The human dimension in the assessment of medicines

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RISK PERCEPTION OF PRESCRIPTION DRUGS

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ABSTRACT

Background: Experts are perceived to be veridical and to focus only on objective data when evaluating risk. Only a few research studies have attempted to characterize the subjectivity in risk evaluation among experts. **Objective**: The hypothesis of this study is that expert evaluation of a pharmaceutical drug can be partly explained by dimensions that describe the drug and by individual characteristics. **Methods**: Seventy-five medical assessors in 9 EU countries evaluated a list of 28 pharmaceutical drugs using 4 scales: risk, benefit, seriousness of harm, and patients' knowledge of the risk. They were also given a mock "clinical dossier" and asked to rate it on 8 dimensions: risk, benefit, worry, magnitude of the exposure, scientific knowledge of the risk, familiarity of the risk, ethical concerns, and risk acceptability. **Results**: Female assessors perceived significantly higher benefits than men for a large number of the 28 drugs. Principal component analysis of the ratings for the clinical dossiers revealed 2 underlying components: seriousness of harm and scientific evidence. A regression model predicting the risk perception of the drug showed that the variables seriousness of harm (benefit, worry, magnitude of exposure, ethical concerns, and risk acceptability), years of regulatory experience, gender, and type of drug explained 54% of the variability among assessors. **Conclusions**: Assessors' view of the risks associated with pharmaceutical drugs is influenced by worry for patient safety, magnitude of patient exposure, and ethical concerns. These dimensions may influence their perceptions of benefit and risk acceptability. Senior assessors are more risk averse than junior assessors, and female assessors seem to be sensitive to the promise of benefit from medicines and consequently may be less risk averse than male assessors.

INTRODUCTION

The risk research literature is replete with evidence that experts, when asked to evaluate hazards within their area of expertise, are seen to be veridical and to focus only on the formal definition of risk: probability and the magnitude of the harm.[1–3] It is believed that only when asked to make judgments outside their area of expertise that experts rely on their perception of the hazard, which may then be influenced by their values, emotions, fears, and social pressures.[4] This has been the generally accepted view in risk research for the past 3 decades. However, there is an alternate view, not as widely acknowledged, that within their area of expertise, experts may perceive hazards through a prism of values and emotions and may be influenced by overconfidence and/or may rely on heuristics such as availability and affect when making judgments.[5–10] A few authors have called for a reexamination of the data that laid the foundation for the seemingly oversimplified approach to risk perception assigned to experts and have advocated the use of real experts in risk research to increase the understanding of risk perception among this group. In his research among nuclear experts in Sweden, Sjoberg[11–13] provided evidence that expert risk perceptions can be predicted by specific characteristics or dimensions that experts associate with nuclear energy. The results show that dread, familiarity of the risk, tampering with nature, and the involuntary nature of the risk were predictive of expert risk perception.[11–14]

Our understanding of whether experts rely on their perceptions when making risk judgments is further confounded by the methods used within this area of research. For example, in a study of the risk perception of biotechnology products, the expert research group consisted mainly of PhD students, not experts charged with the responsibility to provide risk evaluation of biotechnology products.[15] It is questionable whether the extrapolation of the views of students to experts actively working in the evaluation of the risks associated with biotechnology products aids our knowledge of expert risk assessment. Further- more, the technical information that experts generally use in their risk assessment was not made available to the PhD students.

The influence of individual characteristics, such as gender, in risk taking has been extensively discussed in the literature. In a review of 150 articles on gender differences and propensity for risk taking, Byrnes and Miller concluded that the literature 'clearly' indicated that men take more risks than women[16]; a recent article from Harris and Jenkins has further supported this division.[17] However, it is uncertain whether the differences observed for general risk taking can also be applied to a group of experts. It has also been found that people differ in their risk attitude or perception of a hazard depending on their professional affiliations.[18] The published literature provides ample evidence of individual differences in risk perception among laypersons, but there is very little evidence of these differences among experts.

Our study focuses on experts in the European pharmaceutical regulatory network, specifically, the medical assessors from the National Competent Authorities (NCAs). Each NCA within its respective country is responsible for the control or regulation of medicinal products and does this in collaboration with the Committee for Medicinal Products for Human Use (CHMP). Assessors' judgment of the medicines developed by the pharmaceutical industry is paramount to the health and longevity of more than 500 million people; however, outside the pharmaceutical regulatory world, assessors are an almost invisible group and little is known about how they make judgments about the products they regulate and how they balance benefits and risks.

In 2004, an audit of the process for evaluating medicinal products within the European regulatory network found that there was poor understanding of how regulatory decisions are made. The auditors recommended that the method used to assess benefits and risks of products be improved to prevent accusations of suboptimal or inconsistent decision-making. The CHMP, the body charged with the responsibility of assessing the benefit-risk balance of medical products, launched a 3-year initiative in 2009, the Benefit-Risk Methodology Project. The aim of the project was to improve the consistency, transparency, and communication of the benefit-risk assessment in CHMP assessment reports by "develop[ing] and test[ing] tools and processes for balancing multiple benefits and risks as aids to informed regulatory decisions about medicinal products."[19] The research for this article was con- ducted within the context of the European Medicines Agency Benefit-Risk Methodology project.[20]

The current article examines whether risk perception is shaped by characteristics that assessors may associate with a medicinal product and the role that assessors' individual characteristics may play in the evaluation of these risks. This is accomplished using 2 approaches: first, through the assessment of very broadly defined hazards (several types of medicinal products) for which the assessors were not provided any data; second, by the assessment of 3 specific medicinal products for which the assessors were provided clinical trial data. The hypothesis is that assessors' evaluation of the harm associated with a medicinal product is in part explained by their perception of the drug, which in turn is predicted by dimensions similar to those found by Sjoberg[13] as well as individual characteristics such as gender, professional background, and years of regulatory experience. The study answers the following questions:

Is the risk perception of a medicinal product predicted by the specific characteristics or dimensions associated with that product?
Is there a relationship between risk perception of a medicinal product and the demographic characteristics of an assessor?

METHODS

The study was implemented as a Web-based questionnaire and was launched between June 2010 and October 2010. Members of the CHMP, in 9 participating countries, identified assessors within their NCA with expertise in cardiology, oncology, and the central nervous system (CNS). They also indicated whether the assessor had primarily clinical, safety, or nonclinical expertise; assessors could elect to participate or opt out of the study. Data were collected in 3 phases with each phase lasting approximately 6 weeks: Phase 1: demographic data, Domain Specific Risk Taking scale (DOSPERT)[21] and the psychometric scale adapted from Slovic and others[22]; Phase 2: drug case study using a mock "clinical dossier" and 8 rating scales on benefit-risk dimensions; Phase 3: the Big Five Jackson Inventory personality test.[23] The results for the DOSPERT scale and the Jackson Inventory personality test will be presented in a forth- coming publication.[24] There was no imputation of missing data. Demographic variables of assessors who completed Phase 1 and did not continue to Phase 2 were evaluated for differences between the groups using Fisher's exact test.

Methods Addressing Research Questions 1 and 2 for 28 Types of Medicinal Products

In the psychometric studies conducted by Slovic and others,[22,25,26] laypersons in Sweden, Canada, and the United States were given a list of hazards, many of which were medicinal products, and asked to rate these items on 5 scales covering perception of risk, the benefit, seriousness of harm, knowledge of the risk for those exposed, and warning signs. We replicated this method and asked assessors to rate 28 types of medicinal products (Table 1) using the 4 scales shown in Table 2 (Annex 1, Questionnaire 1). We included only the first 4 scales from Slovic and others[22] because the final scale *("If you heard about a problem associated with this item in which people were seriously harmed, to what degree would this mishap serve as a warning sign, indicating that the risk with this item might be greater than was thought before the problem occurred?"*) was reported by Slovic as not well understood and was not considered to be applicable for our study population.[22]

Correlation Analysis and ANOVA Models across all 28 Types of Medicinal Products

The ratings on each of the 4 scales were collapsed across all products and Spearman correlation coefficients were computed between the risk scale and each of the other 3 scales. Analysis of variance (ANOVA) models were also constructed to assess differences by gender, professional qualifications, and years of regulatory experience. Statistically significant results are reported at the 0.05 level.

