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Benefit-risk methodology project

Report on risk perception study module

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List of abbreviations

DOSPERT	Domain Specific Risk Taking
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
EMA	European Medicines Agency
EPAR	European Periodic Assessment Report
FDA	Food and Drug Administration
HTA	Health Technology Assessment
MAA	Marketing Authorization Application
NCA	National Competent Agency
NDA	New Drug Application
NSAIDs	Non-steroidal anti-inflammatory
PCA	Principal Component Analysis
PrOACT-URL	Problem, Objectives, Alternatives, Consequences and Trade-offs
TA	Therapeutic Area
UMCG	University of Groningen

Executive summary

The EMA Benefit-Risk Methodology Project was initiated in 2009 as a part of the recommendations of the Committee for Medicinal Products for Human Use (CHMP) Reflection Paper[1]. Five (5) work packages (WP) were planned of which 3 have already been completed and the relevant reports adopted [2]. A collaborative agreement to provide supportive research activities to the project was agreed with the Department of Epidemiology at the University of Groningen (UMCG) in the Netherlands. This report summarizes the results of a study conducted under the auspices of this collaboration on risk attitudes and risk perception among medical assessors in the European Regulatory Network.

The existing body of research on perception of risk raises several important questions regarding drug regulation within Europe. Does the precautionary principle cause regulators to be biased against risk within the European Regulatory Network? Do drug regulators exhibit consistent tendencies for either risk propensity or risk aversion? Does individual predisposition towards risk explain the divergent views among drug regulators?

There is evidence that differing views of the benefits and risks lead to inconsistencies in the approval of medical treatments between countries. During 1995 to 2010, of a sample of 325 medicinal products (non-generic) approved by the FDA, 4 applications received a negative opinion by the EMA and 46 applications were withdrawn prior to opinion. Further, there are inconsistencies within the European Regulatory network. Assessors reviewing the same drug application may arrive at opposing or divergent views. Between 1998 and 2011 there were 60 applications where the CHMP opinion was positive by majority but not by consensus[1].

EMA BR project results to date

WP 1 showed that with regard to medicinal products, assessors have different views of what is a risk and what is a benefit.

WP 2 surveyed the theoretical frameworks, tools and methodologies which are available in the literature for assessing systematically benefits and risks, both quantitatively and qualitatively. **PrOACT-URL** (Problem, Objectives, Alternatives, Consequences and Trade-offs) is the qualitative framework that is shown to be most comprehensive and theoretically able to encompass decisions dominated by conflicting objectives[2]. PrOACT provides a generic problem structure, which is adaptable to benefit-risk decision making by regulators and the '-URL' encompasses the **u**ncertainty, the **r**isk tolerance of the decision makers and **l**inkage to other decisions.

WP3 provided preliminary results showing that quantitative modelling can be used among drug regulators to integrate scientific data with expert value judgments allowing the rational for the benefit /risk balance to be more transparent, communicable, and consistent.

[1] Committee for Medicinal Products for Human Use Reflection Paper On Benefit-Risk Assessment Methods In The Context Of The Evaluation Of Marketing Authorization Applications Of Medicinal Products For Human Use (EMEA/CHMP/15404/2007)

[2] Work Package 1 (Description of the current practice of benefit-risk assessment for centralized procedure products in the EU regulatory network (adopted December 2009)
Work Package 2 (Applicability of current tools and processes for regulatory benefit-risk assessment (adopted September 2010)
Work Package 3 (Field tests (adopted June 2011)
Work Package 4 (Development of benefit-risk tools and process)in progress
Work Package 5 (Development of training materials)in progress

Present study

For over 3 decades the research on risk perception has supported a theory that experts have a one-dimensional view of risk, i.e., they focus on the probability and the magnitude of a hazardous occurrence, which when combined is reduced to 'expected loss'[3]. Only when outside their area of expertise does subjectivity impact their judgments[4].

The hypothesis of the current study is that assessors in the regulatory environment, are not one-dimensional but multidimensional in their view of risk and that the observed divergence between experts within the regulatory environment is due to subjectivity in the decision making process.

In order to test the above hypothesis a total of 80 assessors from 9 National Competent Authorities (NCA) in Europe with expertise in the therapeutic areas (TA) of Cardiovascular, Oncology and Central Nervous System were invited to participate in a research study. The study was implemented as a web-based questionnaire and launched between June 2010 and October 2010. Three data collection instruments were used: a questionnaire on general risk attitudes and risk perceptions; risk perception of 28 types of medicinal products; and rating of several benefit-risk dimensions using data from mock 'clinical dossiers' in the therapeutic areas stated above. The research aims were to evaluate the above hypothesis by answering the following questions:

(1) Is the risk attitude among medical assessors consistently risk seeking, risk neutral or risk averse?

(2) Is there a relationship between risk attitude and the perception of risk?

(3) Are there dimensions of a medicinal product (benefit or risk) that predict the risk perception of an assessor?

