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EMEA and the evaluation of health-related quality of life data in the drug regulatory process

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Objectives: This study reviewed the European guidelines of the Committee for Proprietary Medicinal Products (CPMP) on how health-related quality of life (HRQOL) research should be conducted in clinical trials. Published product-level information was also reviewed to investigate the actual role of HRQOL data in the European regulatory process.
Methods: All disease-specific notes for guidance and concept papers on clinical investigations, development and evaluation of human medicinal products, as well as the European Public Assessment Reports (EPAR) of all approved drugs published on the European Agency for the Evaluation of Medicinal Products (EMEA) Web site were evaluated for their HRQOL recommendations.
Results: Only twenty of the fifty CPMP guidance notes for clinical investigation of pharmaceutical products in specific disease areas included a reference to HRQOL. Most of the recommendations were generic and vague, and the terminology used was inconsistent across documents. The EPAR provided nonspecific information about HRQOL and contradictory conclusions on the effect of a drug on HRQOL sometimes occurred in different documents. The criteria used by the CPMP to assess the HRQOL data could not be identified due to an ad hoc approach to the inclusion of data in the EPAR.
Conclusions: A more systematic approach is needed on the way health outcomes data are considered, reviewed, and interpreted by the regulatory authorities. For this to be achieved, CPMP should develop general guidelines on the importance of HRQOL and how research should be conducted if data are to be included in the registration process.

Keywords: Clinical trials, Drug regulation, Health status, Health-related quality of life instruments, Quality of life

Outcomes research is increasingly conducted alongside clinical trials (38). The importance of health-related quality of life (HRQOL) measures is well recognized by the scientific community, the pharmaceutical industry, regulators, and payers (32;38;43). HRQOL measures provide an understanding of the impact of disease and its treatment on the patient's daily life and functioning, and they represent a patient-perceived indicator of the benefit of medical interventions (46). Therefore, the number of clinical trials incorporating the measurement of HRQOL has increased substantially in recent years (35). In oncology research, for example, HRQOL has been identified as the second most frequently used outcome after

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survival (32). Additionally, HRQOL may provide relevant information to third-party payers and doctors making decisions regarding the use of a therapy and the impact that the medical treatment has on patients' health status and well-being (44;46).

Currently, marketing authorization agencies do not require HRQOL evidence for the approval of new drugs. Given the increasing importance associated with this information being included on drug labels, the industry is investing more toward providing HRQOL information (4). European pricing and reimbursement authorities, on the other hand, formally require, or will consider, HRQOL data to decide whether a medicine actually provides "value for money." Following the example of Australia and Canada, several European countries, such as the United Kingdom, Sweden, and the Netherlands, have started, or are about to start, using health outcomes and economic criteria in decision making on the public reimbursement of pharmaceuticals. To facilitate the process, reimbursement authorities, such as the National Institute of Clinical Excellence in the United Kingdom, have published guidelines for the preparation of the submissions made by the pharmaceutical industry (39). Most of these guidelines distinguish and separately discuss HRQOL assessment and the assessment of utilities among the possible measures of clinical effectiveness of treatments.

However, there are many methodological issues and controversies surrounding the investigation of health outcomes that provide real challenges for the conduct of research, analysis, review, interpretation, and the use of results. Issues specific to HRQOL evaluations include the definition of clinically meaningful changes in HRQOL scores, the handling of missing and censored data, and the integration of the length of life within HRQOL outcomes (38). Other methodological concerns include (i) the type of instruments to be used (generic versus disease specific) (2;34), as the selection of HRQOL measures for clinical trials requires attention to the appropriateness, psychometric characteristics, and practicality of the available instruments (42); (ii) whether the overall results from one instrument should be presented or whether the presentation of results from the individual domains of the instrument is valid; and (iii) whether it is the patient, the doctor, or the general population who should complete the questionnaires (47). Finally, the interpretation of HRQOL data may be different, depending on the person who uses the information; for example, a clinician, a health policy-maker, a regulatory authority, or a pharmaceutical company (48).

As a result of increased interest in HRQOL, there has been an effort to provide guidance to researchers on the conduct of HRQOL research. Since 1997, two initiatives that recently merged and were renamed ERIQA (European Regulatory Issues on Quality Assessment), were launched in Europe. Their aims were to bring together HRQOL researchers, the pharmaceutical industry, and representatives of regulatory agencies to discuss the role and value of HRQOL within the specific context of drug registration and reimbursement, and to agree on recommendations for HRQOL assessment in clinical research and the integration of this information into the regulatory process. A checklist for designing, conducting, and reporting HRQOL studies in clinical trials was published by ERIQA (4). At the same time, similar initiatives were launched in the United States by the Food and Drug Administration in collaboration with the Health Outcomes Committee of the Pharmaceutical Research and Manufacturers Association (PhRMA-HOWG), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Quality of Life Research (ISOQOL) (30;41). PhRMA-HOWG, ISPOR, ISOQOL, and ERIQA have now created the Patient Reported Outcomes Harmonization Group with the mission to "harmonize patient reported outcomes issues used in drug development and evaluation."

