Electrocardiographic assessment for therapeutic proteins—scientific discussion

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Electrocardiographic monitoring is an integral component of the clinical assessment of cardiac safety of all compounds in development. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline recommends a dedicated study to evaluate drug-induced effects on cardiac repolarization ("thorough QT/QTc study"). There has been limited published information on QT interval changes secondary to therapeutic proteins; however, in theory, biologic therapies may affect cardiac electrical activity either directly or indirectly. This article summarizes scientific discussions of members of the Cardiac Safety Research Consortium and includes possible approaches to consider for the clinical evaluation of drug-induced QT prolongation in development programs of therapeutic proteins. (Am Heart J 2010;160:627-34.)

The QT interval on an electrocardiogram (ECG) represents the time for ventricular depolarization and repolarization. Increases in the QT interval have been associated with torsades de pointes (TdP), a rare but potentially fatal arrhythmia, which can be caused by a number of factors including genetic predisposition, physiologic conditions (eg, changes in electrolytes or autonomic tone), various medical conditions (eg, congestive heart failure, left ventricular hypertrophy), and in some cases the use of drugs that delay cardiac repolarization.[1] Drug-induced TdP is a significant safety concern and has been one of the major reasons for delays in approval, labeling with "box" warnings, nonapproval, or withdrawal of pharmaceutical products from the market.[2] Drug-induced QT interval prolongation is currently the most commonly used surrogate marker for predicting the risk of TdP in large populations exposed to a drug. As a result, current guidance from regulatory authorities, the International Conference on Harmonization (ICH) E14 (clinical), and the ICH S7B (nonclinical) guidelines call for a rigorous evaluation to assess the potential of most new, systemically available drugs to prolong the QT interval before approval.[3,4]

The ICH E14 guidance document was written with an emphasis on small molecule drugs and does not specifically address the QT assessment for therapeutic proteins.[3] There is currently no consensus about whether and how to apply the principles of ICH E14 to therapeutic proteins or, more broadly, what level of clinical QT assessment is necessary for such therapies. This is an important issue because therapeutic proteins have major differences in safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles compared with small molecule drugs, and are playing an increasingly important role in the pharmacologic armamentarium for a wide variety of indications.

The Cardiac Safety Research Consortium (CSRC) is a public-private partnership developed to advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the Food and Drug Administration's Critical Path Initiative as well as other public health priorities. This article discusses possible approaches to consider for the clinical evaluation of drug-induced QT prolongation in development programs of therapeutic proteins. The CSRC views expressed in this white paper are only suggestions for clinical development of therapeutic proteins and do not

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represent new regulatory policy. For preclinical recommendations, the reader is referred to the ICH S7B guideline and the review paper by a working group from the Safety Pharmacology Society.[4,5]

Background

Biologic products are a diverse and rapidly growing category of agents with the potential to treat a large variety of diseases. Broadly speaking, "biologics" comprise a wide array of products primarily composed of sugars, proteins, nucleic acids, cellular and tissue components, or whole tissues. Table I summarizes the functional classification of therapeutic proteins as suggested by Leader et al.[6] The focus of this discussion will be on therapeutic proteins including monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), and nonantibody polypeptides such as cytokines, growth factors, enzymes, immunomodulators, and fusion proteins. Vaccines, allergenics, tissues, gene therapies, and blood products will not be discussed.

Because protein therapeutics are designed to act at highly specific targets, adverse reactions are most commonly a result of exaggerated pharmacology. Within a development program, the amount of safety risk that can be tolerated will be based on the expected benefit and the benefit-risk assessment of alternative therapies. The level of sensitivity required to detect safety signals will be inversely proportional to the risk tolerance. For example, a compound with low risk tolerance in a non–life-threatening disease, with other therapeutic alternatives available, will require higher sensitivity to detect drug-induced QT effects than compounds with documented life-saving benefits in areas of unmet clinical need. In any case, understanding potential safety risks is an essential component of any drug development plan; and risk management activities intended to optimize therapeutic interventions can only be implemented with knowledge of expected benefits and risks. As described in the ICH E14 guidelines,[3] appropriate ECG monitoring is considered a component of the clinical assessment of cardiac safety and is expected for all compounds in development, including therapeutic proteins.