(4) Is there a relationship between risk perception of a specific drug and the demographic characteristics or general risk attitude of an assessor?

Results from the DOSPERT assessment

The results from the Domain Specific Risk Taking (DOSPERT) scale showed that assessors do not have a consistent risk attitude (risk seeking, risk neutral, risk averse) across the 5 life domains measured (social, financial, health/safety, recreational, and ethical). Depending on the context, (such as, social or financial), assessors changed their appetite for risk taking and their perceptions of associated risks. However, the results do show a relationship between risk attitude and risk perception in that assessors have a weak but statistically significant perceived risk averse attitude within 4 of the 5 domains, i.e., the more risky an activity was perceived by the assessors, the less likely they were to engage in it. The lack of a very strong correlation indicates that risky perception of an activity is not the only determinant of whether the assessor would engage in such an activity; however it does give some insight into what we now believe to be a multidimensional mental map of risk among assessors.

Results of the 28 types of medicinal products assessment

Assessors were asked to evaluate a list of 28 types of medicinal products on 4 perception scales: benefit, risk, seriousness of harm to those exposed, and the knowledge of potential harm for those exposed. Oncology products scored the highest on the 'risk perception' scale and on the 'seriousness of harm to patients' scale, while insulin, vaccines and antibiotics had the highest mean scores on the 'benefit' scale. Assessors gave the lowest score for insulin on the' knowledge of the harm' scale, followed by oncology and AIDS medications. Female assessors saw more benefit for almost all the products on the list; the junior assessors (1-3yrs) provided statistically different scores on 3 of the 4 scales measured but for only a few products; safety assessors compared to efficacy assessors reported higher risk scores for almost all the products; there was mixed differences by professional qualification (MD, PhD, Pharmacists).

Our interpretation of the results from all four scales is that in keeping with their role as gatekeepers of medical products assessors view these products as predominantly beneficial with mid to low risks when used appropriately but with the potential for serious harm when misused and they believe that patients are mostly aware of the potential for harm from medicinal products.

Results of the mock 'Dossier' assessment

Assessors were further asked to review a mock 'clinical dossier' for three medicinal products, depending on their area of therapeutic and clinical expertise, and to provide responses on their perception of the risk associated with the product (risk dimension), and seven other dimensions all measured on a seven-point scale. The results from a combined principal component analysis revealed 2 latent components explaining 59% of the total variance. The subsequent regression model, explaining 54% of the variability among the assessors, showed that the assessors' ratings on the risk dimension scale is predicted by perceived worry regarding safety, the magnitude of people exposed to the risk, the ethical issues associated with the drug. These dimensions were inversely correlated to benefit and risk acceptability. The precision of the scientific knowledge or unfamiliarity with the potential risk did not predict the assessors risk dimension responses. In addition, the observed relationship was mediated by gender, the medicinal product under review, and number of years in a regulatory role. Traditionally, assessors are believed to focus only on the probability of the risk and the magnitude of the event when reviewing a potential hazard. These results show, as found in a study among nuclear scientists[5], that risk perception among experts is more complex than previously believed.

Conclusion

The Risk Perception study is an important contribution to the EMA Benefit Risk Methodology project in that it explores individual risk perception systematically with the methodologies of behavioural decision science and surveys. The results increase our understanding of the results of WP 1 which identified differences among assessors in their views of risk and benefit. In the current report it is shown that differences in how risky a drug is perceived may be ascribed to some extent to gender, number of years in a regulatory role, the drug in question, but also and importantly be influenced by specific benefit and risk dimensions.

The study results further supports WP 2, which surveyed theoretical frameworks, tools and methodologies. In this frame-work the 'R' step is crucial and yet neglected by any study in the domain of BR modelling. The data reported here indicate that assessors may be perceived risk averse and in addition, their risk tolerance may be predicted by what is known in behavioural decision sciences as the 'affect heuristic'[6]. Increased awareness of the subjective component of their decision making may help assessors identify situations where their values enter into risk assessments and whether this may introduce biases. The implementation of decision-making support tools could support the regulatory process by: adding transparency; increasing consistency; and improving the current process of group discussion to balance individual attitudes towards risk.

The recommendation of the report is that greater attention should be directed at establishing the risk tolerance of each assessor to allow greater self awareness and self management of his or her tolerance level for risk. Building on the data presented in this report a short tool could be developed to identify where assessors fall on a benefit-risk grid. The differing levels of risk could then be openly discussed within the Rapporteur and Co-rapporteur groups prior to the writing of the assessment reports and 'steps taken to neutralize the subjectivity in risk analyses or qualify the results of their deliberation in light of it'[7]. This tool would provide support to WP 4 which will propose a comprehensive methodology for evaluating benefits and risks using both qualitative and quantitative methods and for WP 5 where training documents for assessors in the use of the new methodology will be developed.

