

Wyeth Pharmaceuticals

Wyeth

Date: December 22, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0377: September 13, 2004 (69 FR 55163-55164)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the ICH draft (step 2) guideline entitled, *ICH E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (dated June 10, 2004).

Wyeth is one of the world's largest research-based pharmaceutical and health care companies. It is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medications, with leading products in women's health care, cardiovascular, central nervous system, anti-inflammatory, infectious disease, hemophilia, and oncology categories, and is also a major manufacturer of preventative vaccines. As such, Wyeth is committed to the development of innovative medicines that will treat unmet medical needs and maximize benefits for patients while minimizing risk.

Wyeth appreciates the opportunity to comment on the above-mentioned ICH draft guideline, and trusts that the Agency will take these comments into consideration when preparing the final guidance document on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. We recognize that evaluation of the potential risks associated with prolongation of the QT interval is extremely important. We are concerned, however, that certain aspects of the draft guidance are overly rigid and could, unless modified, lead to misleading study results that could impede drug development and potentially lead to delays or termination of development of important new treatments. We are also concerned that while the objectives of the draft guidance (section 1.2) state that the document provides "recommendations" to sponsors, it is possible that regulatory agency reviewers will interpret and apply them as verbatim requirements. The draft guidance should be modified to make it clear that alternative approaches may be considered.

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Accordingly, we are making the following recommendations with the intent of offering alternatives that would 1) provide a more flexible and efficient approach for assessing QT/QTc prolongation, 2) provide QT/QTc data from clinical subjects earlier than would otherwise be obtained, 3) improve the proposed methods and criteria for data analysis, thereby reducing the risks of obtaining a false positive result, and 4) offer alternatives in scenarios where conducting the “thorough” QT/QTc study could have unacceptable risks to patients or healthy volunteers.

Recommendations for Alternative Approaches for Evaluation Risk of QT/QTc Prolongation:

Reference is made to Section 2.1, Design Considerations (Lines 153-155), which proposes that in general; *drugs should receive an electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarization (“thorough QT/QTc study”).* The draft guideline also recognizes that *additional factors* (Lines 162-165) could influence the need for such a study including, duration of treatment, metabolic profile, pharmacodynamic duration of action, and previous experience with the same chemical or pharmacological class. For a variety of reasons explained below, we believe that the “thorough” QT/QTc study should not be considered mandatory for all systemically absorbed drugs. We further recommend that an alternative approach involving a comprehensive evaluation of cardiac repolarization in early human studies should be considered an acceptable alternative under appropriate circumstances. This alternative approach would always include an integrated safety evaluation consisting of the following elements:

1. Nonclinical evaluation as described in the ICH S7B guidelines
2. Evaluation of the pharmacologic or chemical class of the drug regarding cardiac prolongation for any known class effects.
3. An evaluation early in clinical development, which would develop initial relationships between dose/concentration of parent drug and metabolites and QT/QTc prolongation following single and repeat dosing. In these early ascending dose studies, serial collections of ECGs would be performed based on the pharmacokinetic profile. A qualified ECG laboratory would be used to evaluate the ECG intervals in a blinded manner. These studies should be placebo-controlled, but would not include a positive control. Typically, a wide range of doses should be tested to evaluate concentrations above the predicted therapeutic concentrations. Estimates are made on single and steady-state pharmacokinetics, including dose linearity. Initial exposure/response relationships for plasma concentration and QT effects would be determined as described in current draft guidelines.

If the results of the integrated safety evaluation (items 1, 2, and 3 above) do not indicate that the drug has potential to prolong cardiac repolarization, we recommend that a “thorough” QT study not be performed. The phase 2-3 clinical development program would include appropriate ECG sampling analyses in the

relevant patient population in accordance with current standards for the claimed indication(s). If cardiac adverse events (that are representative of potential proarrhythmic activity) are reported in subsequent studies, discussions should be held with the Regulatory Agencies, ideally prior to initiation of phase 3 studies, to discuss the need for a thorough study or further ECG evaluation in phase 2/3 studies.

