A COMPARISON OF THE EMEA AND FDA DRAFT GUIDELINES IN CONGESTIVE HEART FAILURE (CHF) WITH PARTICULAR REFERENCE TO QUALITY OF LIFE OUTCOMES

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OBJECTIVES:

Quality of life is increasingly used as a secondary endpoint to supplement morbidity and mortality data in clinical trials in CHF for which regulatory bodies such as EMEA (Tab. I) and FDA (Tab. II) have drafted guidelines.

The aim of the present study was to compare the draft guidelines and to discuss their implications.

Tab. I EMEA (CPMP) Note for guidance on Clinical Investigation on Medicinal Products for the Treatment of Cardiac Failure. Feb 25, 1999

« 3.4. Quality of life
A broad based assessment of the quality of life scales is recommended in heart failure studies because almost all the components of the life quality may be influenced by an intervention for heart failure.

Various quality of life questionnaires have been used in the past and new ones devised. Unless these have been fully validated, evidence of efficacy derived from quality of life questionnaires must be viewed as supportive only.

It is particularly important to consider whether (a) the scale is linear over the range of measurements, (b) is sensitive to the changes anticipated, (c) it is valid and useful to adjust results using the baseline scores, (d) there is any correlation between the score and the objective responses, (e) the observer and the patient should be blinded and (f) training of both the observer and the patient is necessary.

Rating scales to assess quality of life should also be considered and should have been validated beforehand in the context of the proposed trial and its aims. The effects of therapy on daily activitiy and self-care, sleep, recreational and pleasure activities, in performing social roles, intellectual and cognitive functions, life satisfaction and expectations from the therapy require particular assessment. The Minnesota Living with Heart Failure Questionnaire is one of the many systems used in cardiac failure. Translations of questionnaires used should also have been thoroughly validated beforehand. »

Tab. II Proposed guidelines for the Clinical Evaluation of Drugs for the treatment of Heart Failure, Milton Packer, MD, Chair, Cardiovascular Renal Drugs Advisory Committee. Oct 22, 1998

« Global Assessment

The global assessment provides another way of performing an overall assessment of the patient's clinical status. The global assessment asks either the patient or the investigator (or both) to judge whether the patient's overall status has changed since the start of the study, and if so, to estimate the direction and magnitude of the change. This measure may be more likely than the NYHA functional classification to detect meainingful change in clinical status. However, care must be taken to ensure that the global assessment is not influenced by knowledge of physiologic changes (e.g. changes in blood pressure or heart rate) or of side effects that might reveal the true identity of the study medication. If such confounding is likely, consideration should be given the use of independent assessors who are assigned the task of performing a single, prespecified evaluation and are unaware of others aspects of the patient's clinical status. »

« 5.1.5. Quality of life assessments

Several instruments have been developed to quantify the range of physical, emotional, functional and cognitive impairments that adversely affect every aspect of living. A variety of instruments have been used in clinical trials of patients with heart failure: some were developed to assess quality of life in patients with any chronic illness, whereas others were specifically designed to evaluate patients with heart failure. Nevertheless, experience with these instruments is limited. All instruments utilize a grading system that weights specific responses before they are combined into a global score, but the weightings used in a

« 2.2.2. Secondary endpoints
2.2.2.1. Quality of life
Prominent components of quality of life measures which require addressing are physical function, social end emotional function, intellectual function, leisure activities, sexual adjustment, perceived health status, life satisfaction and interpersonal relationships. »

specific instrument may not reflect the relative importance of theses symptoms to the patient. Furthermore sponsors should prespecify which domains are likely to be influenced by a new drug and should avoid evaluating a wide array of aspects of quality of life in the hope that one or two domains may be favorably affected by treatment. »

METHODS

The current guidelines from EMEA and the FDA were reviewed and analyzed with regard to methodological and design issues

A comparison of some quality of life issues in the EMEA and FDA draft guidelines is shown in Tab. III

Tab. III Draft guidance documents on quality of life issues in clinical trials in CHF

	FDA (Oct 22, 1998)	*EMEA (Feb 25, 1999)*
QL domains	Measure a few relevant QL domains	Measure a broad range of QL domains
QL questionnaire	----	The Living with Heart Failure Quest.
Global measure	To be used	----
Psychometric properties	Not mentioned	Validation required
Duration of follow up	Not mentioned	Not mentioned
Patients lost to follow up	Not mentioned	Not mentioned
Other issues	Standardized administration ----	Standardized administration Training
Translations	----	Validation required

RESULTS

The EMEA guidelines require measurement of 12 quality of life domains, whereas the FDA proposes the avoidance of evaluating a wide array of quality of life aspects. No guidance is given with regard to the use of generic or specific questionnaires or to requirements for psychometric properties. Design issues such as

Implications:

The observed differences in recommended quality of life methodology create difficulties in conducting international multicenter studies that accomodate both the European and US agency requirements. Both guidance documents fall to address pertinent questions such as duration of follow-up, patients lost to follow-up, and patient

duration of follow-up or problems related to patient selection, bias due to mortality and loss of follow-up are not addressed.

The EMEA requirements will result in exactly the problems that the FDA want to avoid, i.e. inclusion of all aspects of quality of life in the hope that one or two domains may be favorably affected by treatment. The relevance of many of the quality of life domains to elderly and incapacitated CHF patients (e.g. occupational activities, sexual satisfaction, interpesonal relationships) must be questioned. In the FDA document no reference is made to standardization or documentation of translations.

selection biaises, and how to account for mortality. Without guidance on design issues, future studies may vary considerably in scope and quality, which makes impossible to compare the results.

CONCLUSION:

The draft guidelines incorporating qulaity of life outcomes are welcomed. However, further and more detailed guidance is required as well as greater degree of harmonisation between the EMEA and the FDA.