Table 1. List of 28 Types of Medicinal Productsa

Acne medicines	Biotechnology products
Aspirin	Products for cholesterol
Blood pressure drugs	Diet products
Products for depression	Products for Alzheimer's disease
Products for anxiety	Acne medication
Erectile dysfunction (Viagra)	Products for epilepsy
Smallpox vaccination	Antibiotic products
Sleeping pills	Products for osteoporosis
Products for osteoporosis	Nicotine replacement (patches)
Birth control pills	Non-steroidal anti-inflammatory products
Herbal medicines	Insulin
Products for AIDS	Vitamin pills
Laxatives	Vaccines
Products for arthritis	Products for asthma
Cancer chemotherapy	Products for ulcers

[a]HRT, Botox injections, and allergy products used in the studies by Slovic and others[22,25,26] were not included in the current study.

Correlation Analysis and Mann Whitney and Kruskal Wallis Tests for Each Product, by Scale

Mean ratings for each product type were computed and box plots created for each scale. Supplemental tables are available showing the variability of the ratings by product and scale. Products are referred to as having a high or low score by using a median split to categorize the ratings. To examine the individual differences in the evaluation of the 28 medicinal products, multiple comparisons were made using Mann Whitney and Kruskal Wallis tests where appropriate. Differences in the mean scores for each product, by scale, were evaluated by gender, professional qualifications (MD, PhD, pharmacists, other), and years of regulatory experience (1–2 years, 2–3 years, 3–5 years, 51 years). As the study is hypothesis generating and not hypothesis testing, no adjustments for multiplicity were made. Therefore, a conservative approach was taken in reporting the results, and only the test statistic and the statistically significant *P* values (0.01) are presented.

Methods Addressing Research Questions 1 and 2 for the 3 Mock Dossiers

In the second phase of the study, assessors were given a mock clinical dossier and asked to complete the questionnaire (Annex 1, Questionnaire 2). For cardiology, the product was indicated for treatment of chronic stable angina pectoris; for oncology, the indication

was treatment of non-small cell lung cancer; for CNS, the indication was for treatment of neuropathic pain. Data for the mock dossiers were adapted from the original product dossiers, Day 80 assessment reports, and European Public Assessment Reports.[27] The result was a shortened version of a real dossier with product-identifying data; such as drug name, manufacturer, and dates, removed or substituted. The assessors received the dossier consistent with their area of expertise (cardiology, CNS, oncology, clinical, safety, or nonclinical) and were asked to review the dossier and to rate the medicinal product on 8 dimensions (risk, benefit, worry, magnitude of the exposure, scientific knowledge of the risk, familiarity of the risk, ethical concerns, and risk acceptability)[15] (Table 3). They were constrained not to consult with their colleagues because the aim of the study was to collect individual responses.

Testing the Applicability of Applying Principal Component Analysis to Ratings Collapsed across the 3 Products in the Mock Dossiers

Before we applied the principal component analysis (PCA) method it was important to evaluate whether the assessors' responses for the dimensions were different by product, for example, whether the risks for the oncology product were in actuality more worrisome than those for the cardiovascular product. First, the variability of the dimension scores was examined for each product in the mock clinical dossiers. A regression model was also created for the 7 dimensions (excluding risk) with a categorical variable representing the 3 medicinal products as the independent variable. The aim was determine whether the medicinal product predicted the responses any of the 7 dimensions. If the *F* statistic was not significant, meaning that the medicinal product did not predict the responses, the dimension was retained for the PCA. The risk dimension was not included in this analysis because the relationship for the risk scores was later evaluated by constructing a regression model with all fixed factors and covariates.

Methods for the Principal Component Analysis

The ratings of the 7 dimensions (excluding risk) for the mock clinical dossier were assessed using a PCA model with the aim of discovering any latent factors underlying the structure of the data that may cause the observed variables to co-vary. In response to the criticism by Sjoberg and by other investigators[28,29] that earlier studies inflated the explanatory power of the components by averaging the responses across participants, the raw data were used in the PCA model to reflect individual differences in perceived risk. There was no forced extraction of components, and the scree plot from the component analysis was used to guide the component selection. The rotation method reported is varimax.[30,31]

Table 2. Scales on Which the 28 Medicinal Products Were Rated[a]

Risk To what extent would you say that people who are exposed to this item are at risk of experiencing personal harm from it? (1 = They are not at risk; 7 = They are very much at risk)
Benefit In general, how beneficial do you consider this item to be? (1 = Not at all beneficial; 7 = Very beneficial)
Seriousness of Harm If an accident or unfortunate event involving this item occurred, to what extent are the harmful effects to a person likely to be mild or serious? (1 = Very mild harm; 7 = Very serious harm)
Knowledge of the Risk for Those Exposed To what extent would you say that the risks associated with this item are known precisely to people who are exposed to those risks? (1 = Risk level not known; 7 = Risk level known precisely)

[a]Only the first 4 scales used in the studies by Slovic and others[22,25,26] were included in this study.

Table 3. Dimensions on Which the Mock Clinical Dossier Were Rated[a]

Risk Dimension To what extent would you say the patients who are exposed to this product are at risk of experiencing harm from it? (1 = They are not at risk; 7 = They are very much at risk)
Benefit Dimension In general, how beneficial do you consider this product to be? (1 = Not at all beneficial; 7 = Very beneficial)
Magnitude Dimension In your estimation, how many people in the world would be exposed to this product? (1 = Very few people; 7 = Many people)
Worry Dimension How much does the patient exposure to this product worry you? (1 = Not at all worrisome; 7 = Very worrisome)
Scientific Knowledge Dimension How precise is the scientific knowledge of the hazards associated with this product? (1 = Low knowledge; 7 = Very high knowledge)
New Risk Dimension Are the hazards associated with this product new, or old and familiar? (1 = Very well known; 7 = Very new)
Ethics Dimension To what extent does this product pose an ethical dilemma? (1 = No ethical dilemma; 7 = Very important ethical dilemma)
Risk Acceptability Dimension To what extent do you think the hazards associated with this product are acceptable to obtain the benefits? (1 = Not at all acceptable; 7 = Definitely acceptable)

[a]Adapted from Savadori and others.[15] Reprinted with permission from John Wiley and Sons.

Regression Models Evaluating the Risk Dimension Scores Using the PCA Components and Individual Characteristics

The PCA analysis allows us to reduce the data and describe the relationship between variables, but it is also of interest to assess the predictive power of the components on the risk dimension. The extracted components were included as the independent variables in a regression model with the risk dimension as the dependent variable. The normality assumption for the error term was checked by histograms and P-P plots of the residuals. In addition, a general linear model (GLM) was used to evaluate the relationship between the risk dimension scores (how risky the assessors perceived the medicinal product) and the statistically significant component obtained from the PCA, along with 3 categorical variables for gender, regulatory experience, and the medicinal products. Profile plots of the estimated marginal means were generated to examine the results of the GLM. All statistical analyses were conducted using SPSS 18.

RESULTS

Demographics

Of the 80 assessors enrolled in the study, 94% responded for Phase 1; 5 assessors were identified by their agency but did not participate. For Phases 2 and 3 the response rate was 78%; 16 assessors did not continue after Phase 1. There was no difference found for age, gender, role in the agency, regulatory experience, or therapeutic area expertise between the dropouts from Phase 1 and those who continued to Phase 2 and 3.

As shown in Table 4, the group was equally balanced by gender; 31% were between 39 and 20 years old. The majority of the assessors were medically qualified, MD (38%), with the balance of assessors having attained higher education, PhD (25%), and pharmacy (10%) degrees. Internal assessors, those who work directly for the NCA, comprised the majority of the group (76%), whereas 16% were external assessors who are affiliated with universities and/or hospitals but collaborate and provide their expertise when requested by the NCA; 6 CHMP members also participated in the study. Assessors with more than 5 years of experience comprised the majority of the group (45%).

Table 4. Demographic Characteristics of the Study Population

Variable	Characteristic	Frequency	Percentage
Gender	Male	38	51%
	Female	37	49%
Age	Between 20 and 39	23	31%
	Between 40 and 49	30	40%
	Between 50 and 59	18	24%
	Over 60	3	4%
Professional qualifications	MD	27	36%
	MD/PhD	11	15%
	PhD	19	25%
	PhD/Pharm	3	4%
	Pharmacist	10	13%
	Other	5	6%
Role in NCA	CHMP member	6	8%
	Internal assessor	57	76%
	External assessor	12	16%
Years of regulatory experience	0–1 year	6	8%
	1–2 years	6	8%
	2–3 years	12	16%
	3–5 years	17	23%
	> 5 years	34	45%

Results for Research Questions 1 and 2 for the 28 Types of Medicinal Products (Collapsed across All Products)

The strength and the direction of the relationship between risk perception and the other scales, collapsed across all 28 products, revealed low but positive correlation between perception of risk and perception of benefit (0.235; $P = 0.043$); a positive correlation between perception of risk and perception of the seriousness of harm (0.344; $P = 0.002$); and no statistically significant relationship between perception of risk and perception of the knowledge of harm to those exposed (0.073; $P = 0.531$).

