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REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTH-RELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS

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1. INTRODUCTION (background)

This is not a Guidance on methodological requirements for development, validation and use of Patient-Reported Outcome (PRO) measures in clinical trials. The scope of this reflection paper is to discuss the place that a health-related quality of life (HRQL), a specific type of PRO, may have in drug evaluation process and to give some broad recommendations on its use in the context of already existing guidance documents.

Any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) is called patient-reported outcome (PRO).

The term PRO is proposed as an umbrella term to cover both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc.

In the context of drug approval, HRQL is considered to represent a specific type/subset of PROs, distinguished by its multi-dimensionality. Indeed, HRQL is a broad concept which can be defined as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being. The definition of HRQL has as a common basis the definition of health given by the WHO in 1948: *"Health, is a state of complete physical, mental, and social well-being and not merely the absence of disease"*…

As stated above, the notion of multidimensionality is a key component of definition of HRQL. A single domain, e.g., physical functioning or fatigue, is not considered as a HRQL (i.e. it cannot be the basis for a claim for a global HRQL improvement), even though it is a patient-reported.

In addition, HRQL should be clearly differentiated from the core symptoms of a disease (e.g. pain, migraine, pyrosis…) assessed by the patient himself which are well-accepted primary and secondary efficacy endpoints in registration trials.

2. HRQL IN DRUG EVALUATION PROCESS

The basis for the approval of a new medicinal product is its efficacy and safety in the given condition. Therefore, in the drug evaluation process, the first step for the regulators is usually to assess efficacy and safety of a given drug by using the established efficacy endpoints. As stated above, these endpoints usually concern the core symptoms and signs of the condition, and, in general, will support the indication claim.

In addition, a Company may decide to study the effect of the medicinal product on HRQL.

HRQL assessment is optional. In some cases, it might provide insight in the interpretation of the observed effect on the primary endpoint in terms of consequences for the daily life and social functioning. In any case, HRQL goes beyond the efficacy and safety assessments, which are the basis for approval.

A claim about improvement in HRQL needs to be supported by data collected by instruments validated for use in the corresponding condition.

In theory, both generic and disease specific questionnaires may be used for a given condition. In practice, it is very important to choose the questionnaire which contains/is adapted to explore the domains relevant for the disease and its treatment(s).

Indeed, "HRQL improvement" as a claim implies that the most important and clinically relevant health-related domains of functioning that impact patient's quality of life are known and measured.

In order to approve a global claim that a product "improves HRQL", it would be necessary to demonstrate robust improvements in all or most of these domains.

There are situations where treatment improves specific domains of HRQL (such as physical or social functioning), which are considered important to patients. A company may seek specific claim based on the subset (one or two) of domains of HRQL, if the analysis plan pre-specifies which domains will be targeted as endpoints in the study. In addition, the use of specific HRQL domains as study

endpoints pre-supposes that the HRQL instrument was adequately developed and fully validated prior to measuring the subset of domains chosen. A Company needs to document the change on the pre-defined HRQL domains of interest, and to provide information about the amount of change that is required to be considered as clinically meaningful. In case of positive/relevant results, a specific claim reflecting domain(s) with improvement might be mentioned in the SmPC. It is recommended that the claim always specify the changes observed in **all HRQL domains** for a given condition, including the domains with the improvement, the domains with no change and the domains with the worsening, if any. A full disclosure of complete results should be provided.

The claim in the SmPC with the respect to HRQL (i.e. in section 5.1) will always be considered depending on the strength of the evidence and the relevance (pertinence and importance) of the finding. The strength of the evidence should be based on the rationale for HRQL assessment in the context of the disease/medicinal product, the justification of the choice of the HRQL questionnaire(s), the objectives of HRQL assessment and the hypotheses of HRQL changes, the evidence of validation (and of cultural adaptation/translation if applicable) of the HRQL questionnaire(s), the adequacy of the statistical analysis plan, and the relevance of observed changes.

3. STUDY DESIGN FOR HRQL ASSESSMENT

As a general rule, the validation of HRQL instrument should preferably have been completed before its use in therapeutic confirmatory trials. In principle, the same study should not be used to validate the HRQL instrument and to test for the HRQL change.

If the HRQL instrument planned to be used is not validated (or is insufficiently validated), it is recommended to test it already in the therapeutic exploratory trials to be able to retest it again in therapeutic confirmatory trials. Indeed, if HRQL is planned to be assessed, it should be implemented in drug development plan as early as possible.