The aim of this present study is to review the guidelines of the Committee for Proprietary Medicinal Products (CPMP) (40), which is part of the European Agency for the Evaluation of Medicinal Products (EMEA) on how HRQOL research should be conducted in clinical trials. Additionally, all existing published product-level information will be reviewed to investigate the actual role of HRQOL data within the regulatory process. Although this area is widely investigated for the U.S. environment, an understanding of the use of HRQOL data by the European regulatory authorities has not been extensively researched.

METHODS

In this study, all disease-specific notes for guidance documents and concept papers on the clinical investigation, development, and evaluation of human medicinal products, both adopted and drafted, as well as International Conference on Harmonisation (ICH) guidelines, posted on the EMEA Web site on 13 March 2003, were identified. These documents were then reviewed to identify references to HRQOL recommendations. The keywords used in the search were health status, well-being, quality of life, HRQOL, QOL, HQL, questionnaire, and scale. The content of the documents that contained HRQOL recommendations was then evaluated by considering explicit statements on the use of HRQOL measures.

To investigate how the EMEA considers HRQOL data submitted for a pharmaceutical product in relation to adopted recommendations, the European Public Assessment Reports (EPAR) of all approved drugs that were publicly available on the EMEA Web site on 7 March 2003 were reviewed to identify those that included HRQOL data. The same keywords mentioned above were used. The EPAR that contained HRQOL data were investigated further.

The EPAR reflect the scientific conclusions reached by the CPMP at the end of the centralized evaluation process and summarize the basis for the CPMP opinion in favor of granting a marketing authorization for a specific

medicinal product. The EMEA makes these summaries available to the public by publishing them on the EMEA Web site [http://www.emea.eu.int/index/indexh1.htm] after deletion of commercially confidential information. The documents that are included under the EPAR heading are the abstract, authorized presentations, the product information leaflet, the summary of product characteristics (SPC), labeling, scientific discussion, steps taken after assessment, steps taken after authorization.

The EPAR documents that were relevant to the aims of this study and, therefore, were reviewed are as follows:

(i) The scientific discussion, which is the most detailed description of the scientific evidence from the clinical investigation of each new product and also contains a commentary by the individuals involved in the evaluation process.

(ii) The SPC, which is based on the evidence provided in the scientific discussion and provides a summary of the information about the new pharmacological agent for physicians. After approval, the SPC is the basis for the content of the description of the product to national compendiums.

(iii) The package leaflet, which contains information for the patient who receives the medication.

(iv) The abstract document, which is a summary of the key findings related to the evaluation process of the new product and the decision made by the CPMP on granting authorization. The audience of the abstract is the general public, but it is only disseminated through publication on the EMEA's Web site.

RESULTS

No formal regulatory guidelines currently exist in Europe for HRQOL evaluation in relation to the marketing authorization of pharmaceutical products. However, recommendations have been published by CPMP on the use of HRQOL in clinical investigations within specific disease areas. These guidelines intend to serve as a starting point for discussions on the inclusion of patient reported outcomes data in drug labeling for licensing and promotional purposes (1). Although European standards on this matter still need to be developed, as will be discussed in this study, approval for labeling claims regarding HRQOL has been given for some drugs by national European agencies. These guidelines were identified and are discussed in more detail in this section. Additionally, the EPAR that contained specific information or refer to HRQOL were also identified and are presented.

HRQOL Evaluation in Drug Regulatory Processes in Europe

Of a total of fifty notes for guidance, notes to consider for clinical investigation and ICH guidelines that were identified on the EMEA Web site, twenty guidelines and one ICH document included reference to, or recommendations on, HRQOL. Apolone et al. (1) previously identified thirteen CPMP guidelines and one ICH document that contained statements about HRQOL. However, since 1999, when their research was conducted, seven additional notes for guidance that referred to HRQOL have been published. The disease-specific guidelines are summarized in Table 1.

All of the guidelines that are summarized in Table 1, apart from the guidelines for the evaluation of antiarrhythmics and drugs for HIV infection, considered HRQOL measures as an efficacy outcome in clinical trials. The two guidelines that are the exception referred to the potential use of HRQOL measures for the assessment of the risk-benefit ratio of the new agent. In eleven of these notes for guidance, HRQOL was recommended as a secondary end point; in three of the cases, HRQOL was recommended both as a primary and secondary objective; and finally, in six of the cases, a specification on the type of end point that HRQOL should constitute within clinical trials was not given. The importance of selecting the appropriate end points in clinical trials will be elaborated upon in the discussion section.

