QTc Information in Human Prescription Drug and Biological Product Labeling

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE) William Pierce at 301-796-0521 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

August 2023
Labeling

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance is intended to assist applicants with incorporating QTc interval prolongation-related information into the labeling of non-antiarrhythmic human prescription drug and biological products.[2,3] This guidance provides recommendations to help ensure that clinically relevant information on QTc interval prolongation 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 prolongation-related information in the labeling involving a fictitious subject drug (e.g., DRUG-X (drugozide-x) tablets).[5]

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

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

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

[3] See the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers (R3)* (ICH E14 Q&A (R3) guidance) (June 2017). 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.

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 QT 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 degenerate into ventricular fibrillation, leading to sudden death. The risk of TdP may also be increased for patients with risk factors for QT interval prolongation (e.g., elevated baseline QTc interval, heart failure, hypokalemia, history of long QT syndrome, genetic predisposition, or use of a concomitant medication that prolongs the QT interval or increases exposure to a drug that can prolong the QT interval).

TdP may not be captured 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 QT prolongation is recognized as an imperfect biomarker for proarrhythmic risk, in general, there is a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause prolongation of the QT interval due to inhibition of the delayed rectifier potassium channel.

FDA and the International Council for Harmonisation (ICH) recommend that applicants for most non-antiarrhythmic drugs with systemic bioavailability assess the effect on cardiac repolarization early in clinical development including a clinical electrocardiographic evaluation.[6] The QT corrected for heart rate (QTc) assessment in early clinical development may inform the intensity and continuation of ECG monitoring in late phase clinical trials.

FDA/ICH recommend that sponsors conduct a single clinical trial, named the "thorough QT/QTc study" (TQT study), to assess the effect of a drug on the QTc interval; this trial is typically conducted in healthy subjects who may receive a placebo, a positive control, and therapeutic dose(s) and/or doses above the maximum usual or recommended dose of the drug.[7] 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 2 times) of the high clinical exposure can be used as a substitute for a TQT study.[8] Some patient-specific or drug-specific factors may limit the ability to conduct a conventional

[6] See footnote 3.

[7] See footnote 3.

[8] See footnote 3.

TQT study for certain drugs; therefore, it is recommended, when appropriate, to use alternative strategies to assess the QTc interval effects for these drugs.[9,10]

It is recommended that an integrated nonclinical and clinical QT/QTc risk assessment[11] 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. The sponsor should discuss their proposed clinical and nonclinical studies designed to assess the potential of their drug to prolong the QTc interval with the review division prior to submitting a new or supplemental marketing application.[12]

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 the Cardiac Electrophysiology heading in the *Pharmacodynamics* subsection in the CLINICAL PHARMACOLOGY section.[13] 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.

[9] See the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012).

[10] See S7B Q&As 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).

[11] See S7B Q&As 1.1 and 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] See the guidance for industry *Clinical Pharmacology 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
TQT study (or substitute) excludes a mean 10-millisecond (ms) increase in QTc interval[a]	At the maximum recommended dose *[or At X times the maximum recommended dose]*, clinically significant QTc interval prolongation was not observed.
Alternative QTc study without a positive control excludes a mean 10-ms increase in QTc interval[b]	At the recommended DRUG-X dose (*or At [insert dose] (X times the recommended dose)*), a mean increase in the QTc interval >20 ms was not observed.
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	There is insufficient information to characterize the effect of DRUG-X on the QTc interval.
Clinically significant QTc interval prolongation detected	The largest mean increase in QTc interval was X ms (upper confidence interval = Y ms) after administration of DRUG-X *[insert dose]* (X times the maximum recommended dose) in patients with [*insert study population].* The increase in the QTc interval was (was not) concentration- *[may use dose in place of concentration as appropriate]* dependent *[see Warnings and Precautions (5.x)]*.

[a] No clinically significant QTc interval prolongation is concluded when the mean difference in placebo-corrected QTc interval change from baseline (ΔΔQTc) is less than 10 ms in a conventional TQT study[15] or substitute study (see Section 5.1 of the ICH E14 Q&A (R3) guidance), or when the integrated nonclinical and clinical risk assessments are used.

[b] The upper bound of the two-sided 90% 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 Section 6.1 of the ICH E14 Q&A (R3) guidance).

[14] See footnote 9.

[15] See footnote 9.

For drugs that do not need a QTc interval assessment (e.g., most monoclonal antibodies), the Cardiac Electrophysiology heading and related information may be omitted from this 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 over-the-counter (OTC) drugs, classes of drugs, or foods 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 QT interval prolongation are described in CONTRAINDICATIONS or in WARNINGS AND PRECAUTIONS section(s), then this interaction must be discussed in more detail in the DRUG INTERACTIONS section.[18]

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

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 that are also known or suspected to prolong the QT 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 product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, obtain ECGs when initiating, during concomitant use, and as clinically indicated *[see Warnings and*

[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] See 21 CFR 201.57(c)(8)(i). This recommendation may be adjusted based on the indication for use, duration of use, and patient risk factors.

Precautions (5.x)]. Withhold DRUG-X if the QTc interval is > 500 ms or the change from baseline is > 60 ms *[see Dosage and Administration (2.x)]*.