Conversely, for drugs that belong to a pharmacologic or chemical class of drugs known to prolong the QT interval or where the preclinical profile has demonstrated the potential to delay cardiac repolarization and prolong the QT interval in humans, a “thorough” QT/QTc study should be performed. The sponsor should discuss the timing of the study with the regulatory agency.

Circumstances when a “thorough” QT/QTc study may not be appropriate:

There are additional relevant considerations that should be taken into account when deciding on the need for a “thorough” QT/QTc study, as briefly listed in the draft ICH E14 guideline. In any of the following scenarios (and if the nonclinical studies have not demonstrated a risk of QT prolongation for humans and there are no known class effects) alternatives to the “thorough” study such as the comprehensive early evaluation approach described above should be considered:

1. The pharmacokinetic profile has been evaluated across a wide range of doses and has characterized the effects of gender, age, food, and metabolic inhibition on exposure. If the drug’s pharmacokinetics are uncomplicated (i.e. dose linear and accumulates in a predictable manner) across a wide range of doses/concentrations, and the influences of age, gender, food, and metabolic inhibition are relatively small, the sponsor should be able to provide QT/QTc information from human studies such as the comprehensive early evaluation described above as an alternative to a “thorough” study.
2. Early clinical studies show that plasma concentrations exceeding those that would be experienced by the target population under the “worst conditions”, including metabolic inhibition, do not affect cardiac repolarization. Furthermore, the drug has well characterized exposure-response characteristics, including population-based and dose-response models. For this situation, the sponsor should not need to perform a “thorough” study.
3. If the drug is being developed for an indication limited to short term use, or alternatively, will be administered in a hospital where ECG monitoring is easily employed, a “thorough” study should not need to be performed.
4. If administering suprathreshold doses and/or a positive control poses an unacceptable risk to healthy volunteers or subjects, especially in situations where the therapeutic benefits of the test drug have not yet been demonstrated, a “thorough” study should not be performed.

Recommendation to modify the statistical criteria for interpretation of “thorough” QT/QTc study results

Reference is made to Section 2.1.2, The ‘Thorough QT/QTc Study’: Dose Effect and Time Course Relationships (Lines 262-266) ... *a negative ‘thorough QT/QTc study’ is one where the largest time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is around 5 ms or less, with a one-sided 95% confidence interval that excludes an effect >8.0 ms. This upper bound was chosen to reflect the uncertainty related to the variability of repeated measurements.*

While including a concise, clear definition of a negative thorough QT/QTc study is important, the above definition is not practical due to the intrinsic variability in QTc and the multiplicity inherent in utilizing the largest time-matched mean difference as the decision making endpoint. Even with a crossover design, the sample size needed to properly power a study to meet this specification is problematic. For the reasons explained below, Wyeth recommends that the threshold for a negative study be modified by increasing the upper bound of the 95% confidence interval from 8 to greater than 10 ms and that the definition be revised to accommodate other endpoints.

For a crossover design, assuming an underlying placebo-subtracted difference in mean QTc of 5 ms and a within-subject standard deviation of 9 ms, approximately 114 subjects are required to provide 80% power that the upper bound of the one-sided 95% confidence interval is less than 8 ms at a single time point. The required sample size increases to 156 if the sponsor chooses to power the study at the 90% level and even more subjects are needed if the within-subject standard deviation is greater than 9 ms (note: within-subject standard deviations of 9 ms or more are not unusual). In contrast, the sample sizes decrease to 42 and 58 for studies powered at the 80 and 90% levels, respectively, when the upper bound is increased to 10 ms.

Even larger sample sizes are needed for a parallel design. For a parallel design, assuming an underlying placebo-subtracted difference in mean QTc of 5 ms, within-subject standard deviation of 9 ms, and between-subject standard deviation of 10 ms, approximately 250 and 350 subjects per group are required to provide 80% and 90% power, respectively, that the one-sided 95% confidence bound is less than 8 ms at a single time point. Thus, approximately 1400 subjects are needed to power a parallel design study with 4 groups at the 90% level.

