



November 2, 2004

Via Fax and UPS

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

Re: Docket No. 2004D-0377

International Conference on Harmonisation- Draft Guidance on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; 69 FR 55163 (September 13,04)

Dear Sir/Madam:

Aventis Pharmaceuticals is pleased to provide the following comments on the above-referenced draft guidance entitled, "*E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*".

The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guidance provides recommendations to sponsors concerning clinical studies to assess the potential of a new drug to cause cardiac arrhythmias, focusing on the assessment of changes in the QT/QTc interval on the electrocardiogram as a predictor of risk.

On a general basis, Aventis agrees with the content of this revision, as this document reflects all the scientific current knowledge in this field. However we offer the following comments for your consideration.

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GENERAL COMMENTS

We understand that “*at present, whether non-clinical testing can exclude a clinical risk for QT/QTc prolongation is controversial*”. However, we think that in the absence of any non-clinical signal for a potential to prolong QT/QTc interval, and provided that no drugs from the same chemical or pharmacological class have been associated with QT/QTc interval prolongation, the “thorough QT/QTc study” is not needed.

In any case best efforts should be made to reach a consensus across regions and regulatory authorities on this topic. A lack of harmonisation would make drug development on a global basis difficult.

In case a "thorough QT/QTc study" would be needed, it should not be necessary to conduct it early in clinical development. The study could be conducted at a later stage. Indeed, even in case of positive results (i.e. effect on QT/QTc interval), an expanded and meaningful safety evaluation will still be possible during the late-stage development.

SPECIFIC COMMENTS

1.3 Scope

Lines 140-144: “*While this document is concerned primarily with the development of novel agents, the recommendations might also be applicable to approved drugs when a new dose or route of administration is being developed that results in significantly higher C_{max} or AUC values. Additional ECG data might also be considered appropriate if a new indication or patient population were being pursued*”.

A distinction should be made between novel agents of which the safety database is limited, and line extensions of approved drugs.

For line extensions, it should be clearly stated that additional ECG data are not needed provided that the following conditions are met:

- The “thorough QT/QTc study” conducted during the initial development was negative (i.e. no **intrinsic** effect of the molecule on QT/QTc interval), and
- No signal for QT/QTc prolongation were observed during the other clinical studies conducted during the initial development, and
- No signals for QT/QTc prolongation were observed during post-marketing surveillance.

2.1 Design considerations

Lines 162-165: “*Additional factors that could influence the need for such a study include duration of treatment, metabolic profile, pharmacodynamic duration of action, and previous experience with other members of the same chemical or pharmacological class*”.

Inter- or intra-individual pharmacokinetic / pharmacodynamic variability could also influence the need for a “thorough QT/QTc study”. Accordingly the sentence should be modified as follows:

*“Additional factors that could influence the need for such a study include duration of treatment, metabolic profile, pharmacodynamic duration of action, **inter- or intra-individual pharmacokinetic / pharmacodynamic variability**, and previous experience with other members of the same chemical or pharmacological class.”*

2.1.2 The “Thorough QT/QTc study”: Dose-effect and time course relationships

Lines 226-227: “Although data are limited, it is expected that the results of the ‘thorough QT/QTc study’ would not be affected by ethnic factors”.

In order to avoid contradictory interpretations and to make the text as clear as possible we propose to modify the sentence on the non-influence of ethnic factors as follows:
*“Although data are limited, it is ~~expected~~ **considered** that the results of the ‘thorough QT/QTc study’ would not be affected by ethnic factors.”*

On behalf of Aventis Pharmaceuticals, we appreciate the opportunity to comment on the draft guidance entitled, “E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs”, and thank you for your consideration.

Sincerely,



Steve Caffè, MD
Vice President, Head US Regulatory Affairs