The disease-specific guidelines that recommended HRQOL as an efficacy outcome have been separated into three broad categories:

(i) The notes for guidance that do not recommend the use of HRQOL scales among the primary or secondary end points in clinical trials. These include those for Alzheimer's disease, migraine, and Parkinson's disease.

(ii) The guidelines that refer to the importance of HRQOL as an outcome measure for the particular disease but do not provide any guidance on how HRQOL should be assessed. These guidelines include those for medicinal products for weight control and irritable bowel syndrome.

(iii) The notes for guidance that recommend HRQOL among the treatment objectives. Within this category, there are some guidelines that do not give specific recommendations on the HRQOL instrument that should be used. These include the guidelines for amyotrophic lateral sclerosis, multiple sclerosis, urinary incontinence, cancer, peripheral arterial occlusive disease, stable angina pectoris, acute stroke, and asthma. However, there are also guidelines that propose specific instruments that should be used. Guidelines for osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease, cardiac failure, and rheumatoid arthritis belong to this group.

In addition to these twenty disease-specific notes for guidance, one general guidance document that referred to HRQOL was also identified. The ICH 'Note for guidance on statistical principles for clinical trials' was adopted in February 1998 by the EMEA. It refers to HRQOL by stating that ". . . Measurements relating to quality of life and health economics are further potential primary variables. . .".

Use of HRQOL Data in EPAR

Between January 1995 and March 2003, the EMEA and the European Commission gave Community Marketing authorization to 218 medicinal products for human use. The EPAR

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Table 1. Disease-Specific Notes for Guidance for Clinical Investigation That Refer to Health-Related Quality of Life (HRQOL) and Are Published by the Committee for Proprietary Medicinal Products (CPMP)

Disease	Type of guidance	Date of approval of guidance by CPMP	Type of outcomes	End points	Recommendation on the assessment of HRQOL
Arrhythmia	Note for guidance (7)	November 1995	Safety	—	"The use of antiarrhythmic drugs may be limited by major and minor drug-related side effects impacting on drug tolerance or HRQOL"
Stable angina pectoris	Note for guidance on clinical investigation of medicinal products (8)	November 1996	Efficacy	S	"HRQOL assessment may be considered, provided the questionnaire is validated in the context of the proposed target group"
Alzheimer's disease	Note for guidance on medicinal products (9)	September 1997	Efficacy	—	"Although HRQOL is an important dimension of the consequences of diseases, the lack of validation of its assessment in AD [Alzheimer's disease] does not allow specific recommendations to be made as yet. When adequate instruments to assess this dimension in patients and their care givers become available, HRQOL assessment may be justified in AD trials"
Weight control	Note for guidance on clinical investigation of medicinal products (10)	December 1997	Efficacy	S	Improvement in risk factors, such as psychosocial aspects (measured as HRQOL) can be considered. Choice of secondary efficacy variables should be justified by the applicant and could include variables such as HRQOL
Osteoarthritis	Points to consider on clinical investigation of medicinal products (13)	July 1998	Efficacy	P and S	Functional disability was recommended as one of the primary objectives: 'A disease specific and joint specific instrument such as the Western Ontario Mac Master University osteoarthritis index (WOMAC) or the Lequesne index is recommended to assess disability arising from osteoarthritis of the hip or the knee'. The assessment of HRQOL was recommended as a secondary objective of the clinical trials. No further recommendations were given
Parkinson's disease	Note for guidance on clinical investigation of medicinal products (11)	December 1998	Efficacy	—	"The use of indirect efficacy variables as primary efficacy variable in pivotal studies, such as an improvement in. . . HRQOL. . . is not recommended unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proven"
Chronic obstructive pulmonary disease	Points to consider on clinical investigation of medicinal products (15)	May 1999	Efficacy	P and S	"The primary symptomatic benefit end point should be justified by referencing published data, which support its validity; one example is the St. George's Respiratory Questionnaire (SGRQ)" HRQOL assessment, as a secondary end point, should be justified by referencing published data which support its validity