The power calculations discussed above apply to demonstrating that the one-sided 95% confidence bound is less than 8 ms at a single time point. The proposed definition in the draft E14 guidance of a negative thorough QT/QTc study is even

more stringent. The draft guidance refers to the confidence bound associated with the largest time-matched mean difference. The confidence bound for the largest time-matched mean difference will be less than 8 ms if, and only if, the confidence bounds are less than 8 ms at all sampling time points. For a fixed sample size, requiring the one-sided confidence bounds to be less than 8 ms at all sampling times will reduce the power (i.e., increase the chances of false negatives). Furthermore, the power decreases as the number of ECG sampling time points increases.

This problem can be illustrated as follows. Suppose that a crossover study is conducted in 42 subjects and that mean QTc is compared between the active treatment and placebo at each of 8 sampling time points. If the underlying placebo-subtracted difference in mean QTc is 3 ms and the within-subject standard deviation is 9 ms, then the one-sided 95% confidence bound at a given time point will be less than 8 ms 80% of the time. Moreover, if the underlying placebo-subtracted difference is 3 ms at each of the 8 time points, then the power decreases to approximately 18% (computed via simulation with 5000 runs) that the one-sided 95% confidence bounds will be less than 8 ms at all time points. Given these assumptions, sponsors may need to conduct even larger trials in order to achieve a reasonable chance that the confidence bound associated with the largest time-matched mean difference is less than 8 ms, or otherwise run the risk of having a false positive outcome. Furthermore, we are not aware of any established statistical methodology for powering a study based on the largest time-matched mean difference. Therefore, sponsors are lacking the scientific tools required to design a study based on the largest time-matched mean difference endpoint.

As illustrated in the examples discussed above, we believe that the sample sizes required to power studies to comply with the definition of a negative study in the draft guidance will impede drug development. We strongly recommend that the threshold for a negative study be modified by increasing the upper bound of the 95% confidence interval from 8 to greater than 10 ms, and believe that a 10 ms (or greater) threshold is more scientifically robust based on the inherent variability in QTc. A threshold of 10 ms or greater will decrease the likelihood that a safe and efficacious drug is incorrectly characterized as having a QT prolongation liability without comprising the scientific rigor of the thorough QT/QTc study.

Also, we recommend that the definition of a negative study be modified to accommodate other endpoints, such as the time-matched mean difference in QTc between the drug and placebo at T_{max} or the mean difference in time-averaged QTc over relevant time points. We do not believe that the largest time-matched mean difference is scientifically optimal for a wide range of drugs, and therefore recommend that the final guidance include alternatives such as those suggested above rather than the single method proposed in the draft guidance.



Emphasis on Analysis of mean/median differences (Central Tendency) for interpretation of “thorough” QT/QTc study results

We agree and support the emphasis on population mean/median values versus individual outlier analysis (categorical endpoint) for determining the outcome of the ‘thorough QT/QTc’ study as either positive or negative (section 3.2 of the draft guidance). Our rationale for supporting the emphasis on an endpoint based on mean QTc is described below.

First, establishing non-inferiority of a drug using a categorical endpoint will require a substantially larger sample size compared to decision-making based on the population mean.

Second, using both mean-based and categorical endpoints will further complicate the decision making process due to the application of multiple statistical analyses. The analysis of multiple endpoints inflates the potential for falsely classifying a drug as positive, complicates the powering of such trials, leads implicitly to increased uncertainty for data interpretation, and increases the likelihood that the development of promising drugs will be unnecessarily delayed or terminated.

Third, as stated in the draft guidance (Section 3.2.2, 2 Lines 489-490)... *There is no consensus concerning the choice of upper limit values for absolute interval signals and change from baseline signals.* Therefore, the definition of a negative study based on a categorical endpoint merits scientific debate and research.

Also, it is important to note that the operating characteristics of a categorical endpoint is closely linked to the selected heart rate correction factor. For instance, it is likely that the percentage of subjects with QTc > 450 ms will be larger for QTc computed using Bazett’s method compared to QTc computed using individual subject data.

In closing, we are submitting the enclosed comments in duplicate. Again, Wyeth appreciates the opportunity to comment on the above-mentioned draft guideline, and trusts that the Agency will take these comments into consideration.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President,
Worldwide Regulatory Affairs