1. Background

1.1. Risk as a social construct

In the past three decades developments in science, medicine, and technology have led to an increase in public concern that the promised benefits bring with them serious potential harm to the environment and to human health. In the area of pharmaceutical regulation there have been several high profile medicinal products withdrawn from the market in recent years. The debates before and after the withdrawals reinforces the 'risk as social construct' theory in that individuals do not share the same views on risk. In order to increase our understanding of why there are divergent views for the benefit-risk balance of a medication and how risk is constructed within different groups or among individuals we turn to the disciplines of behavioural decision theory and psychology.

The identification and characterization of risk is a complex task and is not defined similarly in all contexts[8] [9] [10]. An enduring definition most often applied in science is that risk is a measurable, objective function of the probability of an event and the magnitude of that event. An alternative view of risk proposed by social scientists is that risk is not an objective entity but a social construction [11] [12] [13] [14]. People decide what and how much to fear a hazard to which they are exposed[15]. While the objective component of a hazard remains real, i.e., birth defects in families living near nuclear plants, or number of automobile accidents on the highway, social scientists argue that people make subjective decisions with regard to how dangerous they perceive these hazards and that there are specific characteristics of a hazard that influence risk acceptability[16] [17] [18]. As noted by Mary Douglas[19] 'risk is not only the probability of an event but also the probable magnitude of its outcome, and everything depends on the value that is set on the outcome. The evaluation is a political, aesthetic and moral matter'.

The seminal work by Starr[20], showed that the acceptance of risk among the public was not only based on weighting estimates of risks and benefits, but also included a subjective dimension which he identified as voluntariness, i.e., that people are willing to accept greater risks from voluntary activities (e.g., driving) than for involuntary activities (e.g., food preservatives).There have been many challenges to this work but it began an exploration of the subjective component in the construction of risk and launched a new era of research into an alternate view that risk is not an objective entity but a social construction and within this construction there are multiple dimensions of risk[21] [22].

The sections below will outline the case for 'risk as a social construct' not among laypersons but among medically trained experts. I will argue that like laypersons, experts in this context have a subjective component to their risk assessment of medicinal products which is a combination of their general attitude towards risk and the use of a heuristic or 'gut' feelings' reaction depending on situational factors surrounding the product.

1.2. Are european drug regulators risk averse, risk neutral or risk seeking?

It is very often said that western societies have become 'risk averse' and consequently governing bodies have developed regulations which aim to protect the public from any risk[23]. The label of being 'conservative and risk averse' is often directed at drug regulators when a drug application is rejected or withdrawn from the market[24] [25]. Indeed, regulatory bodies within the EU have as a statutory requirement to operate within the context of the precautionary principle which covers cases "*where [the] scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU*"[26]. Consequently, there are known

regional differences that occur between the experts. During 1995 to 2010, of a sample of 325 medicinal products (non-generic) approved by the FDA, 4 applications received a negative opinion by the EMA and 46 applications were withdrawn prior to opinion. Conversely, of the 504 products approved by the EMA during 1995 to 2010, seven had a Not-Approved status from the FDA at the time of the EMA opinion. One could say that patients in Europe were either protected from the risks or denied the benefits of the drug compared to the patients in the United States depending on one's viewpoint. Further inconsistencies are seen within the European Regulatory Network. Between 1998 and 2011, there were 60 applications where regulators reviewing the same data arrived at divergent views[27].

It remains a challenge for regulators to balance increased public demand for long-term health, longevity, and social acceptance (e.g. obesity) with the scientific uncertainty attending drug development and their ethical responsibility which requires that they err on the side of caution when the harm is scientifically plausible but uncertain. The answer to whether medical assessors/regulators in Europe are risk averse with regard to drug regulation may be determined by evaluating individual assessors' attitude towards risk in general life situations and the relationship, if any, to their benefit or risk judgment of a drug.

1.3. Drug regulators as Uni-dimensional evaluators of risk

Experts focus on probability of harm and magnitude when evaluating risk[28] [29] [30]. There has been a general acceptance of this view in the risk research literature for the past three decades. Only in recent years have a few authors called for a re-examination of the data that laid the foundation for this view and have questioned the methodology, the population groups studied, and the seemingly oversimplified approach to risk perception by experts [31] [32] [33] [34]. The global divergence of opinions on issues such as global warming, biodiversity, waste management, nuclear power, sustainable development, electromagnetic fields, pharmaceuticals, biotechnology and human genetics lends credence to the view that the appetite for risk differs between experts, as well as other stakeholders[35]. If we do not accept the traditional explanations identified by Hammond to explain disagreement between experts (incompetence, venality, ideology) then we are required to examine other possibilities[36].

There is scattered evidence that the mind of the expert in making judgments under uncertainty may be as multi-dimensional as found among the public and when challenged may reveal biases or be shown to rely on cognitive shortcuts known as heuristics. As early as 1959, Goldberg reported that clinical psychologists after reviewing results of the Bender Gestalt test did not outperform their secretaries in diagnosing brain damage[37]. Faust also found that clinical psychologists did not perform as well as the results obtained from simple actuarial analysis and did not improve their performance by synthesizing a wide variety of separate pieces of evidence[38]. In the groundbreaking research of Kahneman and Tversky on heuristics and biases and risk perception, they found that[39]:

1. emotion always overrides logic in the decision-making process
2. people suffer from cognitive dysfunction in making decisions because they never have enough information,
3. people are not risk-averse, they are loss-averse.