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Table 1. Continued

Disease	Type of guidance	Date of approval of guidance by CPMP	Type of outcomes	End points	Recommendation on the assessment of HRQOL
Cardiac failure	Note for guidance on clinical investigation of medicinal products (14)	December 1999	Efficacy	S	"A broadly based assessment of the HRQOL 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. . . Unless the HRQOL questionnaires have been fully validated, evidence of efficacy derived from them must be reviewed 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 HRQOL should be considered and should have been validated beforehand in the context of the proposed trial and its aim. 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"
Amyotrophic lateral sclerosis	Points to consider on clinical investigation of medicinal products (16)	October 2000	Efficacy	S	"A well-known general HRQOL scale, validated for this specific category of patients"
Crohn's disease	Points to consider on clinical investigation of medicinal products (17)	June 2001	Efficacy	S	"Secondary end points may include: validated HRQOL measurement, e.g. IBDQ"
Multiple sclerosis	Note for guidance on clinical investigation of medicinal products (19)	July 2001	Efficacy	S	"Few data are available on the validation of specific instruments for HRQOL in patients suffering multiple sclerosis. If a claim with respect to HRQOL in multiple sclerosis is considered, reliable and validated scales should be used"
Acute stroke	Points to consider on clinical investigation of medicinal products (18)	September 2001	Efficacy	S	"At present HRQOL-scales are not among the primarily focussed end points in stroke. If these scales are used, they should be validated for stroke. In case HRQOL-scales are used as additional evidence, special attention should be paid to possible confounding factors such as post-stroke depression or change in the environment that might interfere with the specific treatment effects"

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Table 1. Continued

Disease	Type of guidance	Date of approval of guidance by CPMP	Type of outcomes	End points	Recommendation on the assessment of HRQOL
Peripheral arterial occlusive disease	Note for guidance on clinical investigation of medicinal products (20)	April 2002	Efficacy	S	"In trials with adequate sample size, an assessment of HRQOL may be performed by using properly validated general and disease specific questionnaires"
Rheumatoid arthritis	Points to consider on clinical investigation of medicinal products (draft) (25)	July 2002	Efficacy	P and S	"Physical function (assessed by the patient, e.g. by HAQ, AIMS (function and HRQOL) can be a primary objective in the clinical trials. HRQOL is also established as useful additional secondary end point and can be measured either by RA-specific questionnaires, e.g. AIMS, or generic tests"
Cancer	Note for guidance on clinical investigation of medicinal products (21)	September 2002	Efficacy	S	"HRQOL studies may be used to support symptom control data provided that established HRQOL questionnaires (including for example level of hospitalization etc.) are used, which are relevant to the study population being treated. The choice of the scales/instruments should be justified and the validity of the scale/instrument for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies"
Migraine	Note for guidance on clinical investigation of medicinal products (draft) (24)	September 2002	—	—	"HRQOL measures are not established in migraine, and they should not be used until fully clinically validated"
Asthma	Note for guidance on clinical investigation of medicinal products (22)	November 2002	Efficacy	S	"A number of secondary end points, such as HRQOL, may provide useful information. They measure different aspects of the condition and they should be justified by referencing published data that support their validity"
Urinary incontinence	Note for guidance on clinical investigation of medicinal products (23)	December 2002	Efficacy	—	"Disease specific and generic instruments for measuring HRQOL can be used in trials of products for UI [urinary incontinence]. The instruments used should be properly validated in the target population. A clinically relevant change in prespecified domains (dimensions) of HRQOL should be defined and justified in the protocol of the study. HRQOL data should be considered an extension of an evaluation of efficacy, which can provide meaningful information to the prescriber and the patient. . . If clinically relevant changes have been found, HRQOL data may be included for example in SPC section 5.1 Pharmacodynamics"

Table 1. Continued

Disease	Type of guidance	Date of approval of guidance by CPMP	Type of outcomes	End points	Recommendation on the assessment of HRQOL
HIV infection	Note for guidance on clinical investigation of medicinal products (26)	March 2003	Safety	—	"The use of justified HRQOL instruments in long-term, controlled and preferably double-blind studies may provide additional information of principal importance in the assessment of benefit risk, given the impact of poor tolerability on compliance and psychosocial well-being"
Irritable bowel syndrome	Points to consider on clinical investigation of medicinal products (27)	March 2003	Efficacy	S	"Choice of secondary efficacy end points should be justified by the applicant and should include GI [gastrointestinal] symptoms. . .and HRQOL parameters. HRQOL must, however, be considered as the most important secondary end point"

S, secondary; P, primary; SPC, summary of product characteristics.

documentation of 10 of these products was not available on the EMEA Web site; therefore, 208 medicines were included in our research. From these drugs, only fifty-two contained at least one of our search terms in their EPAR documentation. However, five of these were excluded from the analysis as they were not relevant to our research questions. Three of these five medicines were excluded because the EPAR documents only mentioned that HRQOL is important for the particular disease or that HRQOL should be further evaluated. Two of the five excluded drugs measured physician satisfaction rather than patient satisfaction. Altogether, forty-seven drugs with HRQOL data in their EPAR were identified and included in the review. In Table 2, more detailed data on these EPAR are presented; however, the drugs have been grouped by their generic name and indication when the same substance has been indicated for different diseases; therefore, the results from the evaluation of thirty-three substances are illustrated.

