(i).

[18] Ibid.

[19] Ibid.

[20] See the draft guidance for industry *Drug Interaction Information in Human Prescription Drug and Biological Product Labeling* (October 2024). When final, this guidance will represent the FDA's current thinking on this topic.

A. Use With Other Products Known or Suspected to Prolong the QTc Interval

If the subject drug is known or suspected to prolong the QTc interval, then concomitant use of other products[21] that are also known or suspected to prolong the QTc interval could further increase the risk of clinically significant adverse reactions associated with QTc interval prolongation. In this scenario, FDA generally recommends that clinically significant drug interactions regarding QTc interval prolongation be placed in a separate subsection in the DRUG INTERACTIONS section. For example:

> **7 DRUG INTERACTIONS**
> …
> **7.X Drugs that Prolong the QTc Interval**
> Avoid concomitant use of DRUG-X with other drug(s) with a known potential to prolong the QTc interval.
>
> If concomitant use cannot be avoided:
> - Obtain ECGs when initiating and during concomitant use, and as clinically indicated *[see Warnings and Precautions (5.x)]*.
> - Withhold DRUG-X if the QTc interval is > XXX ms or the change from baseline is > XX ms *[see Dosage and Administration (2.x)]*.
>
> Drugozide causes QTc interval prolongation *[see Clinical Pharmacology (12.2)]*. Concomitant use of DRUG-X with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including torsade de pointes, other serious arrythmias, and sudden death *[see Warnings and Precautions (5.x)]*.

B. Use With Other Products That Affect the Pharmacokinetics of the Subject Drug

If the subject drug (or a metabolite of the subject drug) is associated with concentration-dependent QTc prolongation, then concomitant use with other product(s) that increase the concentrations of the subject drug (or its metabolites) may increase the risk of adverse reactions associated with QTc interval prolongation. In this scenario, FDA generally recommends that clinically significant drug interaction information regarding QTc interval prolongation be placed with information related to the effects of other drugs on the subject drug in the DRUG INTERACTIONS section.[22] For example:

> **7 DRUG INTERACTIONS**
> **…**
> **7.X Effect of Other Drugs on DRUG-X**
> …
> Strong CYP3A Inhibitors

[21] In this context, *other products* refer to all categories of products, including, but not limited to, drugs, food, and dietary supplements.

[22] See footnote 20.

Avoid concomitant use of DRUG-X with strong CYP3A inhibitors.

Drugozide is metabolized by CYP3A. Concomitant use of DRUG-X with a strong CYP3A inhibitor may increase drugozide concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the incidence and severity of adverse reactions, including QTc interval prolongation. Prolongation of the QTc interval increases the risk of torsade de pointes, other serious arrythmias, and sudden death *[see Warnings and Precautions (5.x)]*.

V. QTc INTERVAL PROLONGATION INFORMATION IN THE WARNINGS AND PRECAUTIONS SECTION

When QTc interval prolongation is identified as an adverse reactions or safety hazard that is serious or otherwise clinically significant because it has implications for prescribing decisions or patient management, the WARNINGS AND PRECAUTIONS should generally describe the risks of, or clinically significant adverse reactions from, QTc interval prolongation in patients taking the drug.[23]

Some factors that support including a QTc interval prolongation warning in the WARNINGS AND PRECAUTIONS section include:

- A clinically significant increase in rate of potential proarrhythmic effects, such as TdP, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizure, or sudden death; or

- Results from studies that demonstrate the drug causes a clinically significant QTc interval prolongation, particularly when proarrhythmic activity is consistent with the pharmacology of the drug or related drugs (e.g., human ether-a-go-go-related gene (hERG) positive at low safety margins[24] or in vivo nonclinical QT study that is strongly positive).

When describing the clinically significant risks of QTc interval prolongation in this section, FDA recommends including the following information, as applicable:

- A succinct description of the clinically significant adverse reactions related to QTc interval prolongation that have occurred in patients, including TdP, other clinically significant ventricular arrythmias, or sudden death.

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[23] See 21 CFR 201.57(c)(6)(i) and the 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).

[24] See Question 18 (1.2) in the guidance for industry *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers* (August 2022).

- A description of pertinent exclusion criteria in the clinical trial(s) in which these adverse reactions were observed (e.g., exclusion of patients with clinically significant active cardiovascular disease or recent myocardial infarction).

- The percentage of drug-treated patients who developed an absolute QTc interval value of greater than 500 ms over a specific treatment duration.

- The percentage of drug-treated patients with a greater than 60 ms increase in the QTc interval from baseline over a specific treatment duration.