Most cases of drug-related QT prolongation and TdP have been mechanistically linked to functional inhibition of a cardiac potassium ion channel encoded by human Ether-à-go-go Related Gene (hERG). Small molecule drugs (ie, molecular weight <1,000 d) are generally believed to inhibit the hERG channel by entering the cardiac myocyte and binding to amino acid residues on the inner pore surface of the ion channel.[7,8] Larger molecules (ie, molecular weight 1,000-25,000 d), such as some proteins, rarely have been shown to inhibit the hERG channel function either directly, by binding to extracellular channel domains, or indirectly through other secondary mediators.[9,10] Some group I therapeutic proteins (Table I) that have been associated with QT prolongation include insulin, vasopressin, and oxytocin.[11-16] Monoclonal antibodies are large proteins (eg, MW >140,000 d) with high specificity for their target antigens; therefore, it is unlikely that mAbs would directly inhibit the function of hERG or other ion channels responsible for cardiac repolarization.[5] Assuming that mAbs do not indirectly affect the function or survival of cardiomyocytes, it is unlikely that they would affect the QT or have a risk of TdP. However, if mAbs have primary or secondary effects on cardiac function (ie, if the target is expressed on cardiac myocytes and if interaction with the target affects myocyte function or viability),[17-19] then it is plausible that these agents may alter cardiac repolarization dynamics leading to QT prolongation.

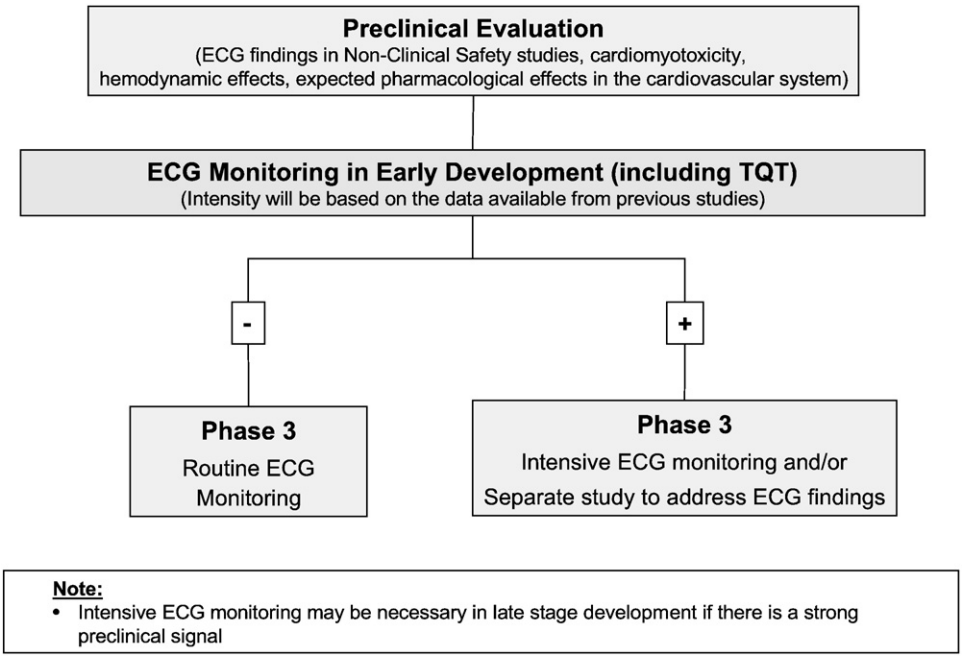
It is critical to develop a rational approach to the QT assessment of therapeutic proteins that carefully considers the different sizes and properties of this heterogeneous group of agents so that the appropriate level of evaluation can be performed given the pretest likelihood of a potential QT effect.[5] In addition, some therapeutic proteins cannot be studied in healthy volunteers, making QT assessment more challenging.[20,21] The CSRC recently published a separate article with suggestions for alternative approaches to proarrhythmic risk assessment when optimal studies are infeasible.[22] The goal of the present document is to provide practical suggestions for how the clinical risk of QT prolongation/TdP might be reasonably assessed for therapeutic proteins in development. These

Table I. Functional classification of protein therapeutics (adapted from Leader et al[6])