In an experiment with a group of statistical experts they found that they used the representation heuristic when making intuitive judgments, i.e., they disregarded prior probabilities and instead predicted outcomes that best represented the data[40] [41].

1.4. Study aim

The hypothesis of this study is that the observed divergence between experts within the regulatory environment, is due to subjectivity in the decision making process. Assessors' perception of the risk and/or

the benefit of the drug is reliant on their risk attitudes, the benefit or risk dimensions by which they judge the drug and individual characteristics such as gender. This study aims to answer the following questions:

(1) Is the risk attitude among medical assessors consistently risk seeking, risk neutral or risk averse?

(2) Is there a relationship between risk attitude and the perception of risk?

(3) Are there benefit or risk dimensions of a drug that predict the drug risk perception of an assessor?

(4) Is there a relationship between risk perception of a specific drug and the demographic characteristics or general risk attitude of an assessor?

This report presents the preliminary findings from the EMA/UMCG research study on risk perception. Additional data analyses will subsequently be reported in peer reviewed journals.

2. Study methods

The study was implemented as a web-based questionnaire and launched between June 2010 and October 2010. There were three phases of data collection. Phase 1: demographic data, Domain Specific Risk Taking scale (DOSPERT), the psychometric scale; Phase 2: Drug Case Study and Risk Benefit Dimensions; Phase 3: The Big Five Jackson Inventory personality test. Due to time constraints the results for Phase 3 will not be presented in this report but will be included in subsequent analyses. During the study period assessors were not allowed to skip questions but could log on and off the website until each successive phase were completed.

2.1. Study population

A total of 80 assessors in nine NCAs in Europe were invited to participate in the study. The assessors with expertise in the therapeutic areas (TA) of Cardiovascular, Oncology and Central Nervous System were invited to participate since expertise in above therapeutic areas were necessary for the second phase of the study; several assessors had expertise covering other therapeutic areas in addition to the ones mentioned. The study population was self-selected as participation was on a voluntary basis and only minimal inclusion/ exclusion criteria based on therapeutic area of expertise were applied.

2.2. Data collection and analysis

There was no imputation of missing data. Demographic variables of assessors who completed Phase 1 and did not continue to Phase 2 or Phase 3 were evaluated for differences between the groups using Fisher's Exact test.

2.2.1. General risk attitude and risk perception

In the first phase of the study, demographic data were collected covering gender, country, age, family status, education level, years in regulatory role, clinical area of expertise (clinical efficacy, clinical safety, non-clinical), and therapeutic area of expertise.

In order to measure individual differences in risk attitudes the Domain Specific Risk Taking scale (DOSPERT)[42] was administered (Appendix A). A number of scales have been developed to capture risk attitudes or behaviour but the DOSPERT was found to be most appropriate to the aims of this study as it captures attitudes towards risk taking within several defined domains (social, financial, health/safety, recreational, and ethical) that encompass general life situations. Individual differences in the health/safety and ethical domains were particularly important to this study as it was considered most relevant to the role of the medical assessors. In addition the DOSPERT scale was considered to be very relevant as it is able to

capture not only the attitude towards risk taking activities but also the measurement of an individual's perception of the riskiness of that activity.

The description of the scale provided by the authors is as follows: The *risk-taking* responses of the 30-item version of the DOSPERT Scale evaluates behavioral intentions -or the likelihood with which respondents might engage in risky activities- originating from five domains of life (i.e., ethical, financial, health/safety, social, and recreational risks), using a 7-point rating scale ranging from 1 (*Extremely Unlikely*) to 7 (*Extremely Likely*). Sample items include "Having an affair with a married man/woman" (*Ethical*), "Investing 10% of your annual income in a new business venture" (*Financial*), "Engaging in unprotected sex" (*Health/Safety*), "Disagreeing with an authority figure on a major issue" (*Social*), and "Taking a weekend sky-diving class" (*Recreational*). The *risk-perception* responses evaluates the respondents' gut level assessment of how risky each activity is, using a 7-point rating scale ranging from 1 (*Not at all*) to 7 (*Extremely Risky*)[43].

2.2.1.1. Data Analysis

For the risk taking and risk perception scales the ratings are added across all items of a given domain subscale to obtain risk taking scores. Higher scores suggest a propensity for greater risk taking in that domain. Similarly for the risk perception scale, item ratings are added across all items of a given subscale to obtain risk perception scores. Higher scores suggest perceptions of greater risk in that domain. As per convention, these subscales are considered as measuring unobserved latent variables[44]. Due to the need to discuss the results in light of previous published work, statistical analytic procedures as found in the literature were applied. Responses were treated as interval variables for the purpose of statistical analysis. However there is no assumption of normality and we have therefore reported non-parametric results where appropriate.