Results of ANOVA models examining the differences by gender, years of regulatory experience, and professional qualifications for each of the 4 scales show a statistically significant difference between gender for the benefit scale ($F = 7.576$; $P = 0.007$) as well as a difference in the mean scores for the knowledge of the exposed scale when examined by years of regulatory experience ($F = 2.715$; $P = 0.037$). All other coefficients were non-significant.

Results for Research Question 1 by Scale and for Each Product

Box plots displaying the range of the data by product and scale are shown in Figures 1–4. The products are ranked from lowest to highest mean score. Vita- min pills had the lowest rating on both the risk and seriousness of harm scales, whereas oncology drugs had the highest rating on these scales. Further examination of the relationship between the scales, by product, showed that the benefit-risk correlation observed when the ratings were collapsed is attributable to 7 products. Inverse correlations (high benefit- low risk) were seen for AIDS products (–0.256; $P = 0.028$), birth control pills (–0.270; $P = 0.019$), insulin (–0.234; $P = 0.044$), ulcer products (–0.236; $P = 0.041$), and vaccines (–0.303; $P = 0.001$), and positive correlations (high benefit-high risks) were seen for Alzheimer's disease (0.266; $P = 0.022$) and biotechnology products (0.265; $P = 0.022$). The seriousness of harm ratings were very closely correlated to the risk perception of a product. Twenty-five of the 28 products achieved statistical significance and were positively correlated on these 2 scales. Weak correlations were found for the following products: AIDS; biotechnology; oncology; laxatives; non-steroidal anti-inflammatory products; sleeping pills; vitamins; smallpox vaccination; anxiety; diet; birth control pills; depression; cholesterol products; insulin; arthritis products; asthma products; epilepsy; and vaccines. Moderate correlations were found for products for Alzheimer's disease; aspirin; herbal medicines; ulcer products; erectile dysfunction; nicotine replacement; and osteoporosis products. The analysis of the perception of risk and knowledge of the risk for the exposed showed only 3 products for which a pattern was detected. Assessors gave high scores for risk perception of oncology products and low scores for patients' knowledge of the associated harms (–0.245; $P = 0.034$). For arthritis (0.275; $P = 0.018$) and erectile dysfunction products (0.313; $P = 0.007$), the results seem to indicate that assessors perceive these products to be risky and that patients have a high knowledge of the associated risks.

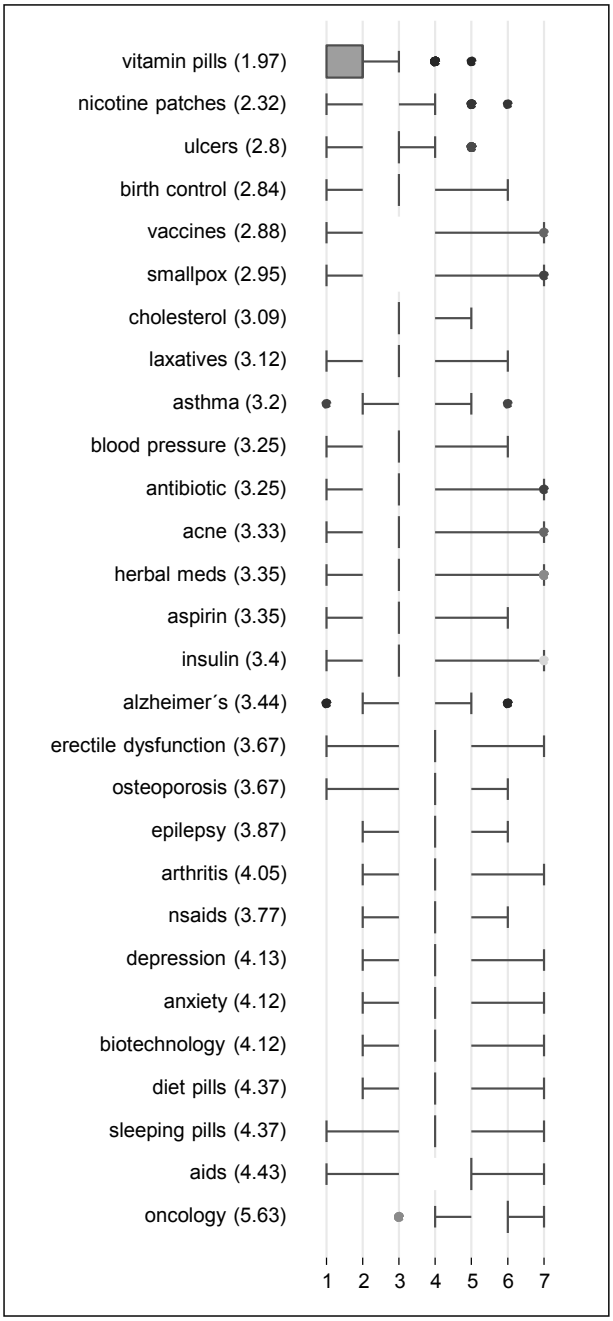

Figure 1. Box plots of the mean scores for 28 types of medicinal products ranked from lowest to highest score: "To what extent would you say that people who are exposed to this item are at risk of experiencing personal harm from it?" (1 = They are not at risk; 7 = They are very much at risk).

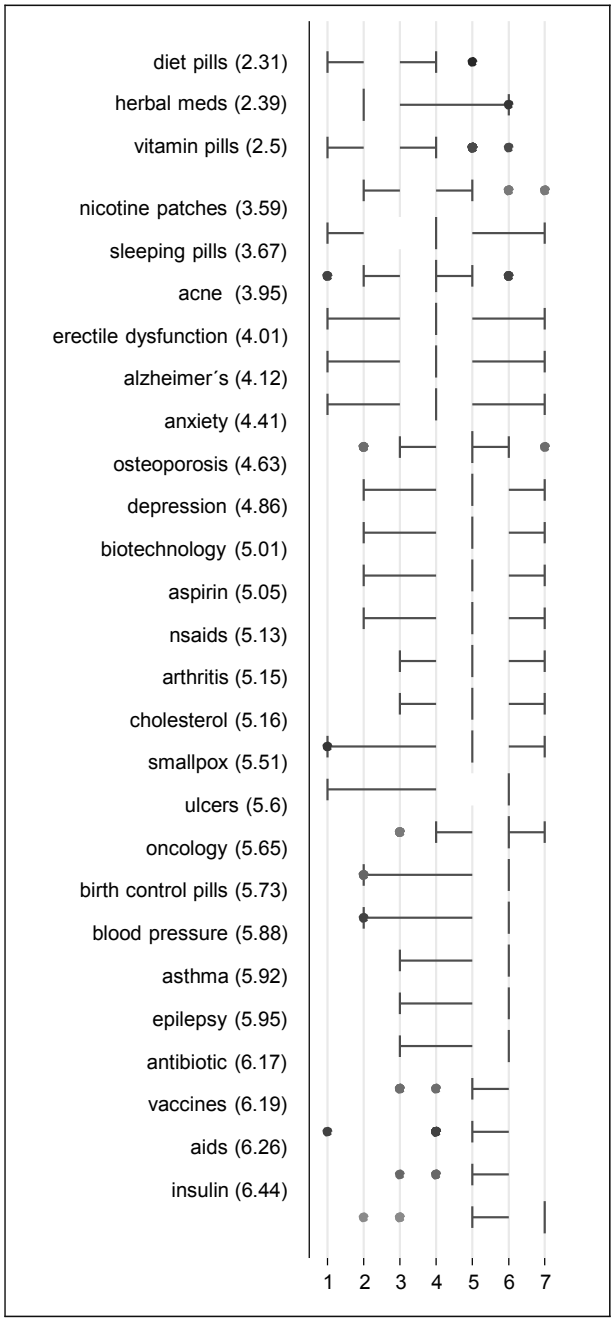

Figure 2. Box plots of the mean scores for 28 types of medicinal products ranked from lowest to highest score: ''In general, how beneficial do you consider this item to be?'' (1 = Not at all beneficial; 7 = Very beneficial).