Types	Examples
Group I: enzymes or regulatory proteins	
Ia: replacing a protein that is deficient or abnormal	Insulin, growth hormone (GH), coagulation factors
Ib: augmenting an existing pathway	Erythropoietin, filgastrim, interferon
Ic: Providing a novel function or activity	Botulinum toxin, bivaluridin, streptokinase
Group II: targeted proteins	
IIa: interfering with a molecule or organism	Monoclonal antibodies (mAbs) and immunoadhesins
IIb: delivering other compounds or proteins	Gemtuzumab ozogamicin, ibritumomab tiuxetan
Group III: vaccines	
IIIa: protecting against a deleterious foreign agent	Hepatitis B surface antigen (HBsAg), human papillomavirus (HPV) vaccine
IIIb: treating an autoimmune disease	Anti-*Rhesus* (Rh) immunoglobulin G
IIIc: treating cancer	In development
Group IV: protein diagnostics	
	Purified protein derivative (PPD), thyrotropin, arcitumomab

Groups III and IV are not covered in this document.

Figure 1



ECG monitoring plan.

recommendations are based, wherever possible, on evidence published in the medical literature.

ECG monitoring for therapeutic proteins in early development

As described in the ICH E14 guidelines, evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application.[3] Good-quality ECG data will help to assess the potential for proarrhythmic drug-induced ECG changes, including prolongation of the QT interval. In routine clinical practice, a single ECG is recorded per time point; and the main focus is the overall clinical interpretation. However, more intensive recordings are implemented when the goal is to understand therapeutic-induced changes in ECG intervals over time (eg, evaluation of QT, PR, and QRS in intensive ECG studies).

Figure 1 describes a general approach for ECG monitoring in drug development. Assessment of QT effects is suggested in early clinical development programs (eg, single ascending dose studies, multiple ascending dose studies, phase 2a studies) regardless of the preclinical findings. The intensity of the ECG monitoring is defined based on the data available from previous studies as well as the risk tolerance (ie, indication and therapeutic options available).

A well-conducted early clinical program with robust ECG monitoring in an adequate number of subjects will facilitate assessment of QT effects and will better define the ECG monitoring needs in future studies. Some of the reasons for the collection of intensive ECG recordings in early development studies include:

- Easier to perform intensive monitoring because subjects are often confined
- Easier to standardize ECG equipment, which is difficult in later-phase development
- Easier to collect PK information to correlate with QT because the patients may only be at a single/few sites
- Subjects' willingness to undergo extra ECG monitoring
- The highest doses often being tested, which will help evaluate the "worst case scenario" for the compound

Good-quality data are a prerequisite to obtain useful information that will enable development of meaningful conclusions regarding a compound's safety. Table II describes some suggestions to obtain good-quality ECG recordings. The clinical development of therapeutic proteins frequently involves studies in patients with significant comorbidities and comedications, which impose limitations to ECG collection and interpretation.[23,24] Moreover, therapeutic proteins may be associated with changes in autonomic tone (eg, infusion or injection site reactions), potentially confounding the

Table II. Considerations for obtaining quality ECG recordings and optimizing QT measurement

ECG machine	• Digital recordings. • ECG machine with adequate maintenance. • If possible, use the same model for all subjects.
Subject handling	• Rest ≥5 min before ECG recordings. Avoid autonomic influences (eg, phlebotomy, TV, sleep). • Time matched assessments on the day before dosing to control for circadian variations. • The timing of subsequent ECGs and the conditions under which they are recorded should strictly match those at baseline. Conditions to be standardized include electrode placement, position, food intake, activity level, stressors, and room temperature. • Capture the ECG before any concomitantly scheduled procedure (eg, blood draws or PD assessments). • Avoid ECG recordings for first hours after meals. • If possible, in early clinical studies, exclude subjects with personal or family history of QT prolongation, and/or long QT syndrome, or prolonged QTc at baseline. • If possible, in early clinical studies, exclude subjects whose ECGs have QRS or T wave perceived to be unfavorable for a consistently accurate QT measurement (eg, neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low-amplitude T wave, merged T and U waves). • Any adverse event that occurs around the time of ECG collection should be recorded (eg, nausea, pain, infusion reaction).
ECG recordings	• Replicate recordings at each time point to reduce variability in the assessment of the QT interval. • Collect PK samples at time of ECG recording to allow exposure-response evaluations. Ensure that the ECGs are collected before the PK draws to avoid changes in heart rate and autonomic tone due to venipuncture. • Number of ECG time points postdose should allow characterization of the effects over time; for example, collect ECGs at Tmax and at minimum 2-3 other postdose time points including steady state (timing of ECG recordings is compound specific).

evaluation of QT. In any case, the best possible ECG recordings are advocated in early development to optimize clinical safety detection and evaluation.