As reported in the DOSPERT publication, the data were categorized in order to describe the attitudes and perception towards risk. Within each domain risk seeking, risk neutral and risk averse categories were created for the risk taking and risk perception scales. Assessors whose subscale score was 1 standard deviation above or below the mean were risk seeking or risk averse respectively, otherwise they were categorized as risk neutral. Across the domains two broad groups were created, general risk attitude and perceived risk attitude. Each assessor was classified as seeking, seeking /neutral, neutral, neutral/ averse, averse, mixed categories based on her/his designation found previously within each of the domains. If an assessor was identified as Risk Seeking within each domain then her/his general risk attitude was categorized as Seeking and similarly for perceived risk attitude.

Frequencies of the risk taking and risk perception by domain are presented. Frequencies of the general risk attitude and perceived risk attitude categories across domains are also presented. Statistical analyses of the correlation between mean risk taking score and mean risk perception score within each domain were assessed and Spearman correlation coefficients are reported. Differences in the risk taking or risk perception score for several demographic variables were assessed using the Kruskal Wallis and the Mann Whitney tests where appropriate.

2.2.2. Risk perception of 28 types of medicinal products

Assessors were given a list of 28 types of medicinal products (Appendix B) and asked to provide ratings using the scales shown in Table 1. The list of products was adapted from the studies conducted by Slovic et al., [45] [46] [47] where laypersons in Sweden, Canada and the United States were given a list of hazards, several of which were medicinal products, and asked to rate these products on five scales covering perception of risk of the product, benefit of the product, the seriousness of harm, the knowledge of the risk for those exposed, and warning signs. In our study we included only four scales as the fifth scale in the Slovic et al, 2007 paper was considered not well understood and did not translate well for our group of respondents.

2.2.2.1. Data analysis

As stated previously, while not ideal to treat ordinal data, such as those obtained from Likert scales, as interval data, in cases where we have done so it is to allow comparison with previously reported analyses. Consequently, mean ratings by medicinal product type were computed and plotted for each scale. We have also reported the data, more accurately, by frequency of the responses. Spearman correlation coefficients for the risk scale and each of the other three scales were computed and statistical significant results reported at the 0.05 level. However, no averaging of the scales across the list of products was carried out as is customary in many risk perception studies. Mann Whitney or Kruskal Wallis methods, which test the null hypothesis that the distributions in two or more samples have identical distribution functions against the alternative that the distributions differ, are considered appropriate for this type of data. Differences between groups were calculated by product for gender, professional qualifications (MD, PhD, Pharmacists, Other), years of regulatory experience (1-2yrs, 2-3yrs, 3-5yrs, 5+yrs) and the clinical area of expertise (clinical efficacy, clinical safety, non-clinical, other).

Table 1. Scales used to rate the list of 28 types of medicinal products

Scales on which the 28 medicinal products were rated
Risk to those exposed 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)
Benefits 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 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)

Adapted from Slovic, P., Peters, E., Grana, J., et al., (2007) Risk Perception of Prescription Products: Results of a National Survey. Drug Information Journal, *vol. 41, pp. 81–100.*

2.2.3. Risk perception measured using a mock 'Clinical Dossier' for 3 drug products

In the second phase of the study, assessors were given a mock 'clinical dossier' for a real drug product from one of three therapeutic areas, Cardiovascular, Central Nervous System or Oncology, consistent with their therapeutic and clinical area of expertise. Data for the mock 'dossier' were adapted from the product dossiers, Day 80 assessment reports and European Public Assessment Reports (EPARs) where available. The result was a shortened version of a real dossier as it would have been time prohibitive to use the original marketing authorization application (MAA) which can run to thousands of pages. Where possible, all product identifying data, such as drug name, manufacturer and dates were removed or substituted. The assessors were asked to review the dossier as they would in a real drug assessment and to rate the drug product on eight scales: risk, benefit, dread or worry regarding safety, magnitude of the exposure, scientific knowledge of the risk, familiarity of the risk, ethical concerns and risk acceptability (Table 2). They were constrained not to consult with their colleagues as the aim of the study was to collect individual responses to the dossier.