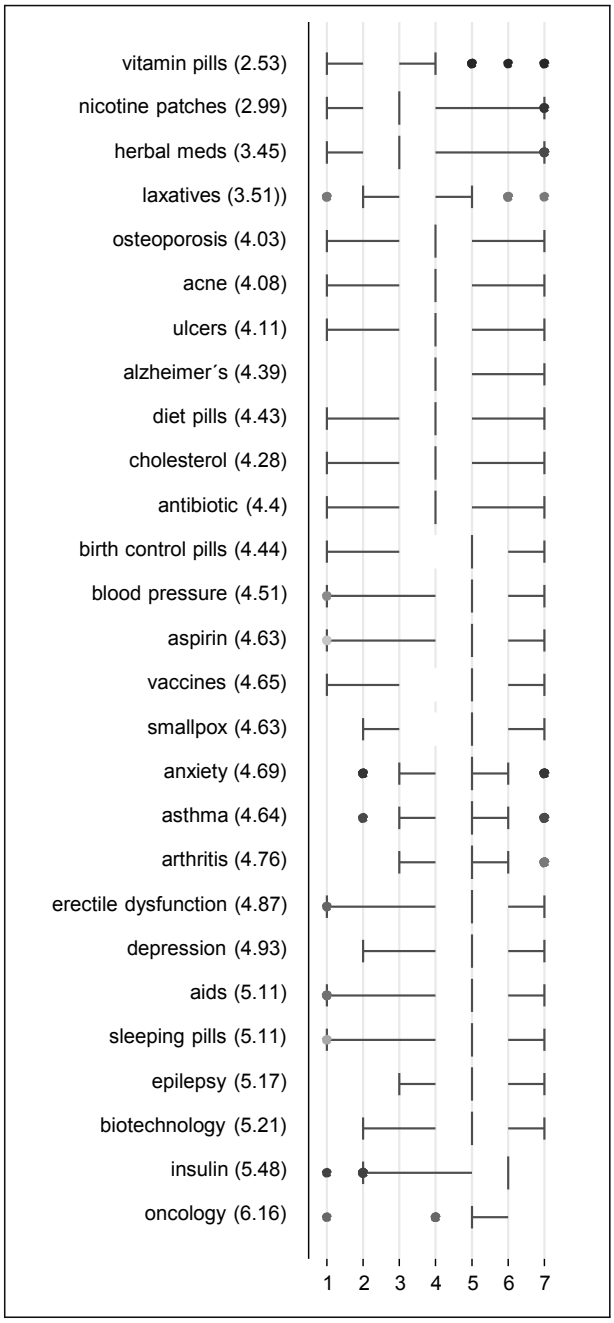

Figure 3. Box plots of the mean scores of 28 types of medicinal products ranked from lowest to highest score: "If an accident or unfortunate event involving this item occurred, to what extent are the harmful effects to a person likely to be mild or serious?" (1 = Very mild harm; 7 = Very serious harm).

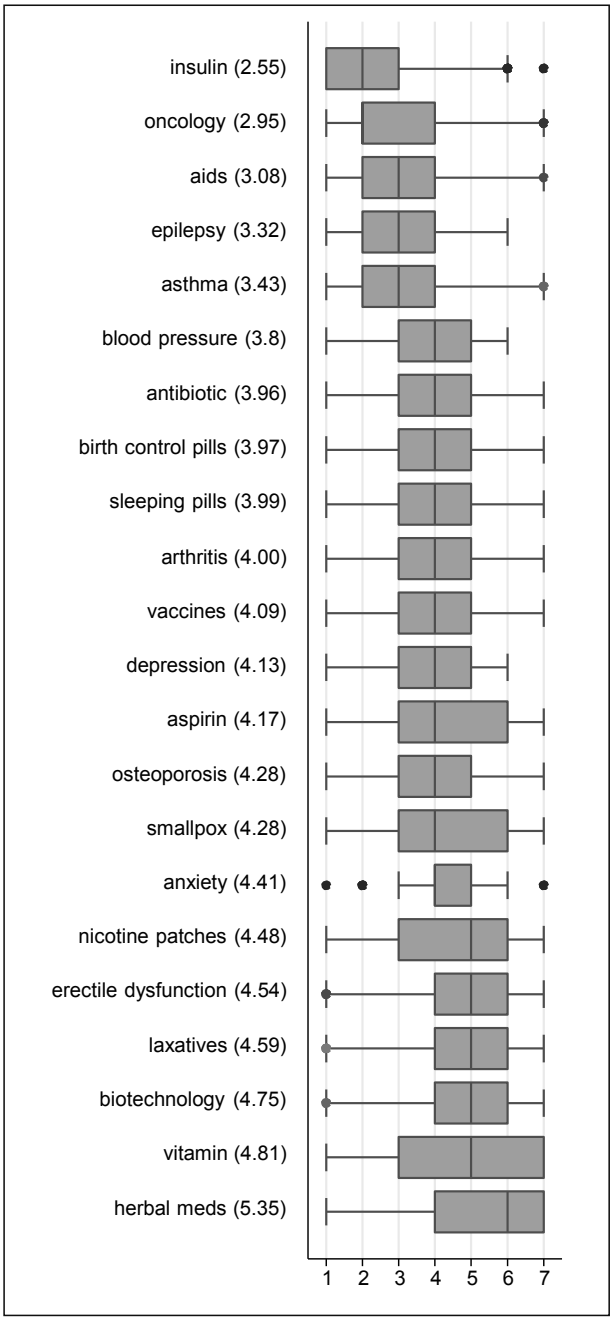

Figure 4. Box plots of the mean scores for 28 types of medicinal products ranked from lowest to highest scores: 'To what extent would you say that the risks associated with this item are known precisely to people who are exposed to those risks?" (1 = Risk level not known; 7 = Risk level known precisely).

Results for Research Question 2 for Each Product, by Scale

An examination of the differences in mean risk perception scores by gender revealed that female assessors saw higher risks for diet products (452.5; $P = 0.006$) than did their male counterparts. For other products there was no significant difference between genders. On the benefit scale, female assessors saw greater benefit than male assessors for a number of products: Alzheimer's disease (387.5; $P = 0.001$), arthritis (399.5; $P = 0.001$), biotechnology (466; $P = 0.009$), oncology (404; $P = 0.001$), and epilepsy (472.5; $P = 0.001$). No statistically significant differences by gender were found for the 'seriousness of harm' and the 'knowledge of the risk for the exposed' scales.

The comparison of the perception of medicinal products by professional qualifications (MD, PhD, pharmacists, and other [statisticians, master's degree]) revealed few differences. For the risk scale, assessors in the 'other' category indicated a higher perception of risk for cholesterol products (14.298; $P = 0.003$) compared with the other groups. The MDs reported higher scores on the knowledge of the risk scale for acne (13.065; $P = 0.004$), whereas the 'other' group reported higher scores on the knowledge of the risk scale for epilepsy products (11.338; $P = 0.010$).

There were few statistically significant differences observed for the risk perception of the medicinal products by the number of years of regulatory experience (1-2, 2-3, 3-4, 5+ years). Assessors in the 2- to 3- year group reported higher risk scores for blood pressure products (13.393; $P = 0.010$). No statistical differences between the categories were found for the benefits or the seriousness of harm scale. On the scale measuring the assessors' perception of patients' knowledge of the associated risks, the 3- to 5-year group reported higher scores for asthma products (14.621; $P = 0.004$), whereas the 2- to 3-year group reported higher scores for ulcer products (13.382; $P = 0.01$).

Results for Research Question 1 for the 3 Mock Dossiers

Prior to collapsing the data across the 3 medicinal products for the PCA analysis, we examined the mean rating of each product for the 7 dimensions and saw no great disparities in mean scores (Table 5). As a further evaluation of the potential influence of the specific products on the ratings of the dimensions, 7 regression models as described in the methods section were constructed. The results showed that the products in the mock dossiers (treatment for chronic stable angina pectoris, non-small cell lung cancer, and neuropathic pain) did not predict the scores on the dimensions. The distributions of the dimensions were found to have normal distributions; therefore, the PCA analysis was performed using the entire sample (i.e., no separation by product).