- A summary of the relationship of dose or concentration to increases in the QTc interval (e.g., "DRUG-X causes a dose- [or concentration-] dependent QTc interval prolongation").

- A description of the risk of increased QTc interval prolongation with concomitant use of other products (e.g., prescription drugs, nonprescription drugs, or dietary supplements), when serious or otherwise clinically significant adverse reactions related to increases in the QTc interval are reasonably associated with concomitant use.

- Cross-reference(s) to more detailed information in the DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, DRUG INTERACTIONS, or CLINICAL PHARMACOLOGY sections, as applicable. See Section IV of this guidance for more information.

The information in the WARNINGS AND PRECAUTIONS section should provide steps to prevent or mitigate clinically significant adverse reactions or risks associated with QTc interval prolongation.[25] Some steps that may be taken to prevent or mitigate the risk of such clinically significant adverse reactions include:

- Assessing the QTc interval via an ECG at baseline, during treatment (e.g., every X weeks), and as clinically indicated;

- Obtaining serum electrolytes (including potassium, calcium, phosphorus, and magnesium) at baseline and during drug treatment as clinically indicated, and correcting electrolyte abnormalities;

- Avoiding the concomitant use of products that may increase the risk of the QTc interval prolongation or may increase concentrations of the subject drug (if QTc interval prolongation appears concentration-dependent);

- Contraindicating the use of the drug or avoiding the use of the drug in patients who are at significant risk of developing TdP, including those with congenital long QT syndrome, uncontrolled or significant cardiac disease, recent myocardial infarction, ischemic

[25] See footnote 14.

cardiomyopathy, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism; and

- Recommending dosage modification(s) based on increases in the QTc interval or development of clinically significant adverse reactions associated with QTc interval prolongation. The specific recommendations to modify the dosage or administration of the subject drug based on increases in the QTc interval should be included in the DOSAGE AND ADMINISTRATION section, rather than in the WARNINGS AND PRECAUTIONS section.[26]

VI. QTc INTERVAL PROLONGATION INFORMATION IN OTHER SECTIONS OF LABELING

A. BOXED WARNING

Certain contraindications or serious warnings, particularly those that may lead to death or serious injury (e.g., TdP), may be required by FDA to be included in the BOXED WARNING. A boxed warning for QTc interval prolongation is recommended when there is reasonable evidence of a causal association between the drug and any of the following:

- TdP
- Polymorphic ventricular tachycardia or signs or symptoms of serious or life-threatening arrythmias
- Other life-threatening cardiac adverse reactions with QTc interval prolongation
- Extensive QTc prolongation (e.g., >20 msec) for drugs indicated in a patient population that is also at high-risk for cardiac arrhythmias
- Cardiac death with QTc interval prolongation

When there is a boxed warning for QTc interval prolongation, the boxed warning must briefly explain the risk and must refer to more detailed information on QTc interval prolongation in the CONTRAINDICATIONS section or in the WARNINGS AND PRECAUTIONS section.[27]

[26] See the 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 FDA's current thinking on this topic.

[27] 21 CFR 201.57(c)(1). Also see the 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).

B. DOSAGE AND ADMINISTRATION Section

If there are recommended dosage modifications for the subject drug (e.g., dosage reduction, dosage interruption, or permanent discontinuation) to reduce the risk of QTc interval prolongation or clinically relevant adverse reactions associated with QTc interval prolongation, this information, as well as information on the recommended frequency of ECG monitoring, should be included in the DOSAGE AND ADMINISTRATION section.[28]

If the only dosage modification information for the subject drug is related to QTc interval prolongation (i.e., there are no other dosage modification recommendations for other adverse reactions), consider presenting the recommendations in a subsection entitled **2.x Dosage Modifications for QTc Interval Prolongation** in the DOSAGE AND ADMINISTRATION section. For example:[29]

> **2 DOSAGE AND ADMINISTRATION**
> …
> **2.x Dosage Modifications for QTc Interval Prolongation**
> If torsade de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious or life-threatening arrythmia occur with DRUG-X use, permanently discontinue DRUG-X *[see Warnings and Precautions (5.x)]*.
>
> With DRUG-X use, if the absolute QTc interval value is increased to more than XXX ms or the QTc interval increased more than XX ms from baseline, then *[see Warnings and Precautions (5.x)]*:
>
> - Withhold DRUG-X until the QTc interval is less than XXX ms, then resume DRUG-X at the same dosage *[if the recommendation is to reduce the dosage, then state the recommended reduced dosage (e.g., "Reduce the oral DRUG-X dosage to X mg once daily")]*.
> - Obtain an ECG at least every X weeks and as clinically indicated.