2.2.3.1. Data analysis

As the data from the mock 'clinical dossiers' were from three separate therapeutic areas it was important to evaluate whether the assessors' responses for the benefit and risk dimension scales were different by drug, that is, whether the risks for the oncology drug were in actuality more worrisome than those for the cardiovascular drug. In addition a regression model was built for each dimension scale with a categorical variable for therapeutic area as the independent variable and the model results checked for significant differences in the dimension scores between the therapeutic areas. If the F statistic was not significant, that is, the therapeutic area did not predict the responses, the dimension was retained for the principal component analysis. The ratings of seven scales (Table 2) for the mock 'clinical dossier' were then submitted to a principal component analysis with the aim of discovering any latent components underlying the structure of the data that may cause the observed variables to covary. Responding to the criticism by Sjoberg and others[48] [49] that earlier studies inflated the explanatory power of the components by averaging the scale 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 (Figure 6) from the component analysis was used to guide the component selection. The rotation method reported is varimax. The extracted components were later used in a regression analysis with the responses from the Risk Dimension as the dependent variable and the extracted components as the independent variables. The normality assumption for the error term was checked by histograms and P-P plots of the residuals. In addition, a general linear model was used to evaluate the relationship between the risk dimension scores, the components from the principal components analysis along with 3 categorical variables for gender, years in a regulatory role, and a variable representing the 3 medicinal products reviewed. Profile plots of the estimated marginal means were generated to examine the results of the GLM model. All statistical analyses were conducted using SPSS 18.

Ordinal regression analysis was performed in order to further evaluate the relationship between the responses for the Benefit Dimension and the Risk Dimension of the drug reviewed by assessors and their general risk attitude. The risk attitude categories were created in the results from the DOSPERT scale. The five categories were collapsed into two, seeking, seeking/neutral, neutral, mixed as one category and neutral/averse, and averse as the other. All the variables in this analysis were treated as categorical variables and the regression performed to estimate the log-odds of being in category j or beyond. A positive coefficient denotes an association of increases in the predictor variable with higher scores in the dependent variable. A negative coefficient denotes an association of increases in the predictor variable with lower scores in the dependent variable[50].

Table 2. Benefit-Risk Scales used for Rating the Mock 'Clinical Dossier'

Scales on which the mock clinical dossier were rated
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)
Dread 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 know; 7=Very new)

Scales on which the mock clinical dossier were rated
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)

Adapted from Savadori L, Stefania S, Elrado N, Reno R, Finucane M, Slovic P. Expert and Public Perception of Risk from Biotechnology. Risk Analysis. 2004; 20(5):1289-99.

3. Results

3.1. Study population and demographics (appendix d)

Of the 80 assessors enrolled in the study, 94% responded for phase 1; five 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 on after Phase 1. There was no difference found for age, gender, role in the agency, time in role or therapeutic area expertise between the dropouts from Phase 1 and those who continued on to Phase 2 and Phase 3.

As shown in Table 3, the group was equally balanced by gender; the assessors were predominantly older, only 31% were between 39 and 20 years old. The largest proportion of the assessors were medically qualified doctors (38%) followed by PhD (25%). Dual qualification was 13% for MD/PhD while only 3% with dual Pharmacists and PhD qualification. Internal assessors, those who work directly for an NCA, comprised the majority of the group, 76%, while 12% were external assessors who collaborate with the NCA and provide additional expertise. A few members of the Committee for Evaluation of Human Medicines (CHMP) also participated in the study (8%). Table 3 shows the countries which participated, along with the years of in a regulatory role. France had the largest group, 24%, of senior assessors (5yrs +), followed by Germany. Several agencies have a relatively small number of staff and could therefore only provide a limited number of assessors to participate.

3.2. General risk attitudes and risk perception

The results from the DOSPERT scale used to evaluate behavioural intentions, or the likelihood with which respondents might engage in risky activities, within five domains (social, financial, health/safety, recreational, and ethical) are shown in Table 4. Within each domain, for both the risk taking and risk perception scales, assessors were predominantly risk neutral with risk seeking as the next largest category. When risk taking was evaluated across the domains as shown in Table 5, very few, only 2 assessors were risk seeking for all domains and no assessor was risk averse for all domains. Similarly for the perceived risk attitude, only 2 assessors were categorized as being perceived risk seeking for all domains and 2 were perceived risk averse for all domains. There was no consistency found in the assessors' risk attitudes; they changed depending on the domain.

Previous work in this area has shown a relationship between willingness to engage in risky activities depending on how risky the activity is perceived. This was evaluated by a correlation analysis between risk taking in each domain and the corresponding risk perception of the activity. There was weak but statistically significant inverse relationship between mean risk taking score and mean risk perception score (Table 6) for all domains with the exception of the social domain. The more risky an activity is viewed by the assessors, the less likely they are to engage in it. This inverse relationship is interpreted by Weber as evidence of a stable personality trait called perceived risk aversion.

It was of interest to see whether differences were evident for risk taking or risk perception based on country, gender, professional qualifications, or level of years in regulatory role. Very few differences were found; among the countries the only difference was for the risk perception for health/safety domain and for the recreational domain. The mean rank scores were lowest among the Irish in both cases, i.e., lower perception of risk, while the highest ranks, i.e., higher risk perception was reported by assessors in France, Spain, and Portugal (Table 7).Women were less likely than men to engage in the activities measured in the recreational domain and found them more risky than men (Table 8).