In summary, 24 percent of the thirty-three substances that contained HRQOL data in their EPAR were indicated for the treatment of cancer (eight substances); 9 percent were indicated for the treatment of erectile dysfunction (three substances), hepatitis, HIV, and diabetes. The remaining 42 percent (fourteen drugs) covered Fabry disease, Kaposi's sarcoma, lymphomatous meningitis, rhinitis, AIDS-related Kaposi's sarcoma, facial hirsutism, renal failure, epilepsy, growth failure, obesity, atrial fibrillation, Gaucher disease, acromegaly, and schizophrenia.

The scientific discussion documents for all the thirty-three substances included information or referred to the effect that the drug under examination has on the HRQOL of patients. Nine SPCs also included reference to HRQOL, as well as three abstracts. Finally, none of the substances had a reference to HRQOL in their package leaflet (Table 2).

In nineteen of the thirty-three cases, the treatment under review had some positive effect on the HRQOL of the patients; in eleven of the cases the drug did not have a beneficial effect over the comparator in terms of improving HRQOL, while for three substances the results from clinical trials on their effect on HRQOL were not mentioned in the EPAR. However, for only eight of the thirty-three substances was there a clarification on whether the HRQOL changes observed with treatment were statistically significant or clinically meaningful (Table 2). In twenty of the thirty-three cases the name of at least one of the HRQOL instruments that were used in the clinical trials was mentioned (Table 2).

DISCUSSION

Measurement of HRQOL has been extensively used as a standard of therapeutic efficacy (16). Usually it represents a patient-centered approach to assessing functional status and well-being that integrates the impact of both medical treatment and disease. As the evaluation of HRQOL end points in drug development continues to grow, interest in using these outcomes for labeling and promotional purposes increases (3;4;42). However, inclusion of HRQOL information in drug labels and promotion is still limited, although it could be valuable for prescribers and payers.

The challenge facing the industry, regulatory agencies, and the scientific community is to develop robust HRQOL instruments and to reach consensus on the criteria for evaluating the scientific validity and clinical meaningfulness of data that will ultimately be used for labeling, reimbursement decisions, and promotion (36). In Europe, after the drug has been authorized, the inclusion of HRQOL claims in the label could be crucial for pricing and reimbursement negotiations and for differentiating a drug from other competing

Table 2. Drugs with Health-Related Quality of Life (HRQOL) Data in their European Public Assessment Reports (EPAR)

Generic name	Indication	Name of HRQOL instrument used	"Difference" in HRQOL with treatment	HRQOL data included in scientific discussion	HRQOL data included in SPC	HRQOL data included in package leaflet	HRQOL data included in abstract
Agalsidase beta	Fabry disease	SF-36	"Slight improvement, not statistically significant"	Yes	Yes	No	No
Alitretinoin	Kaposi's sarcoma	N/A	"Improvement for completers of the clinical trials"[a]	Yes	No	No	No
Apomorphine	Erectile dysfunction	N/A, International Index of Erectile Dysfunction (IIEF)	"N/A, Improvement in most of the IIEF domains"[a]	Yes	No	No	No
Capecitabine	Cancer	EORTC-QLQ-C30, QLQ-C30-BR23	"Similar values for both arms in the trial"	Yes	No	No	No
Cytarabine	Lymphomatous meningitis	FACT-CNS, Mini Mental State	"No statistically significant difference"	Yes	Yes	No	Yes
Desloratadine	Rhinitis	SF-36, Rhinoconjunctivitis HRQOL Questionnaire (RQLQ)	Treatment was "proved to be effective in alleviating the burden of disease"[a]	Yes	Yes	No	No
Docetaxel	Cancer	QLQ-C30	"HRQOL scores were comparable and stable in both arms"	Yes	Yes	No	No
Dofetilide	Atrial fibrillation	N/A	"An improvement in HRQOL was shown"[a]	Yes	Yes	No	No
Doxorubicin	Breast cancer	EORTC-QLQ-C30-BR23	"No change was observed"	Yes	No	No	No
Doxorubicin	AIDS-related Kaposi's sarcoma	AIDS-related Kaposi's sarcoma HRQOL questionnaire: N/A MOS-HIV Health Survey questionnaire	Statistically significant changes in some of the domains of the questionnaires	Yes	No	No	Yes
Efavirenz	HIV	MOS-HIV Health Survey questionnaire	N/A	Yes	No	No	No
Eflornithine	Facial hirsutism in women	Subjects Self-Assessment Questionnaire (SSAQ)	Statistically and clinically important changes	Yes	Yes	No	No
Epoetin beta	Renal failure	N/A	"Significant impact on the HRQOL in the patients' on treatment"[a]	Yes	No	No	No
Insulin glargine	Diabetes	Diabetes Treatment Satisfaction Questionnaire, Well-Being Questionnaire (WBQ)	N/A	Yes	No	No	No
Insulin lispro	Diabetes	N/A	No improvement	Yes	No	No	No
Interferon alfa-2b	Hepatitis B and C, Cancer	N/A	"Improved HRQOL scores for the responders"[a]	Yes	No	No	No
Interferon alfa-2b	Hepatitis C	SF-36	No improvement	Yes	Yes	No	No
Levetiracetam	Epilepsy	N/A	No improvement	Yes	No	No	No
Miglustat	Gaucher disease	N/A	Clinically important changes	Yes	No	No	No
Nelfinavir	HIV	Karnofsky performance status	Yes, but not clinically important	Yes	No	No	No
Olanzapine	Schizophrenia	Quality of Life Scale (QLS)	"Significant greater improvement"[a]	Yes	No	No	No