There is no consensus regarding approach, number of subjects needed, or development stage during which to address a biologic's clinical QT risk. Specific analyses and subject numbers will follow largely from what is known about the study product as well as the benefit-risk profile of its proposed indication. Given the variability inherent to small studies and the monitoring limitations in some clinical development programs, these kinds of studies may only be able to detect major QT changes. However, for some high-risk indications with higher risk tolerance (eg, oncology) and very low pretest probability for QT effects (eg, mAbs), it could be justified that the main focus should be on assessing potential for major ECG changes. For example, in a clinical study with QTc SD of 19 ms for the change from baseline of QTc, $\alpha = .05$, under the independence assumption, using a normal approximation, a sample size of 40 subjects per arm will have at least 85% power to exclude an effect of 20 ms (ie, the upper limit of the 90% CI is <20 ms) when the "true" effect is up to 10 ms at each of 4 ECG time points.[25] If appropriate, the ICH E14 guidance document recommends the thorough QT (TQT) study as the highest standard of evidence for exclusion of a clinically significant QT risk.[3] Nonetheless, alternatives may be acceptable if a TQT study is infeasible.[22]

When a TQT study may not be needed

Given the low likelihood for ion channel interactions because of their large size and high target specificity,[5] mAbs and other large targeted therapeutic proteins (eg, fusion proteins, which are created by joining parts of 2 different genes) will generally not need a TQT study. However, collecting sufficient ECG data during development to exclude a clinically important effect (direct or indirect) on cardiac electrical activity, including QT interval, would be an important component of safety assessments. Whether further intensive QT assessment is necessary will depend on the safety signals detected and the benefit-risk implications for the proposed indication(s).

Suggested approaches for when a TQT study is considered

The available evidence, although it is limited, suggests that certain smaller therapeutic proteins might have the ability to cause QT prolongation and/or TdP by either binding directly to the potassium channel or acting indirectly, through secondary mediators, influencing cardiac channel function.[11,12,16,26] Therefore, it has been suggested that smaller therapeutic proteins, especially those that would be expected to bind less specifically to a target than an antibody, undergo a QT evaluation similar to the one recommended in ICH E14. This includes but is not limited to most nonantibody peptides and polypeptides.

Antibody-drug conjugates may require a TQT study if there is a reason to believe or evidence to suggest that the small molecule component of the ADC or its metabolites might become systemically available in humans.[27]

A TQT study, as recommended in the ICH E14 guidelines, is typically conducted in healthy volunteers and usually includes 4 arms: placebo, a positive control, and two doses of the new molecular entity (including one dose that is a significant multiple of the anticipated therapeutic dose).[3] However, therapeutic proteins are frequently developed to treat severe and life-threatening

diseases (eg, cancer, severe inflammatory diseases) that might preclude the evaluation of the QT effects in a standard TQT study.[28] Situations where some aspects of this study may be impractical or unethical to implement include the following:

- The use of healthy volunteers when there are significant safety or tolerability issues (eg, cytotoxicity, immunogenicity)
- The use of a placebo arm in life-threatening diseases
- When there is low PK variability in the target population (eg, large molecules given parenterally with low probability of metabolic interactions), use of supratherapeutic doses may be less relevant
- When the maximal tolerated dose (MTD) is the selected therapeutic dose, supratherapeutic doses may not be possible to study.

In such cases, including as many of the key components of the ICH E14 TQT study as possible, with solid rationale explaining the reasons to deviate from the E14 guidance, may justify the proposed alternative safety monitoring plan. Detailed approaches on assessing proarrhythmic potential of drugs when optimal studies are infeasible are included in a separate CSRC article.[22]

QT assessment in earlier phases will allow characterization of potential significant effects and ensure that appropriate risk minimization can be established before phase 3 studies. The degree of monitoring required in subsequent studies will be based on the data acquired in preclinical and early clinical studies (Figure 1). For compounds with high risk tolerance, dedicated QTc evaluation, if needed, may be delayed to late development (phase 3 or even phase 4), either as a TQT or as substudy during phase 3, provided that a satisfactory alternative ECG assessment strategy has been provided in the early trials.