The PCA analysis revealed 2 components accounting for 59% of the total variance between assessors. After rotation, the first component loaded on the following dimensions: benefit, magnitude of the exposure, worry about the harm to those exposed, ethics, and risk acceptability. The second component loaded on the scientific knowledge of the risk and unfamiliarity of the risk. The components were labeled "seriousness of harm" and "scientific evidence," and the plot of these components is shown in Figure 5; each end of the vertical and horizontal axis shows how the dimensions are both correlated with and in opposition to the other dimensions. The robustness of the results was evaluated by using residuals from the previously described 7 regression models (excluding risk) in a PCA. The results for this second PCA model were very similar to the previous results, with 2 factors emerging accounting for 60% of the total variance among the assessors.

Table 5. Descriptive Statistics for the Rating of the Clinical Dossiers on Eight Dimensions, Mean (Standard Deviation)

	Clinical Dossier		
	Cardiology	**Central Nervous System**	**Oncology**
Risk dimension	3.53 (1.18)	3.62 (1.20)	4.35 (1.11)
Benefit	4.12 (1.58)	3.14 (1.46)	3.76 (0.89)
Magnitude	3.76 (1.56)	4.10 (1.45)	3.57 (1.47)
Worry	4.00 (1.54)	3.86 (1.49)	4.29 (1.31)
Scientific knowledge	3.88 (1.73)	3.43 (1.63)	3.76 (1.37)
New risk	4.18 (1.74)	3.76 (1.48)	3.57 (1.08)
Ethical	2.59 (1.37)	3.10 (1.48)	3.76 (1.58)
Risk acceptability	4.59 (1.50)	3.67 (1.65)	4.33 (1.56)

Results for Research Question 2 for the 3 Mock Dossiers

A multiple regression model with perceived risk for the medicinal products as the dependent variable and the 2 extracted components as the independent variables explained 29% (adjusted R^2) of the variance between the assessors, with the "seriousness of harm" component predicting the risk dimension scores (b = 0.67; P \ 0.001; 95% confidence interval [CI], 0.395–0.944). No statistically significant relationship was found between the risk dimension scores and the scientific evidence component (b = 20.009; P = 0.95; 95% CI, 2283 to 0.266). In order to test our hypothesis of the influence of the assessors' individual characteristics on risk perception, the regression model predicting the risk dimension scores was expanded to include gender, years of regulatory experience, and the medicinal products. Fifty-four percent (adjusted R^2) of the variability is now explained in

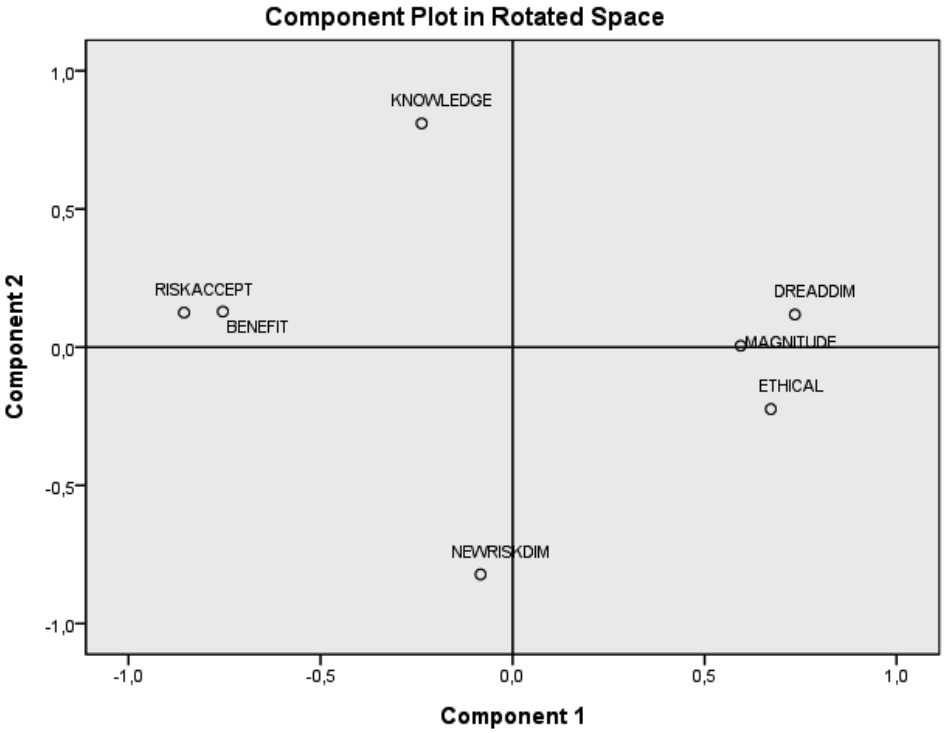

Figure 5. A plot of the two components from the PCA analysis.

the new model. Controlling for "seriousness of harm" (worry for the safety, magnitude, ethics, benefit, risk acceptability) (F = 30.443; P = \.001), we found that senior assessors reported statistically different scores than junior assessors (F= 2.925; P = 0.036). This is shown in the profile plot of the estimated marginal means from the GLM (Figure 6). When the data are collapsed across all medicinal products, the plot shows that junior assessors, of both genders, reported lower risk scores than did senior assessors. The model also included a 2-way interaction term for gender by medicinal product (F= 3.956; P = 0.029), which can be seen in the profile plot from the GLM (Figure 7). Male assessors reported a statistically significantly greater risk than did female assessors but only for the cardiology product. Gender by years of regulatory experience approached but did not achieve statistical significance (F= 2.542; P = 0.058), and the 2-way interaction term medicinal product by years of regulatory experience (F = 1.236; P = 0.310) and one 3-way term, gender by product by regulatory experience (F= 1.562; P = 0.217), were not statistically significant.

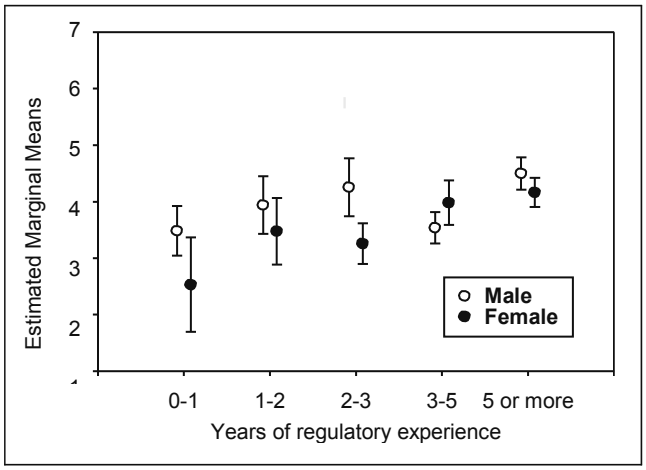

Figure 6. Estimated marginal means of risk dimension score by gender and years of regulatory experience.

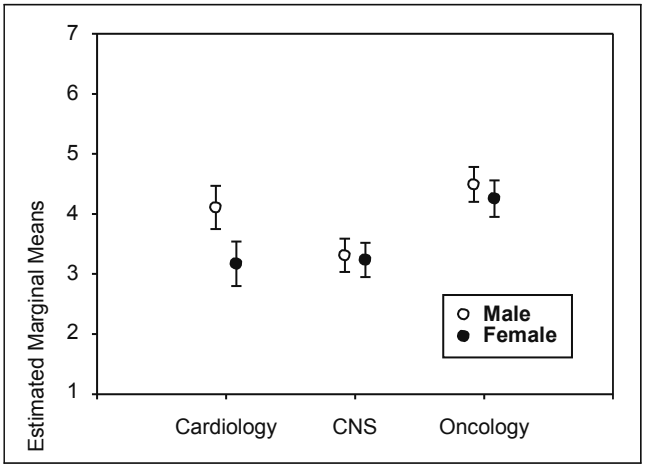

Figure 7. Estimated marginal means of risk dimension score by gender and medicinal product.

DISCUSSION

To our knowledge this is the first study of risk perception conducted with expert assessors in the pharmaceutical regulatory network in Europe. The results support the hypothesis that the evaluation of a medicinal product is in part explained by assessors' value system, that is, the perception of the product and by their individual characteristics.

Research Question 1

In their role as regulators of medicinal products, assessors are required to judge the merits of the products based on the clinical trial data, that is, the probability of the benefit as well as the probability of the harms. From the results of this current study it appears that the assessment of the products may be explained by other dimensions in addition to the above-mentioned probabilities. In very broad terms, assessors' perception assessors' perception of the riskiness of a medicinal product is highly influenced by the potential for serious harm to the patient. This is seen in the correlation between the risk and seriousness of harm dimensions for the 28 medicinal products. However, from the plot of the PCA components (seriousness of harm and scientific evidence) (Figure 5), we see that assessors' perception of the seriousness of harm of a product may be further explained by concepts of worry, the magnitude of the harm, and ethical concerns raised by some aspect of the study, possibly the design or conduct of the clinical trials.