Orlistat	Obesity	N/A	"HRQOL seemed to improve[a]	Yes	No	No	No
Pegvisomant	Acromegaly	N/A	N/A	Yes	No	No	No
Ribavirin	Hepatitis C	N/A	"Improved HRQOL scores for the responders' with treatment"[a]	Yes	No	No	No
Ritonavir	HIV	3 HRQOL instruments: N/A	No improvement in HRQOL was shown[a]	Yes	No	No	No
Sildenafil	Erectile dysfunction	International Index of Erectile Function (IIEF)	Treatment "showed positive effects in HRQOL"[a]	Yes	No	No	No
Somatropin	Growth failure	N/A	No improvement in HRQOL was shown[a]	Yes	No	No	No
Tadalafil	Erectile dysfunction	International Index of Erectile Function (IIEF) (Questions 3 and 4)	Tadalafil found to be superior to placebo. The changes in both questions were statistically significant	Yes	No	No	No
Temoporfin	Cancer	Washington University Head and Neck Questionnaire (UW-QOL)	Yes, improvement was shown[a]	Yes	No	No	No
Temozolomide	Cancer	N/A	"HRQOL scores were maintained or improved with treatment"[a]	Yes	Yes	No	No
Thyrotropin alfa	Cancer	SF-36, Profile Of Mood States questionnaire (POMS)	Yes, in most domains of the questionnaire[a]	Yes	Yes	No	Yes
Topotecan	Cancer	EORTC-QLQ-C30	"QOL measures were not different between the trial arms"	Yes	No	No	No
Trastuzumab	Cancer	EORTC-QLQ-C30	Clinically meaningful improvement in HRQOL in the trials of trastuzumab as monotherapy. No statistically significant changes in HRQOL in the trials with trastuzumab in combination with paclitaxel	Yes	No	No	No

[a] The scientific discussion did not explain whether the difference, improvement, or change in HRQOL was referring to statistical or clinical significance.
SPC, summary of product characteristics; N/A, information not available.

treatments. The only general EMEA guidance that deals with HRQOL measurement and the use of such data is the ICH guidance on statistical principles that refers to the potential use of measurements relating to HRQOL and health economics as further primary variables in clinical trials. However, in most of the EMEA disease-specific guidelines for clinical investigation of new pharmacological agents that referred to HRQOL, HRQOL was recommended as a secondary end point, while in three disease-specific guidelines (rheumatoid arthritis, osteoarthritis, and chronic obstructive pulmonary disease), HRQOL measures were recommended both as primary and secondary end points. The choice of the primary end points of the clinical trial should be clinically relevant to the focus of the trial, reflect the therapeutic goals expected for the investigated agent and the clinical benefit the applicant wishes to claim in the future SPC (12). Examples of the most important objectives in the treatment of each disease and, therefore, the important end points that should be used in the clinical trials, were given within the recommendations but were not accompanied by references to supporting published data. However, the recommendation stated that the sponsor should cite published data that support the validity of the measurements that are used in the clinical trials to demonstrate the effect of the investigated drug in the relevant disease. With regard to the secondary end points, the recommendations stated that they should be supportive measurements related to the primary objective of the clinical trial or measurements of effects related to the secondary objective, but that their use should also be justified by referencing published data that support their validity.

The choice of the appropriate end points is important, because the regulators use the results from the primary end point analyses as the basis for labeling claims, and although they reluctantly use the results from secondary end points, they can consider them as supportive evidence. Therefore, if a comprehensive HRQOL marketing campaign is desired, trials should be designed accordingly (36).