Regarding the timing of HRQL assessment related to the marketing authorisation, broadly two situations may be met:

1/ The medicinal product has no marketing authorisation. A Company may choose to study effect on HRQL simultaneously to the efficacy/safety of the medicinal product in pivotal (phase III) trials. In this case a study may be powered to test both for the efficacy of the test drug versus placebo and/or active comparator as appropriate, and for the HRQL change. In this case, efficacy endpoint and HRQL are co-primary endpoints. Alternatively, the hierarchical testing of endpoints may be applied (see Statistical analysis and hypothesis).

2/ Test drug has obtained marketing authorisation, or: HRQL is decided to be studied once efficacy and safety of the test drug have already been shown in the target population. In this situation, it may be difficult to perform a study versus placebo if the product has already shown efficacy and obtained MA. HRQL change due to the test drug may be compared to HRQL change due to an active comparator.

A study incorporating both efficacy and HRQL change (e.g. non-inferiority for efficacy and superiority for HRQL) may be an appropriate design.

4. STATISTICAL ANALYSIS AND HYPOTHESIS

If it is intended to make a claim for a product based on HRQL data, such a claim should be supported by an analysis of trial data, driven by a priori formulated hypothesis; the latter should be detailed in the statistical analysis plan. Such hypothesis should be based on some prior knowledge such as data from phase II trials and literature review.

In general, the methodology for assessing the effect on HRQL is similar to the methodology used in any efficacy trial, except for issues related to the nature of the instruments, which are generally composed of multi-items, and multi-domains. Briefly, it is recommended that HRQL instrument be previously validated for the condition studied (e.g. validity, reliability, responsiveness and interpretability for the specific condition/setting) and that study design be adapted to address for multiplicity issues (see CHMP Points to Consider on Multiplicity issues in clinical trials CPMP/EWP/908/99), missing data (see Points to Consider on Missing data CPMP/EWP/1776/99),

timing of assessment, sample size/power and expected difference, randomisation scheme, blinding, study duration, analysis plan, interpretation, introduction of bias and assay sensitivity.

The recommended method of control for multiplicity of endpoints in this setting is a hierarchical testing of endpoints. The most important (efficacy) endpoint is tested first; if it is significant, then the second endpoint (HRQL) can be tested. If the first endpoint is not significant, then no further testing is undertaken. The number of patients, necessary to support the change in the primary endpoint, is frequently sufficient to test for the HRQL change. In some situations, the number of patients is far too large and the trial is then overpowered, and allows to demonstrate significant but very small differences in HRQL scores, which are not relevant. Therefore, every effort should be made to ensure that the sample size calculated for the primary endpoint is adequate for demonstrating hypotheses made a priori on the HRQL assessment. The assessment of HRQL in a subset of the sample should be justified.

By its nature, HRQL assessment (multi-items, multi-domains, repeated over time) increases the issue of multiplicity. There are other possible approaches to this issue. One as stated earlier is to pre-specify a subset of HRQL domains which will be the basis for a specific claim. Other methods may include correction of p-values, hierarchical testing (if the domain considered as the most important is significant, the second domain is tested) or global test procedures. To report only a global score across domains, although it may reduce the number of tests, is not adequate as it will reduce the information on HRQL multidimensionality and may mask or overestimate HRQL treatment differences in important domains. The method for handling multiplicity should be stated a priori in the statistical analysis plan.

The relevance of HRQL changes should always be justified by the sponsor. At best, this relevance should have been defined a priori in the protocol, as it constitutes the basis for generating hypotheses.

The minimal important difference (MID) may be used when powering the studies. It should be kept in mind however that the determination of MID should be based upon a combination of statistical reasoning and clinical judgment and none of them on its own is sufficient.

ADDITIONAL REMARKS

In severe, life-threatening diseases, such as cancer, HRQL may provide an important information. In all cases, there must be confidence that the observed HRQL benefit is achieved without any reduction in efficacy (e.g. through reduced toxicity, attained by reducing the dose…). The impossibility of blinding in some studies may create bias. Therefore, open-label studies are not recommended.

In chronic non life threatening conditions requiring long term treatments, when the two drugs have similar efficacy and safety, the information on HRQL might be important for the choice of one medicinal product over the other in the current clinical practice.

HRQL assessment may also be of interest chronic diseases with acute exacerbations (e.g. asthma, rheumatoid arthritis, migraine). Both in relapsing and remitting symptom-driven conditions and in chronic stable conditions, a long-term trials (3–6 months or more) are recommended. Very short-term trials (15 days, 1 month) are discouraged as they assess more the improvement of the daily living due to the effective treatment in a given condition rather than the HRQL in its multidimensionality.