It would appear that assessors in their review of a dossier for a medicinal product may use, to some extent, the formal definition of risk, that is, the probability and the magnitude of the harm, to judge the riskiness of a product. Data for the probability of the harm is provided by the manufacturer in the product dossier in which the observed clinical and nonclinical adverse events are discussed. What is often insufficiently discussed is the uncertainty around the statistical point estimates, so assessors are often left to determine for themselves the degree of uncertainty associated with the data they review.

We see that the magnitude dimension is also very relevant to the assessment because the potential for harm once the drug is on the market forms part of the uncertainty in the assessment of clinical trial data. How many patients will be exposed to the product, and how will the harms observed in the clinical trial be reflected in the wider patient population? These are important considerations for regulators. However, the additional information provided by this study is that the magnitude of the harm is also positively correlated with 'worry' which may be interpreted in this context as an emotional reaction generated by the concerns regarding patient safety.

From these results it would seem that the magnitude of the harm is not purely data driven - that is, the number of morbidity and/or mortality events observed in the clinical

trial - but rather is open to interpretation, and some assessors may infer greater or lesser impact or consequences for the potential harm of a medicinal product than do other assessors who view the same data.

A further correlation between the worry and magnitude dimensions with the ethical dimension was also seen. Although assessors were not asked to specify what ethical concerns they had when reviewing the dossiers, the literature on ethics and clinical trials provides ample evidence of the types of ethical issues with which assessors may struggle.[32–34] Ethical concerns may arise during the evaluation of clinical trial results: questions surrounding the issue of equipoise; the decision to treat patients in a clinical trial with placebo when adequate standard care is available; the conduct of clinical trials in populations other than where the product will be marketed; and the ethics of conducting poorly designed clinical trials that expose patients to potential risks but are not statistically powered to answer the research question.

That this dimension is seen to be correlated with the worry and magnitude dimension lends further support to our view that the assessment of clinical trial data may invoke the value system of individual assessors. The dimensions seen on the right horizontal axis in Figure 5 may act as cues for determining what represents a risk, but curiously this may also affect the perception of the benefit. The inverse relationship seen in the results from the PCA analysis shows that when the potential harms associated with a product cause the assessors great concern, which may be due to potential or observed morbidity or to mortality from the treatment; when the exposure may affect a large number of people and/or the product raises ethical concerns, then assessors may consider the product to have low benefit and low risk acceptability. This inverse relationship between benefits and risks is consistent with work by Alhakami and Slovic,[8] in which the concepts of benefits and risks appear to be confounded in people's minds and lead to an erroneous belief that activities or technologies judged high in risks are consequently low in benefit and vice versa. However, research in the field of finance shows a positive relationship between the return and the risk involved in an investment and contradicts the view that benefits and risk are innately inverse. [9,35] In the field of medicine we see possibilities where increased survival or other positive benefits from a treatment may also involve a high probability of adverse events. Clearly, benefit and risks should be assessed separately; however, our results show for the 3 products we measured, that an inverse relationship might exist in the minds of the assessors.

Scientific evidence, is formed by two dimensions: the precision of the scientific knowledge and the familiarity of the risk posed by the products. If we refer again to the formal definition of risk, that is, the probability of harm and magnitude, one would expect to see a correlation between the dimensions forming the "scientific evidence" component and

the magnitude dimension; however, for the assessors these dimensions clearly represent different concepts and as a result form separate components. The lack of predictability of the "scientific evidence" component for the risk dimension is an unexpected finding given that it is reason- able to think that experts' risk perception could be predicted by the precision of the science or the lack thereof or by the familiarity or unfamiliarity of the risk. It may be that our result is due only to chance and is not a true picture of the relationship between scientific knowledge and risk perception, and it would be necessary to replicate the study to see whether this is a consistent result. One conclusion that may be drawn from the analysis of the rating for both the list of 28 types of products and the mock dossiers is that the psychometric paradigm, with its focus on dimensions such as worry, magnitude of the harm, scientific knowledge, or familiarity with the risk, provides only a partial explanation of the differences between assessors of medicinal products and that other variables may be working in conjunction with the psychometric paradigm.

Research Question 2

The influence of individual characteristics and the role that they play in risk perception of medicinal products were also examined for the list of the 28 types of products and for the 3 dossiers. Gender difference was of particular interest, as it has been reported that gender influences how risks are perceived and that women generally see higher risks than do men.[16,17] In this study only a few of the 28 products received higher risk scores from the female assessors; however, female assessors perceived significantly higher benefits than did men for several products in the list. One possible explanation for this may be related to the finding by Harris and Jenkins that in the positive domain—a term defined by Harris as "behavioral choices offering a chance of substantial gain and imposing a relatively small but certain cost" - women were willing to take higher risks than were men.[17] The influence of experience and professional qualifications was not as readily detectable as the gender difference for the ratings of the 28 products because very few differences were found for any of the 4 scales.

That gender as well as regulatory experience may play a role in the risk perception of medicines is further supported by the results of the regression analysis of the rating for the mock dossiers. When the main effects of the "seriousness of harm" component, the 3 medicinal products and individual characteristics of gender and years of regulatory experience were included in the extended regression model, this model explained 54% of the variability between assessors. The statistically significant interaction term in the model adds to the complexity of the relationship between risk perceptions and individual and situational characteristics, but the following picture seems to emerge. Assessors with 5 years or more experience may be more risk averse than are junior assessors; that is,

length of time within an institution mandated to protect the public health may lead senior assessors to be more conservative than junior assessors who are beginning their careers. Female assessors reported lower risk scores than did male assessors for all products, but this difference was statistically significant only for the cardiology product; therefore, it is not possible to state that female assessors are unequivocally less risk averse or more risk seeking than male assessors. Surprisingly, cardiology products were not on the list of 28 products for which female assessors saw greater benefit than did male assessors; therefore, it cannot be said that the results are due to a particularly benevolent view that female assessors have of all cardiology products. However, there may be aspects specific to the product in the dossier that influenced female assessors' views of the risk or their view of the benefits. Our results with regard to gender and years of experiences seem to be in contrast with the findings of Barke and Jenkins-Smith,[36] who found in a study of perceived risks for nuclear waste that female experts and younger scientists were more risk averse than their peers. A unique dynamic may exist within pharmaceutical regulation whereby female and junior assessors are more sensitive to the promise of benefit from medicinal products and therefore see less risk. Over time, this sensitivity may decrease.

The following limitations and directions for future research are noted. Although the authors believe that the results generate interesting hypotheses regarding risk perception among medical assessors, the size of the study population limits generalization to all assessors working within the EU pharmaceutical regulatory network. The questionnaire covering all 3 phases required a large investment of time from the assessors, and a choice was made to limit the number of dimensions for the mock dossier to what were considered core dimensions. The consequence is a reduced number of components and a lack of granularity of the dimensions. Assessors only reviewed the dossier matching their area of expertise, and although this is consistent with the internal organization of many NCAs (i.e., clinical experts focus on the clinical data), our study created an artificial environment in that discussion between clinical, safety, and nonclinical assessors, a vital part of the review process, did not occur. Future research in this area should include a larger number of assessors and an expanded list of dimensions that may reveal other important components, pro- vide greater granularity of the dimensions, and explain a larger proportion of the variability between assessors. In addition, it would be better to focus on one therapeutic area, perhaps with several specific products, and include assessors who have the expertise to contribute to all aspects of the evaluation. Gender differences in risk assessment among evaluators of risk require further research as differences in risk perception were noted for only one medicinal product. This is nonetheless an important finding and requires further exploration as there is a paucity of data on the decomposition of the risk perception among adults when they are involved in making risk assessments

CONCLUSIONS

Regulatory evaluation of medicinal products involves determining the balance between the benefits promised by the product and the attending potential harms. This process requires reviewing the objective data and determining the probability and the magnitude of the harm, but in doing so assessors' belief systems and values are also engaged. The variability among the assessors, that is, differences in how worried they are regarding the safety of the product or differences in the emphasis placed on ethical issues, may influence how they judge the risk of a product. We do not conclude from these results that assessors rely solely on this individual judgment in preparing their assessment reports. Over the course of the 210 days of a product review, an assessor's perception is very likely mediated by gathering additional data from the product manufacturer and through discussions with colleagues who may have similar or divergent perceptions of the product, and it is through this discourse that a final assessment is made.