In general, most of the recommendations that referred to the measurement of HRQOL were generic and vague, using nonstandard terminology that was also inconsistent across the documents. Moreover, there was no consensus on which instruments should be used for the assessment of HRQOL. In some guidelines, the use of generic instruments was recommended; in others, the use of disease-specific questionnaires was stressed; whereas in still others, the use of both instruments was mentioned. Some of the guidelines stated "disease-specific and generic instruments for measuring HRQOL can be used. . ." (23), or "the use of justified HRQOL instruments. . ." (26), or a "well-known general HRQOL scale. . ." (16), while other guidelines do not give any specific guidance on how HRQOL should be assessed. For example, in the guidance on the antiarrhythmics (7) the only statement on HRQOL was: "the use of antiarrhythmic drugs may be limited by major and minor drug-related side effects impacting on drug tolerance or HRQOL." One would have thought, through experience over the years and as health outcomes research progresses, that the guidelines would become more systematic regarding the terminology they use and the guidance they provide regarding what the regulators consider to be robust HRQOL data to support a labeling claim. However, to date, this finding does not seem to be the case.

On the other hand, there are two examples of recommendations that are clear on the importance of HRQOL: the important characteristics that the chosen HRQOL instrument should possess, and how the HRQOL data might be used within the regulatory process. These guidelines refer to urinary incontinence (23) and cardiac failure (14).

The guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence states that "the primary aim for developing new drugs for urinary incontinence should be to obtain a subjective improvement or cure of symptoms for the patient" and that "HRQOL data should be considered an extension of an evaluation of efficacy, which can provide meaningful information to the prescriber and the patient."

The guidance on cardiac failure is the only one that includes details on the criteria to be satisfied by the chosen HRQOL instrument and the way the research on HRQOL should be conducted. The Minnesota Living With Heart Failure Questionnaire is included in the guidance as a disease-specific HRQOL instrument that is widely used in cardiac failure, but the guidance does not restrict the researchers to the use of this instrument.

Among all drugs with HRQOL data included in their EPAR (Table 2), only those treatments for cancer, HIV, and obesity were included in the disease areas for which CPMP recommendations explicitly mention that HRQOL can be used as an end point in the clinical trials supporting the efficacy or safety of the investigated agent. The cancer guideline (21) did not provide any specific recommendations on the HRQOL instrument that should be used. However, in most cases the EORTC QLQ-C30 questionnaire was used, which is the most widely used cancer-specific HRQOL measurement (29;37). The other HRQOL instruments that were used in cancer trials were the Washington University Head and Neck Questionnaire (UW-QOL) and SF-36 alongside the Profile of Mood States questionnaire (POMS). UW-QOL has been widely used as a head- and neck-specific quality of life questionnaire. It is short and simple to process, and its minimum clinically important difference has been defined (45). Trask et al. (49) also suggested that the combination of POMS and SF-36 is a valid approach for assessing the effect that emotional distress caused by cancer-specific worries has on the health functioning of patients.

In the case of weight control, the CPMP guideline was particularly generic (10), and no information on the questionnaire that was actually used in the clinical trials was given

in the EPAR of orlistat. The difficulty, however, in interpreting the HRQOL data was clearly stated in the scientific discussion document that stated "although subjective and difficult to interpret, HRQOL seemed to improve. . .".

Finally, the CPMP guideline that refers to HIV infection (26) was particularly vague on how HRQOL should be assessed, acknowledging, however, the potential value of these data in assessing the risk benefit ratio of the agent. The two HRQOL questionnaires that were mentioned were the Medical Outcomes Study HIV Health Survey (MOS-HIV) and the Karnofsky scale performance status. MOS-HIV is a brief, comprehensive HRQOL measure used extensively in HIV (50). The Karnofsky scale of performance status is a measure of health status that is widely used for HIV-infected persons, although few studies have documented its validity for HIV (28).

The remainder of the products evaluated are for the treatment of diseases for which either CPMP recommendations do not include HRQOL data, such as diabetes and schizophrenia, or for which recommendations have yet to be developed, such as rhinitis. This finding shows that, if HRQOL data are submitted for drugs for which relevant CPMP recommendations do not explicitly mention HRQOL end points, the EMEA still reviews them. However, this finding raises the question that, if HRQOL data are important enough to be included in the EPAR, then why has the importance of HRQOL not been mentioned in the CPMP guidance for that specific disease?

The HRQOL data included in the scientific discussion of different drugs varied in terms of the detail they included. In twenty of the thirty-three evaluations (Table 2), the name of the HRQOL instrument used was not specified. Usually only one disease-specific HRQOL questionnaire was used. Less frequently, only one generic questionnaire was used, or a generic and a disease-specific questionnaire were used together, or two generic questionnaires were used, or finally, two disease-specific questionnaires were used together (Table 2).