The question of whether risk taking or risk perception in a specific domain is related to risk taking or risk perception in any of the other domains was explored. There was a weak but positive correlation between ethical risk taking and risk taking in the financial and health/safety domains (Table 9). There was also a

weak but positive correlation between ethical risk perception and risk perception in all other domains (Table 10). The results here seem to show that the more risk seeking the assessor in terms of ethical activities, the more risk seeking they appeared in the financial and health/safety domains. For perception, the more risk averse their perception in the ethical domain, the more risk averse their perception for all other domains. In other words, the assessors' ethics seems to be related to willingness to undertake risk in other areas of life and also how risky those activities are perceived.

3.3. Risk perception of 28 medicinal products

In this section of the study assessors were given 28 types of medicinal products to rate, on a 7 point scale. The scales covered the risk, the benefit, the seriousness of harm and the knowledge of the risks for those exposed. Frequencies for each of the scales are shown in Tables 11-14. The mean and median scores for each item are given in Table 15. Histogram plots of the mean scores by drug type and scale are shown in Figures 1-4; and a dot-plot showing both the risk and benefit perception of the medicinal products. The dot plot of the benefit and risk scales seem to show an inverse relationship (high benefit- low risk) for several of the medicinal products (Figure 5).

In previous work by Alhakami et al[51], investigators found an inverse relationship between perceived risk and benefit among non-experts and concluded that there is a confounding of the benefit-risk relationship in people's minds; risk is not considered independently from benefit. The higher the risk, the lower the benefit is considered – and vice versa. But it is not ideal to view benefits and risks in this way as each should be judged on its own merits and not as simply an inverse of the other. This is believed to be a heuristic that people use to understand complex situations. It was therefore of interest to see whether what seems to be inverse relationships in the dot plot (Figure 5) was supported by statistical analysis of the risk/benefit scales. Weak, but statistically significant results were found for inverse correlations between benefit and risk for AIDS products, birth control pills, insulin, ulcer products, vaccines, and positive correlations between benefit and risk for Alzheimer's disease and Biotechnology products (Table 16).

The mean judgments of the risk and 'seriousness of harm to those exposed' were positively correlated for the majority of the products. However, the correlations are relatively weak with the strongest (>.5) being Alzheimer's disease products, acne products and ulcer products (Table 17).

There was also a weak but positive correlation between the mean ratings for risk and 'knowledge of the risk for those exposed' for arthritis products, erectile dysfunction products, and an inverse correlation for oncology products (Table 18).

There are several publications which show modest but consistent differences for gender in the evaluation of attitudes towards risk[52] [53]. It was therefore of interest to test if differences by gender exists in the assessor's evaluation of our list of medicinal products. Table 19 showed there was a statistically significant difference in the risk scale for diet products and sleeping pills i.e., women saw higher risks for these types of products. For the benefit scale women saw greater benefit than men for Alzheimer's disease, anxiety, arthritis, asthma, biotechnology, blood pressure, cholesterol, depression, oncology, osteoporosis and epilepsy. They also saw greater 'seriousness of harm' for AIDS and blood pressure medicines. No differences were found by gender for the 'knowledge of the risk for the exposed' scale.

In previous research it has been found that people may differ in their risk attitude or perception of a hazard depending on their professional affiliations[54]. In this study, assessors can be considered to be of the same professional affiliation, however it may be possible that they differ in views of risk by professional qualification, years in regulatory role, or clinical area of expertise (safety or efficacy). In Table 20, results are presented for perception by professional qualifications of Medical Doctor, PhD, Pharmacists, and Other (statisticians, Masters Degree). On the risk scale assessors in the 'Other' qualifications indicated an increased risk for cholesterol products; the PhDs reported an increased benefit for oncology on the benefit

scale; the MDs and Pharmacists reported higher scores for NSAIDs and arthritis respectively, on the 'seriousness of harm' scale; and MDs saw greater harm to the patients for products for acne, while the 'Other' group saw greater harm to the patient for products for epilepsy, oncology and osteoporosis.

In Table 21 we see statistical differences for the years in regulatory role categorized as 1-2 yrs, 2-3 yrs, 3-5 yrs, and 5+ yrs. Assessors in the 2-3 yr. group reported higher risk scores for blood pressure and the 1-2 yr. group reported higher risk scores for oncology products. In the 2-3 yr. group higher benefits for herbal medicines were reported and no statistical differences between the years in regulatory role categories found for seriousness of harm scale. On the scale measuring the assessors' perception of the knowledge of the risks known to the patient, the 3-5 yr. reported higher scores for asthma while the 2-3 yr. group reported higher scores for birth control pills, blood pressure, and ulcer medications while the 1-2 yr. group reported higher scores for cholesterol and osteoporosis.

In several agencies assessors are also divided by their clinical area of expertise. Differences were examined for the categories of Clinical Efficacy, Clinical Safety, Non-clinical, and 'Other'. The clinical safety assessors saw increased risk for several products on the risk scale (Table 22); they reported increased benefit for NSAIDs. The group labelled 'Other' reported higher perception scores for acne medications on the seriousness of harm scale and the clinical safety assessors reported higher scores for Alzheimer's, asthma, insulin and oncology products for 'knowledge of the risk among those exposed'.