ECG evaluation

The following are considered components of the analysis of ECG data:

1. Measures of central tendency: mean absolute, baseline-adjusted, and placebo- and baseline-adjusted HR, RR, QT, QTc, PR, and QRS for each assessment time point, including 2-sided 90% CIs, as well as maximum mean and baseline-adjusted values for each parameter
2. Categorical analysis of QT: number and percentage of individuals with absolute QT/QTc values >450, >480, and >500 ms, and number and percentage of individuals with changes from baseline >30 and >60 ms
3. Number and percentage of individuals with abnormal morphological ECG findings
4. Number and percentage of individuals with adverse events that could be associated with arrhythmia (eg, palpitations, dizziness, syncope, cardiac arrhythmias, sudden death).

Given that many drugs and disease states affect heart rate, it is important to ensure that an appropriate QT correction formula is used. Scatter plots of QTc versus HR can demonstrate suitability of the correction formula, that is, one that generates a slope of QTc versus HR as close to zero as possible.

Understanding the relationship between exposure and QT changes provides important information on the potential pharmacologic effects on cardiac repolarization.[29,30] Strategic planning in early development, with the collection of high-quality ECG recordings and correlated PK assessments, will allow concentration-QT change modeling from data pooled across dose groups in a single study or across clinical studies. Benefits of this early ECG monitoring and PK/PD modeling approach include the following:

- Understanding of the expected QT and PK variability in the target population could be more informative than the potential maximum mean change at specific dose levels.
- Accounting for many different sources of variability (eg, age, sex, disease effects, comedications)
- Increase in study power and reduction of the risk of false positives from small studies
- Evaluating potential delayed effects
- Predicting QT effects at doses not studied
- Determining a significant concentration-QT relationship could obviate a TQT study. However, lack of a significant correlation would not be sufficient evidence to conclude that the study drug does not cause QT prolongation.

As valuable as exposure-response modeling is to characterize drug-induced QT prolongation, it is also important to identify its complexities and limitations; and the modeling approach selected needs to be justified. Therapeutic proteins often have nonlinear PKs (eg, mAbs against cell-surface antigens), and the PDs may not have a direct correlation with serum or plasma exposures (ie, lag periods between administration and response, or persistent response after complete clearance). In addition, many factors can influence the response, including receptor mediated clearance, disease status, and physiology of the system being targeted. Exposure response modeling approaches that account for delayed effects may be more useful in characterizing the PK/PD relationship for therapeutic proteins that do not directly inhibit hERG or other ion channels responsible for cardiac repolarization.[30-33] Similar PK/PD modeling

approaches can also be applied to other ECG intervals (eg, PR and QRS).

Monitoring during late clinical drug development

Consistent with the ICH E14 guidance document, cardiac safety assessment in phase 3 studies includes ECG monitoring and review of adverse events for potential drug-induced arrhythmias. The intensity of ECG monitoring during later-phase studies will depend upon the results of a TQT study, if performed, and/or the ECG data obtained in early-phase clinical studies. A dedicated ECG study documenting the absence of treatment-related effects on the QTc interval, the PR interval, the QRS duration, and heart rate should allow for collection of baseline and periodic on-therapy ECGs in accordance with the clinical standards in the therapeutic area. A TQT study that suggests a potential ECG effect will lead to more intensive ECG monitoring during phase 3 if continued development is considered appropriate based on a benefit-risk analysis. Scheduling of the ECG data collection to coincide with the expected maximum PD effect on the parameter of interest would seem most important, and ECG collection performed at both early and late time points over the treatment period would allow one to describe acute and late effects. Further investigations might also be warranted to characterize dose and concentration relationships of the therapeutic protein on the QT/QTc interval. If a TQT study cannot be performed in healthy volunteers because of safety or tolerability concerns with the compound, a QT study in the population of interest might be considered; or more intensive ECG assessments may be warranted in phase 3 studies. Such ECG evaluation plans should be discussed with regulatory authorities.