Drugozide-x 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 (PK) of the Subject Drug

If DRUG-X is associated with concentration-dependent QTc prolongation, then concomitant use with other product(s) that can increase its concentrations may increase the risk of a clinically significant QTc interval prolongation and adverse reactions associated with QTc interval prolongation. For example:

7 DRUG INTERACTIONS

…

7.X Effect of Other Drugs on DRUG-X

Strong CYP3A Inhibitors

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

Drugazide-x is metabolized by CYP3A. Concomitant use of DRUG-X with a strong CYP3A inhibitor may increase drugozide-x 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 information 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.[20]

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

[20] 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).

- An increased rate of potential proarrhythmic effects, such as TdP, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizure, or sudden death, or;[21]

- 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 concentrations or in vivo nonclinical QT study that are 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 sudden death, TdP, or other clinically significant ventricular arrythmias.

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

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

- The percentage of 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 an 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, OTC drugs, or nutritional supplements), when serious or otherwise clinically significant outcomes related to increases in the QTc interval are reasonably associated with concomitant use. Include cross-reference(s) to more detailed information in the DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS, or CLINICAL PHARMACOLOGY sections, as applicable. See Section IV of this guidance for more information.

The warning should provide steps to take to prevent or mitigate clinically significant adverse reactions or risks associated with QTc interval prolongation.[22] Some steps that may be taken to prevent or mitigate the risk of such clinically significant adverse reactions include:

[21] See the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006).

[22] See footnote 9.

- Assessing the QTc interval via an ECG at baseline and during treatment as clinically indicated;

- Obtaining serum electrolytes (including potassium, calcium, phosphorous, and magnesium) at baseline, during 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 drug (if QTc interval prolongation appears concentration-dependent);

- Avoiding concomitant use or contraindicating 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, heart failure, 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 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.[23]

VI. QTc INTERVAL PROLONGATION INFORMATION IN OTHER SECTIONS OF LABELING

A. BOXED WARNING Section

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:[24]

- Cardiac death with QTc interval prolongation

- TdP

- Polymorphic ventricular tachycardia or signs or symptoms of serious or life-threatening arrythmias

[23] 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 thinking on this topic.

[24] When there is a BOXED WARNING for QTc interval prolongation, there must be more detailed information on QTc interval prolongation in the CONTRAINDICATIONS section or in the WARNINGS AND PRECAUTIONS sections. See 21 CFR 201.57(c)(1).

- Other life-threatening cardiac adverse reactions with QTc interval prolongation

B. DOSAGE AND ADMINISTRATION Section

If there are recommended dosage modifications (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 QTc interval assessment (ECGs) should be included in the DOSAGE AND ADMINISTRATION section.[25]

If the only dosage modification information for a 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:

2 DOSAGE AND ADMINISTRATION

…

2.x Dosage Modifications for QTc Interval Prolongation

Table 2 provides recommended dosage modifications for QTc interval prolongation.

Table 2: Recommended DRUG-X Dosage Modifications for QTc Interval Prolongation

Adverse Reaction	Severity	Monitoring and Dosage Modifications for DRUG-X
QTc Interval Prolongation *[see Warnings and Precautions (5.x)]*	Torsade de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious or life-threatening arrythmia	Permanently discontinue DRUG-X.
	QTc interval absolute value greater than XXX ms or Increase in QTc interval greater than XX ms from baseline	• Withhold DRUG-X until QTc interval is less than XXX ms, then resume DRUG-X at *[same or reduced dosage]*. • Obtain an ECG at least every X weeks and as clinically indicated.[26]

[25] See footnote 23.

[26] This recommendation may be adjusted based on the indication for use, duration of use, pharmacokinetic parameters of the drug, and patient risk factors.

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**.[27]

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 any possible therapeutic benefit.[28] 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.[29]

For drugs in which serious adverse reactions associated with QTc interval prolongation have been observed with use of the drug, consider including a contraindication in patients with congenital long QT syndrome or uncompensated heart failure. For example,

> **4 CONTRAINDICATIONS**
> DRUG-X is contraindicated in patients with a history of long QT syndrome or uncompensated heart failure *[see Warnings and Precautions (5.x)]*.

If the concomitant use of a drug (e.g., DRUG-X) with another drug (or drug class) increases the risk of clinically significant adverse reactions related to QTc interval prolongation such that the risk of 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.[30] Adverse reactions associated with QTc interval prolongation that appear in the WARNINGS AND PRECAUTIONS section must also be listed in the ADVERSE REACTIONS section.[31]

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[27] FDA recommends discussing the specific dosage modifications for the drug with the appropriate review division.

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

[29] Ibid.

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

[31] See 21 CFR 201.57(c)(6) and 21 CFR 201.57(c)(7).

E. PATIENT COUNSELING INFORMATION Section

If a drug has a warning 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 (e.g., identification of these risks; the mitigation strategies that are pertinent to patients including self-monitoring information, and information on when to contact a healthcare provider, seek emergency help, or immediately discontinue the drug).[32] For example,

17 PATIENT COUNSELING INFORMATION

…

QTc Interval Prolongation

Inform patients that DRUG-X causes QTc interval prolongation and may increase the risk of Torsades de pointes, other ventricular arrythmias, and sudden death. Inform patients that ECG monitoring will be obtained before and during treatment with DRUG-X. 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)]*.

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