Nonetheless, the study results indicate evidence of assessor variability, that is, the influence of individual characteristics such as gender and years of regulatory experience on perceived risk and the use of what we believe may be a heuristic—risk is the opposite of benefit. It is conceivable that the introduction of individual perceptions of the potential risks and benefits for a medicinal product assessment could have several undesirable consequences; it could potentially lengthen the drug assessment time as regulators with divergent views try to reach a majority opinion, and it may also lead to inconsistencies in product assessments over time, even within a drug class, as the final opinion may be the result of the risk perception prevailing at the time of the assessment. We believe that the results lend support to the view that assessors of medicinal products may benefit from the use of decision-making tools to increase both internal and external transparency of their risk assessment. As presented in the recent paper by Phillips and others,[37] modeling of the benefit-risk assessment for medicines is possible, but greater efforts and more research may be needed to design the tools appropriate to the needs of the assessors and to integrate them into the current process of benefit-risk evaluation.

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REFERENCES

1. Slovic P, Fischoff B, Lichtenstein S. Rating the risks. Environment. 1979;21(3):14–20.
2. Flynn J, Slovic P, Mertz CK. Decidedly different: expert and public views of risks from a radioactive waste repository. Risk Anal. 1993;13:643–8.
3. Kletz TA. Risk—two views: the public's and the experts'. Disaster Prev Manag. 1996;15:41–6.
4. Fischoff B, Kadvany J. Risk: A Very Short Introduction. New York: Oxford University Press; 2011.
5. Billings RS, Schaalman ML. Administrators' estimations of the probability of outcomes of school desegregation: a field test of the availability heuristic. Organ Behav Hum Perform. 1980;26:97-114.
6. Wallsten TS, Budescu DV. Encoding Subjective Probabilities: A Psychological and Psychometric Review. Research Triangle Park, NC: Report to the Strategies and Standards Division of the U.S. Environmental Protection Agency; 1980.
7. Christensen-Szalanski JJJ, Bushyhead JB. Physicians' use of probabilistic information in a real clinical setting. J Exp Psychol Hum Percept Perform. 1981;7(4).
8. Alhakami AS, Slovic P. A psychological study of the inverse relationship between perceived risk and perceived benefit. Risk Anal. 1994;14:1085–96.
9. Finucane M, Alhakami A, Slovic P, Johnson S. The affect heu- ristic in judgment of risks and benefits. J Behav Decis Mak. 2000(13):1–17.
10. Slovic P, Finucane ML, Peters E, DG MacGregor. The affect heuristic. In: Gilovich T, Griffin D, Kahneman D, eds. Heuristics and Biases: The Psychology of Intuitive Judgment. New York: Cambridge University Press; 2002.
11. Sjoberg L. A discussion of the limitations of the psychometric and cultural theory approaches to risk perception. Radiat Protect Dosimetry. 1996;68:219–25.
12. Sjoberg L. Factors in risk perception. Risk Anal. 2000;20(1): 1–11.
13. Sjoberg L. The allegedly simple structure of experts' risk per- ception: an urban legend in risk research. Sci Technol Human Values. 2002;27(4):443–59.
14. Rowe G, Wright G. Differences in experts and lay judgements of risk: myth or reality? Risk Anal. 2001;21:341–56.
15. Savadori L, Stefania S, Elrado N, Reno R, Finucane M, Slovic P. Expert and public perception of risk from biotechnology. Risk Anal. 2004;20(5):1289–99.
16. Byrnes JP, Miller DC, Schafer WD. Gender differences in risk taking: a meta-analysis. Psychol Bull. 1999;125:367–83.
17. Harris CR, Jenkins M. Gender differences in risk assessment: why do women take fewer risks than men? Judm Decis Mak. 2006;1(1):48–63.
18. Lynn FM. The interplay between science and values in regulat- ing environmental risks. Sci Technol Human Values. 1986;11: 40–50.
19. European Medicines Agency. Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisations Applications of Medicinal Products for Human Use. 2008. (EMEA/CHMP/15404/2007) Accessed at: http: www. ema.europa.eu/Special topics, Benefit-risk Methodology.
20. European Medicines Agency. Benefit-risk Methodology Pro- ject. European Medicines Agency; 2009.
21. Blais A-R, Elke W. A Domain-specific Risk-taking (DOSPERT) scale for adult populations. Judm Decis Mak. 2006;1:33–47.
22. Slovic P, Peters E, Grana J, Berger S, Dieck G. Risk perception of prescription products: results of a national survey. Drug Inform J. 2007;41:81–100.

23. John OP, Naumann LP, Soto CJ. Paradigm Shift to the Integra- tive Big-Five Trait Taxonomy: History, Measurement, and Concep- tual Issues. In: John OP, Robins RW, Pervin LA, eds. Handbook of Personality: Theory and Research. New York: Gilford Press; 2008.
24. Beyer A, Fasolo B, Hillege H, de Graeff P. Risk attitude and personality traits predict perceptions of benefits and risks for medicinal products: A field study of European medical assessors. Value in Health 2015; 18:91-99.
25. Slovic P, Kraus N, Lappe H, Letzel H, Malmfors T. Risk percep- tion of prescription products: report on a survey in Sweden. Phar- maceut Med. 1989;4:43–65.
26. Slovic P, Kraus N, Lappe H, Major M. Risk perception of pre- scription products: report on a survey in Canada. Can J Public Health. 1991;82:S15–S20.
27. European Medicines Agency. Procedures for Marketing Authorization. European Medicines Agency; 2006.
28. Schu¨tz H, Wiedemann PM. Judgments of personal and envi- ronmental risks of consumer products: do they differ? Risk Anal. 1998;18(1):119–29.
29. Hermand D, Karsenty S, Py Y, Guillet L, Chauvin B, Simeone A, et al. Risk target: an interactive context factor in risk perception. Risk Anal. 2003;23(4):821–8.
30. Costello AB, Osborne JW. Best practices in exploratory factor analysis: four recommendations for getting the most from your anal- ysis. Practical Assessment, Research and Evaluation. 2005;10(7):1–9.
31. Fabrigar LR, Wegener DT, MacCallum RC, Strahan EJ. Evaluat- ing the use of exploratory factor analysis in psychological research. Psychol Methods. 1999;4:272–99.
32. Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. N Engl J Med. 2011;364(5):476–80.
33. Miller FG, Rosenstein DL. The therapeutic orientation to clin- ical trials. N Engl J Med. 2003;348(14):1383–6.
34. European Medicines Agency. Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities (EMA/ 121340/2011). 2012.
35. Ganzach Y. Judging risk and return of financial assets. Organ Behav Human Decis Process. 2001;83:353–70.
36. Barke RP, Jenkins-Smith H. Politics and scientific expertise: scientists, risk perception, and nuclear waste policy. Risk Anal. 1993;13:425–9.
37. Phillips L, Fasolo B, Zafiropoulos N, Beyer A. Is quantitative benefit-risk modelling of drugs desirable or possible? Drug Discov Today Technol. 2011;8(1):3-10.

ANNEX 1_QUESTIONNAIRE 1

EMA_Risk Perception_Personal Demographic

1. EMPLOYMENT

Thank you for agreeing to participate in the Risk Perception module of the EMA Benefit Risk Methodology Project. All the answers you provide will be anonymized and kept confidential. The questions in the following questionnaire are not related to specific drug products. There is no correct or incorrect answer. We are interested in general responses regarding risk attitudes. It will take approximately 10-20 minutes to complete this section. By clicking 'Next' you are agreeing to participate in the study.