The debate on the type of HRQOL instruments that should be used if these data are to be used in health-care decision-making is still on-going. Generic questionnaires can be used in various populations regardless of the disease, and they permit comparisons across patient populations. However, it is argued that their major limitation is lack of responsiveness. Disease-specific questionnaires, on the other hand, are designed for a particular patient group and focus on aspects that are specific to the condition and deemed to be clinically important. Therefore, they should more appropriately reflect patient change in response to treatment (5). Some experts support the use of different types of HRQOL instruments in one clinical trial, as they play complementary roles (31;33). Dowie (6), on the other hand, argues that a generic measure is "intended to cover the full range of health outcomes," whereas the disease-specific measure is, by definition, intended to cover a narrower range. On the basis of this distinction of intention, it is argued that, in most cases, the generic questionnaire should be used alone and never should be used together with a disease-specific instrument. Therefore, the decision of the type of instrument that will be used in a study should be driven by the scope of the study and the future use of the data. For example, if the objective is to compare drugs indicated for the same disease, then a disease-specific instrument should be used where available.

Of all the products with HRQOL data in their EPAR documentation, only nine discussed these data in the SPC (Table 2). In general, HRQOL data were presented briefly in the SPCs without mentioning specific results. A conclusion cannot be reached on whether the fact that a significant difference in patients' HRQOL is observed between the product being evaluated and the comparator during clinical trials is important enough to warrant the incorporation of this information in the SPC. There are examples (Table 2) where a significant difference between the HRQOL data for the two products was not observed and the data were still included in the SPC, and there are examples when the opposite has occurred. For example, the SPC of docetaxel states: "In both arms, quality of life measured by the EORTC questionnaire was comparable and stable during treatment and follow-up"; the SPC of thyrotropin alfa mentioned: "Quality of life was significantly reduced after thyroid hormone withdrawal, but maintained following either dosage regimen of Thyrogen"; and in the SPC of cytarabine: "No statistically significant differences were noted in secondary endpoints such as duration of response, . . . quality of life and overall survival." On the other hand, there are examples when significant differences in HRQOL were mentioned in the scientific discussion, but the SPC did not refer to these data (Table 2).

By reviewing the EPAR that referred to HRQOL and were published for the same drug, some discrepancies were identified between the different documents. An example that demonstrates this is the quote in the SPC of agalsidase beta that states that "Quality of life scores slightly improved during the first year of treatment," while the scientific discussion states that "no statistically significant differences in HRQOL were observed when analyzing the tertiary endpoints." Moreover, the scientific discussion of thyrotropin alfa states that "Data on HRQOL were collected and showed differences in favor of Thyrogen on most items," while the SPC states that "HRQOL was significantly reduced after thyroid hormone withdrawal but maintained following either dosage regimen of Thyrogen."

None of the package leaflets contained information related to HRQOL that was included in the scientific discussion, and only three drugs (Table 2) contained HRQOL information in their abstract. In one case, the results from the clinical trials that were included in the scientific discussion and the SPC showed no difference when the HRQOL of the two groups was compared. However, despite this finding, a

statement on potential HRQOL improvement with cytarabine was included in the abstract. The abstract stated that "DepoCyte has a more convenient schedule of administration compared to conventional ara-C, as it reduces the need for multiple injections and this may impact quality of life favorably."

CONCLUSION

Only twenty of the fifty CPMP notes of guidance for clinical investigation of pharmaceutical products in specific disease areas include reference to, or recommendations on, HRQOL. Most of these recommendations are generic and vague. Moreover, terminology and recommendations are not consistent across documents.

There is evidence to suggest that HRQOL data are routinely discussed in the regulatory review process if the company submits this information, and this finding is evidenced by HRQOL data starting to appear in a product's EPAR. However, EPAR provide little and nonspecific information about the HRQOL outcomes of products, their meaning and the way they were derived. Moreover, in some instances, contradictory conclusions on the effect of the drug on HRQOL are presented in different EPAR documents for the same substance. Finally, the criteria used by the CPMP to assess the HRQOL data could not be identified, as the decision to include these data in the EPAR appears to be taken on an ad hoc basis.

Further research is needed to better understand and establish the value of HRQOL data in the decision-making process within specific disease areas. To ensure consistency, there is a need for a more systematic approach across therapy areas in considering health outcomes and how they are reviewed and interpreted by regulatory authorities. For this to be achieved, the CMPM should develop clear general guidelines on the importance of HRQOL and on the required criteria underlying appropriate HRQOL instruments if these data are to be included in the drug registration process. Recognizing that the role of HRQOL is more important in some disease areas than others, specific disease-specific guidelines should also be issued on how and when HRQOL assessment should be integrated into studies for registration purposes. However, this strategy will only be possible if experts on outcomes research are involved in the preparation of recommendations for HRQOL assessment within clinical trials and if regulatory agencies, particularly the EMEA, have appropriate expertise on the principles of outcomes research. This approach will allow for the proper review, assessment, and interpretation of such data and ensure the meaningful use of HRQOL information.

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