The eligibility criteria for phase 3 trial designs will be influenced by the results of the early development studies. A broader spectrum of patients likely to receive the therapeutic protein if it is approved may be included if lack of a QT interval effect has been demonstrated. However, when a QT effect has been observed or has not been assessed, the baseline threshold QTc that warrants exclusion needs to be carefully defined; and consideration should be given to excluding subjects with known risk factors for TdP or use of concomitant medications known to prolong the QT interval. Depending on the drug or the disease under study, it may not be appropriate to exclude patients with a prolonged QTc interval at baseline, especially if no alternative therapies exist and a life-saving treatment benefit may be observed.[20,34] Criteria for discontinuing a patient from a clinical trial should take into consideration the study population and risk-tolerance level deemed appropriate.

During the conduct of these later-phase trials, changes in ECG parameters continue to be monitored; however, emphasis is placed on identifying outliers (eg, QT/QTc >500 ms or >60 ms change from baseline) and monitoring adverse event reports for potential drug-induced arrhythmias (eg, syncope, TdP, ventricular fibrillation, sudden death). Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs), groupings of terms from one or more MedDRA System Organ Classes that relate to a defined medical condition, can aid in identification of arrhythmias and overall cardiac safety.[35]

Table III. Approaches for risk management

Activities aimed to characterize the risk
- Preclinical evaluation: more detailed in vitro and in vivo studies
- Enhanced pharmacovigilance data collection looking for events relating to QT prolongation and TdP
- Data mining from safety databases (ie, AERS) for potential class effects
- Postmarketing clinical studies to evaluate QT changes or arrhythmic events
- Registries
- Observational epidemiological studies

Risk minimization actions
- Communication in the label
- Prescriber and patient education programs (eg, risk evaluation and mitigation strategy)
- In-hospital use
- Specific monitoring
- Restricted access
- Reminder systems
- Avoidance of concomitant therapies or metabolic conditions (eg, hypokalemia) that will lead to QT prolongation

AERS, Adverse Event Reporting System.

Risk management approaches in the postmarketing phase

In the postapproval phase, risk surveillance and management plans will depend upon available safety information, the risk tolerance, and the target population. At a minimum, adverse event data can be reviewed for reports of QT prolongation, TdP, and other serious cardiac arrhythmic events such as ventricular fibrillation and sudden cardiac death.

When further risk management during the postmarketing phase is needed, one or more of the approaches presented in Table III may be considered.[36,37]

Summary and conclusions

There is limited published information available on ECG effects secondary to therapeutic proteins; however, in theory, biologic therapies may affect cardiac electrical activity either directly or indirectly. In an effort to begin addressing this potential risk, members of the CSRC working group held a scientific discussion on the topics outlined in this article. There is general consensus that early clinical development programs of systemically

bioavailable therapeutic proteins include ECG assessments. Because biologic therapies comprise a diverse group of molecules with very different properties, the amount and type of ECG data considered adequate and appropriate should be individualized based on the type of product, its mechanism of action, the intended patient population, the drug's anticipated benefit-risk profile, and any emerging data. For smaller, less-targeted proteins and certain antibody-drug conjugates, a TQT study as outlined in ICH E14 or a study that incorporates many of the key components of a TQT study will need to be considered. For most large, targeted therapeutic proteins, such as mAbs and fusion proteins, a TQT study may be considered unnecessary; but sponsors should consider collecting sufficient, good-quality ECG data in early development to assess any potential clinically important QT effect. Alternative approaches can be appropriate; and in these cases, it is suggested that sponsors seek the input of the applicable regulatory authorities to ensure that the appropriate ECG data are collected. Sponsors can use the QT data collected during early development to guide further ECG monitoring and risk management activities in later phase and in the postmarketing setting. The possible approaches provided herein will enable sponsors to collect the QT data to support an optimal use of most biologic therapies. Further discussion and refinements to these suggested approaches will undoubtedly be required as experience and data accumulate and as the collective scientific understanding and regulatory expectations evolve regarding the risk of proarrhythmia with therapeutic proteins.

Disclaimer

The opinions and conclusions expressed in this article are solely the views of the authors and do not necessarily reflect those of the Food and Drug Administration, Health Canada, or any particular pharmaceutical industry.

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