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Weaning off Thorough QT Studies

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In a previous Editorial in *Clinical Pharmacology & Therapeutics (CPT)*, we described early de-risking of drug-induced QT prolongation liability as “one of the greatest achievements of the Drug Safety Science discipline,” since no new drug has been withdrawn from the market due to QT prolongation for over a decade.¹ Undoubtedly, the introduction of the so-called thorough QT study (T-QT) through the seminal International Council for Harmonisation (ICH) guidelines, ICH 14² has played a pivotal role in in this success. However, with parallel efforts and progress in non-clinical proarrhythmic risk assessment, the need for a mandatory T-QT study as a default component of every drug development program has been increasingly called into question, mainly due to the high associated costs (on average ~US \$2 million per study).³ As a result, new ICH guidelines were introduced that provide alternative (cheaper) pathways to evaluate proarrhythmic risk, as reviewed in the Tutorial by Lester *et al.*⁴ in this issue of *CPT*. However, the authors report that despite an early adoption of this new paradigm, currently T-QTs are still being performed in ~50% of drug development programs and this percentage has been stable for the past 7 years. The reasons for this stagnation are not clear, but could be related to a lack of awareness, risk aversion, improvements in the efficiency of T-QT designs, and/or a shift to different compound classes with more complex or unknown QT liabilities.⁴ Additionally, a non-clinical assessment still minimally influences clinical QT evaluation due to a lack of confidence in assay sensitivity, robustness, and translatability.⁵ This issue is addressed in the contribution

from Bétat *et al.*, who report the results of the first dog study of six clinical reference agents performed according to current ICH E14/S7B best practices.⁵ They demonstrate the robustness of such a preclinical model and propose this supports its relevance as a translational predictor of human drug-induced QT prolongation.

The rationale and need for clinical QT assessment for biological modalities is the topic of two other contributions in this issue of *CPT* (Figure 1).^{6,7} Due to their selectivity and molecular size, large targeted proteins such as monoclonal antibodies (mAbs) have such a low probability of blocking the human *ether-a-go-go* (hERG) or other cardiac ion channels that no quantitative QT assessment is required. For example, in a recent *CPT* review, Wu *et al.*⁸ showed that only 14% of peptides and proteins submitted to the US Food and Drug Administration (FDA) were associated with some clinical QTc prolongation and none were likely to be associated with cardiac ion channel blockade and torsade de pointes. However, due to the lack of a clear definition of what is meant by “large targeted proteins,” in practice the exemption for extensive clinical QT assessment is only routinely applied to mAbs. Therefore, with the increased focus on novel biological modalities, the question arises if these should be treated like small molecules or mAbs. In their Perspective, Abernathy & Leishman⁶ make the case that in general the risk of QT prolongation for novel biologicals is sufficiently low that minimal clinical evaluation is required. Qu and co-workers⁷ come to a similar conclusion in their extensive review of QT prolongation data from the literature on 12 investigational

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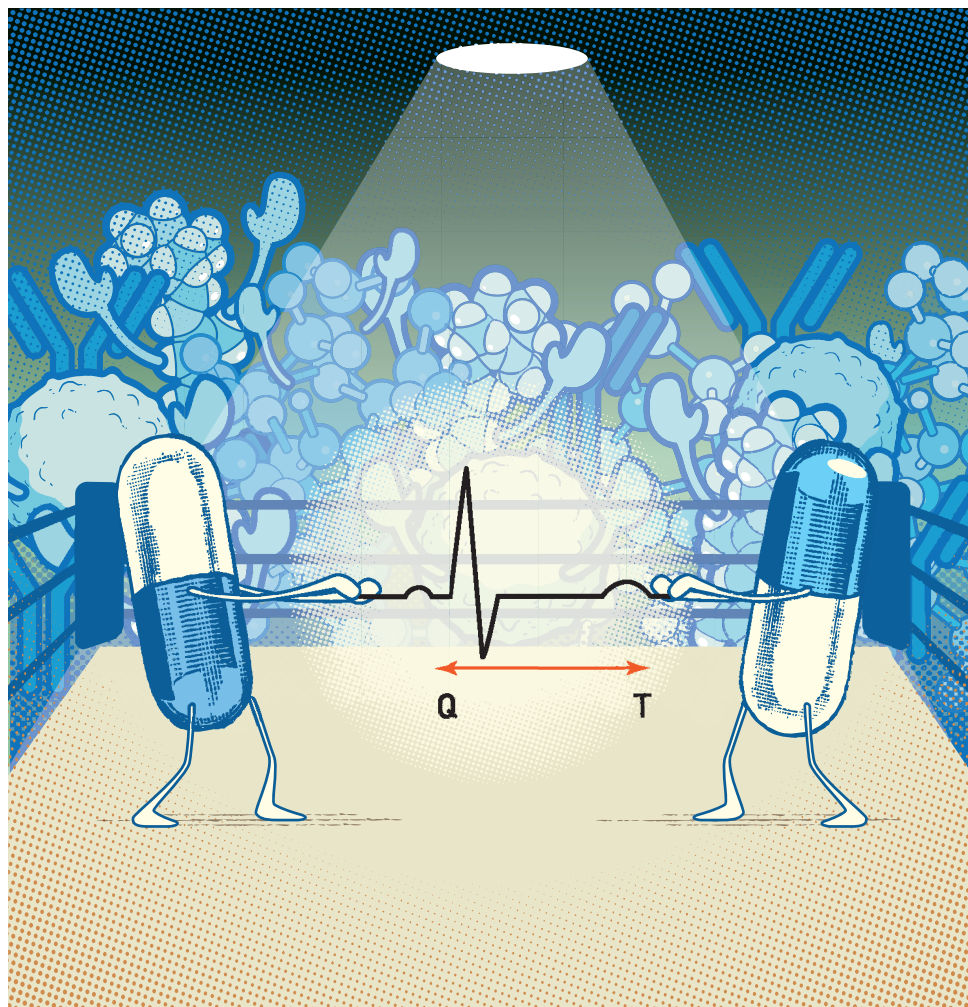


Figure 1 *Clinical Pharmacology & Therapeutics* July 2024 cover image: “Weaning off Thorough QT Studies.”

oligonucleotide therapeutics (ONTs), as well as from the FDA and European Medicines Agency (EMA) Approval Packages on 17 approved/marketed ONTs. ONTs are promising new modalities with intermediate molecular mass (~7 to 15 kDa), which can be used to treat fatal and rare disease by modulating gene expression with a high target specificity. Based on the data from the *in vitro* hERG assay, preclinical *in vivo* and clinical studies, and the FDA Adverse Event Reporting System (FARES) database, the analysis demonstrated no or minimal risk of QT prolongation by ONTs.⁷ Therefore, the authors propose that ONTs have a similar cardiac safety profile as mAbs and should therefore be treated in the same way in terms of QT prolongation testing strategies. Without doubt, drug developers and regulators will reach similar conclusion for most (if not all) novel biological modalities, which raises

the question if QT assessment guidelines could be adapted proactively on an “innocent until proven guilty” basis for such drugs.

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CONFLICT OF INTEREST

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