1. Please indicate the National Competent Authority you represent:

- ☐ Agence Française de Sécurité Sanitaire des Produits de Santé
- ☐ Agencia Española de Medicamentos y Productos Sanitarios
- ☐ Läkemedelsverket
- ☐ College Ter Beoordeling van Geneesmiddelen
- ☐ Medicines and Healthcare products Regulatory Agency
- ☐ Bundesinstitut für Arzneimittel und Medizinprodukte
- ☐ AGES PharmMed
- ☐ Agenzia Italiana del Farmaco
- ☐ Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

2. What term best describes your role within your Agency? (Please tick all that apply)

- ☐ Internal Assessor
- ☐ External Assessor
- ☐ CHMP Member
- ☐ Other

3. What term best describes your role within Agency? (Please tick all that apply)

- ☐ Centralized
- ☐ National
- ☐ Other

4. How long have you occupied your current role?

- ☐ 0-1 year
- ☐ 1-2 years
- ☐ 2-3 years
- ☐ 3-5 years
- ☐ 5 or more years

5. What is your academic qualification? (Please tick all that apply)

- ☐ Medical doctor
- ☐ PhD
- ☐ Pharmacist
- ☐ Other

6. What is (are) your therapeutic area(s) of expertise? (Please tick all that apply)

- ☐ Anti-infectives
- ☐ Cardiovascular Central Nervous System
- ☐ Endocrinology
- ☐ Gastroenterology
- ☐ Haematology and Diagnostics
- ☐ Immunology
- ☐ Metabolism
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Respiratory Rheumatology
- ☐ Vaccines
- ☐ Other

7. In what section of the Marketing Authorisation Application is your expertise most relevant? (Please tick all that apply)

- ☐ Clinical Efficacy
- ☐ Clinical Safety
- ☐ Non-clinical
- ☐ Other

2. DEMOGRAPHICS

8. Are you Male or Female?

☐ Male
☐ Female

9. What is your age category?

☐ Between 20 and 29
☐ Between 30 and 39
☐ Between 40 and 49
☐ Between 50 and 69
☐ Over 60

10. Do you have a family, i.e. children?

☐ Yes
☐ No

Thank you

Thank you for participating in this survey. Your responses are very important and will be kept confidential. Please click 'YES' to lock questionnaire or 'NO' to return and edit you responses.

Survey: EMA_Risk Perception_Classic Psychometric

1. RISK PERCEPTION

In the following pages several medicinal products are shown. Please consider each carefully and provide a response, using a rating scale of 1 to 7, on the riskiness of the products.

1. To what extent would you say that people who are exposed to this item are at risk of experiencing personal harm from it?

Drugs for ulcers	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for AIDS	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Acne medication	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Insulin	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for erectile dysfunction	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for arthritis	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Diet drugs	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Nicotine replacement (patches)	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Herbal medicines	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for asthma	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Vaccines	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Sleeping pills	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Oncology products	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Birth control pills	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for cholesterol	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for Depression	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐

Laxatives	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Blood pressure drugs	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for osteoporosis	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Vitamin pills	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Aspirin	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Smallpox vaccination	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for anxiety	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Biotechnology drugs	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for Alzheimer's disease	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Non-steroidal anti-inflammatory drugs	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Antibiotic drugs	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐
Drugs for epilepsy	Not at all risky ☐	R2 ☐	R3 ☐	R4 ☐	R5 ☐	R6 ☐	Extremely risky ☐

2. BENEFIT PERCEPTION

In the following pages several medicinal products are shown. Please consider each carefully and provide a response, using a rating scale of 1 to 7, on the benefits of the products.

1. In general, how beneficial do you consider this item to be?

Drugs for erectile dysfunction	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Laxatives	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Oncology drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Non-steroidal anti-inflammatory drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Insulin	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for ulcers	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Acne medication	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for asthma	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Birth control pills	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Vitamin pills	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Nicotine replacement (patches)	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Antibiotic drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for anxiety	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for Alzheimer's disease	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for arthritis	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Smallpox vaccination	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for Depression	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for cholesterol	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐

Herbal medicines	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Biotechnology drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Blood pressure drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Vaccines	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Diet drugs	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Sleeping pills	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for AIDS	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Aspirin	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for osteoporosis	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐
Drugs for epilepsy	Not at all beneficial ☐	B2 ☐	B3 ☐	B4 ☐	B5 ☐	B6 ☐	Extremely Beneficial ☐

3. SERIOUSNESS OF HARM

In the following pages several medicinal products are shown. Please consider each carefully and provide a response, using a rating scale of 1 to 7, on the level of harm from use of the following.

3. If an accident or unfortunate event involving this item occurred, to what extent are harmful effects to patient likely to be mild or serious?

Blood pressure drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Nicotine replacement (patches)	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Antibiotic drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for cholesterol	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for ulcers	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Insulin	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for asthma	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Herbal medicines	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for erectile dysfunction	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for AIDS	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Vaccines	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Nonsteroidal anti-inflammatory drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Biotechnology drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for arthritis	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Smallpox vaccination	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for anxiety	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Diet drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐

Drugs for epilepsy	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Sleeping pills	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Aspirin	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for Depression	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for osteoporosis	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Drugs for Alzheimer's disease	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Acne medicines	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Birth control pills	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Oncology drugs	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Laxatives	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐
Vitamin pills	No harm at all ☐	H2 ☐	H3 ☐	H4 ☐	H5 ☐	H6 ☐	Severe harm ☐

4. KNOWLEDGE OF THOSE EXPOSED

In the following pages several medicinal products are shown. Please consider each carefully and provide a response, using a rating scale of 1 to 7, on the knowledge of the risk for those exposed.

4. To what extent would you sat that the risks associated with this item are known precisely to the people who are exposed to those risks?

Smallpox vaccination	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for osteoporosis	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for Depression	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Nonsteroidal anti-inflammatory drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Sleeping pills	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Herbal medicines	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Blood pressure drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for arthritis	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Antibiotic drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Diet drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Biotechnology drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Birth control pills	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Insulin	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Vaccines	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Vitamin pills	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for asthma	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for erectile dysfunction	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐

Drugs for cholesterol	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for anxiety	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Nicotine replacement (patches)	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Acne medicines	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Oncology drugs	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Laxatives	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for ulcers	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for epilepsy	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for AIDS	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Drugs for Alzheimer's disease	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐
Aspirin	Risk unknown ☐	K2 ☐	K3 ☐	K4 ☐	K5 ☐	K6 ☐	Risk known precisely ☐

Thank you

Thank you for participating in this survey. Your responses are very important and will be kept confidential. Please click 'YES' to lock the questionnaire or 'NO' to return and edit your responses.

ANNEX 1_QUESTIONNAIRE 2

1. INTRODUCTION

In this phase of the survey you will base your responses on the pdf file sent to you via email. The information in the attached file is drawn from real life and the aim is to recreate a drug assessment procedure.

2. DRUG SCENARIO

Please complete the questions below after reviewing the pdf file sent to you via email.

***** PDF File for Oncology Case Study*****

***** PDF File for Cardiovascular Case Study*****

***** PDF File for CNS Case Study*****

3. RISK DIMENSION

1. To what extent would you say the patients who are exposed to this product are at risk of experiencing farm from it?

	They are not at risk	R2	R3	R4	R5	R6	They are much at risk
Risk	☐	☐	☐	☐	☐	☐	☐

4. BENEFIT DIMENSION

2. In general, how beneficial do you consider this product to be?

	Not at all beneficial	B2	B3	B4	B5	B6	Very beneficial
Benefit	☐	☐	☐	☐	☐	☐	☐

5. MAGNITUDE OF THE EXPOSURE

3. In your estimation, how many people in the world would be exposed to this product?

	Very few people	M2	M3	M4	M5	M6	Many people
Magnitude of the exposure to the hazard	☐	☐	☐	☐	☐	☐	☐

6. DREAD DIMENSION

4. How much des the patient exposure to this product worry you?

	Not at all worrisome	W2	W3	W4	W5	W6	Very worrisome
Dread	☐	☐	☐	☐	☐	☐	☐

7. LEVEL OF KNOWLEDGE

5. How precise the scientific knowledge of the hazards associated with this product?

	Low knowledge	K2	K3	K4	K5	K6	Very high knowledge
Scientific Knowledge	☐	☐	☐	☐	☐	☐	☐

8. NEW RISK DIMENSION

6. Are the hazards associated with this product new, or old and familiar?

	Very well known	K2	K3	K4	K5	K6	Very new
New risk	☐	☐	☐	☐	☐	☐	☐

9. ETHICAL DIMENSION

7. To what extent does this product pose an ethical dilemma?

	No ethical dilemma	E2	E3	E4	E5	E6	Very important ethical dilemma
Ethical dilemma	☐	☐	☐	☐	☐	☐	☐

10. RISK ACCEPTABILITY DIMENSION

8. To what extent do you think the hazards associated with this product are acceptable to obtain the benefits?

	Not at all acceptable	A2	A3	A4	A5	A6	Definitely acceptable
Risk Acceptability	☐	☐	☐	☐	☐	☐	☐

Thank you

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