However, if there are dosage modification recommendations for other risks in addition to those for QTc interval prolongation, consider including all such dosage modifications in a single subsection entitled **2.x Dosage Modifications for Adverse Reactions**.

C. CONTRAINDICATIONS Section

The CONTRAINDICATIONS section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs

[28] See footnote 26.

[29] The specific dosage modifications may be modified based on the indication, duration of drug use, pharmacokinetic parameters of the drug, and patient risk factors.

any possible therapeutic benefit.[30] Those situations include use of the drug in patients who have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable.[31]

For drugs in which serious adverse reactions associated with QTc interval prolongation have been observed with use, consider including a contraindication in patients at high risk of QTc interval prolongation. For example,

> **4 CONTRAINDICATIONS**
> DRUG-X is contraindicated in patients at high risk of QTc interval prolongation (e.g., *consider including patient populations that are at high risk of QTc interval prolongation*) *[see Warnings and Precautions (5.x)]*.

If the concomitant use of the subject drug with another drug (or drug class) increases the risk of clinically significant adverse reactions related to QTc interval prolongation such that the risk from concomitant use clearly outweighs any possible therapeutic benefit, this section should contraindicate the use of DRUG-X with the other drug (or drug class).

For drugs used for life-threatening conditions (e.g., oncologic diseases) in which serious adverse reactions associated with QTc interval prolongation have been observed, a contraindication is generally not appropriate because the risk of use does not clearly outweigh any possible therapeutic benefit.

D. ADVERSE REACTIONS Section

Adverse reactions associated with QTc interval prolongation (e.g., TdP or other ventricular arrythmias) must be included in the ADVERSE REACTIONS section.[32]

E. PATIENT COUNSELING INFORMATION Section

If a drug has information related to QTc interval prolongation in the WARNINGS AND PRECAUTIONS section, the PATIENT COUNSELING INFORMATION section should generally summarize the clinically significant adverse reactions or risks associated with QTc interval prolongation that should be conveyed to the patient.[33] For example,

> **17 PATIENT COUNSELING INFORMATION**
> …
> QTc Interval Prolongation

[30] See 21 CFR 201.57(c)(5).

[31] Ibid.

[32] See 21 CFR 201.57(c)(7).

[33] See the guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2014).

Inform patients that DRUG-X causes QTc interval prolongation and may increase the risk of torsade de pointes, other ventricular arrythmias, and sudden death. Advise patients or caregivers to seek immediate medical attention if they suspect or develop signs or symptoms associated with the clinical consequences of QTc interval prolongation *[see Warnings and Precautions (5.x)]*.

Drug Interactions
Advise patients to inform their healthcare provider before starting or discontinuing a prescription drug, nonprescription drug, or supplement. Instruct patients not to take other drugs that cause QT interval prolongation with DRUG-X *[see Warnings and Precautions (5.x) and Drug Interactions (7.x)]*.

VII. QTc INTERVAL PROLONGATION INFORMATION IN FDA-APPROVED PATIENT LABELING

If a drug has clinically significant QTc interval prolongation information in one or more sections of the PI (e.g., BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS), the clinically significant adverse reactions or risks associated with QTc interval prolongation should generally be described in FDA-approved patient labeling (e.g., Medication Guide,[34] Patient Package Insert[35]).

For example, if a drug's labeling has information on QTc interval prolongation in the WARNINGS AND PRECAUTIONS section, the **What are the possible side effects of DRUG-X?** section of the Medication Guide or Patient Package Insert would state:

DRUG-X may cause serious side effects, including:

- …
- Changes in the electrical activity of your heart (QTc prolongation). Your healthcare provider may do tests during your treatment with DRUG-X to check the electrical activity of your heart and your body salts (electrolytes). Tell your healthcare provider right away if you get any sign or symptom of QTc prolongation, including:
    - dizziness
    - fainting
    - feeling that your heart is pounding or racing (palpitations)
    - chest pain

[34] See 21 CFR part 208.

[35] See 21 CFR 310.501 and 21 CFR 310.515 for Patient Package Insert requirements for oral contraceptives and estrogen-containing products, respectively.

VIII. SUBMITTING LABELING WITH QTc INTERVAL PROLONGATION INFORMATION

Labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.[36] Therefore, when new QTc interval prolongation-related information becomes available, applicants must submit to FDA proposed labeling in a prior approval supplement (unless the changes are designated as moderate or minor by regulation or guidance) containing the updated QTc interval prolongation information for review as a supplement to the new drug application (NDA) or the biologics license application (BLA).[37]

[36] 21 CFR 201.56(a)(2).

[37] See 21 CFR 314.70(b)(2)(v) and 601.12(f).