3.4. Risk perception for 3 medicinal products

We move from reviewing a general list of medicinal products to three specific products. Assessors were given a mock 'clinical dossier' which contained data for a product within their area of therapeutic and clinical expertise. Cardiologists had data on a product for the treatment of atrial fibrillation, Oncologists received data for a product for the treatment of non-small cell lung cancer, and CNS assessors received data for a product for the treatment of neuropathic pain. Assessors provided ratings for the dossiers using the 8 benefit and risk dimensions shown in Table 2. The results from the regression analysis of the seven scales showed that therapeutic area did not predict the responses on the scales.

Principal component analysis was performed using the entire sample, i.e. no separation or averaging the responses across the therapeutic area. The analysis revealed a 2 component solution, accounting for 59% of the total variance between assessors (Table 23). The scree plot in Figure 6 shows the point at which there is a natural bend in the data where the curve flattens. The components prior to this bend indicate the number of components to be extracted. After rotation, we can see from Table 24 that the first component loaded on the following dimensions: dread or worry regarding safety, magnitude of the exposure, ethics, low benefit and low risk acceptability. The second component loaded on scientific knowledge of the hazards and unfamiliarity of the risk. The components were labelled Seriousness of Harm and Scientific Evidence respectively. The plotted result of the principal component analysis is shown in Figure 7. The robustness of the results were evaluated using a regression model for each of the 7 scales with therapeutic area as the dependent variable and the resulting residuals used in a principal component analysis. The results for the second PCA model were the same as the previous PCA results with 2 components emerging explaining 60% of the data therefore the results from the PCA model 1 are discussed in the remainder of this report.

The results from the PCA model 1 were used in a regression analysis with the risk dimension scores as the dependent variable and the 2 extracted components as the independent variables. The model explained 29% of the variance (adjusted R^2) with a significant relationship between the first component and the risk dimension scores (β=.67; p=.000; 95% CI .395:.944). No statistically significant relationship was found with the risk dimension scores for the drug and the second component (β=-.009; p=.95; 95% CI -283:.266). Assessors judged the risk higher if the drug increased worry regarding safety, had a large magnitude of exposure, posed ethical problems and consequently perceived the drug as having low benefit and low risk acceptability. The low variability explained by the model is in line with previously reported

results from a group of nuclear experts[55]. However, the model of the differences between assessors was improved by using a general liner model and adding several other variables noted in the previous results as being correlated with risk perception, namely gender, years in regulatory role, and the specific drug reviewed. Fifty-four percent (adjusted R^2) of the variability is now explained in the new model. Controlling for Seriousness of Harm (dread, magnitude, ethics) (F=30,443; p=<.001) senior assessors reported higher risk scores than junior assessors (F= 2,925; p=.036). Two-way interaction terms for gender by medicinal product, gender by years in regulatory role and medicinal product by years in regulatory role and one three-way term, gender by product by years in regulatory role were also included in the model. Gender predicted higher risk scores, that is, male assessors saw greater risks than female assessors but only for the cardiology product (F=3,956; p=.029), while gender by years in regulatory role approached but did not achieve statistical significance (F=2,542; p=.058). The profile plot of the estimated marginal means from the GLM model show male assessors reporting higher risk scores compared to female assessors, with the risk scores increasing for both genders among the more senior assessors; however assessors' perception of the risks seem to converge after 3-5 years of regulatory experience (Figure 8).

The results of the ordinal regression model showed no relationship between benefit dimension scores of the drug and risk attitudes identified among assessors using the DOSPERT scale but there was a statistically significant relationship between risk seeking attitude and risk dimension scores of the drug. Those who were categorized as risk seeking were more likely to choose the low risk categories when asked to make a judgment using the risk dimension scale (Table 25).

4. Discussion

Determining the benefit-risk balance of a drug is a complex task and requires assessors to evaluate and synthesize available evidence based on the data provided by the product manufacturer. However, evidence from research in behavioural decision making shows that while humans are good at valuing individual items of evidence, they are less good at synthesizing multiple valuations[56] [57] and in order to simplify complex problems there is a reliance on various heuristic methods which can often leading to biases in judgments[58] [59]. In addition, there maybe one of several theories of risk perception[60] operating among assessors of medical products and it may aid communication both internal and external to the regulatory environment if assessors' perception of risk is made transparent.

Four questions were posed at the beginning of the report:

> (1) Is the general risk attitudes among medical assessors consistently risk neutral, risk seeking or risk averse?
>
> (2) Is there a relationship between general risk attitude and the perception of risk?
>
> (3) Are there benefit or risk dimensions of a drug that predict the risk perception of the assessors, i.e., the responses on the risk dimension scale?
>
> (4) Is there a relationship between risk perception of a specific drug and the demographic characteristics or general risk attitude of an assessor?

The hypothesis that assessors may have a predisposition for a particular risk attitude was evaluated within 5 domains considered to cover many aspects of everyday situations (social, financial, health/safety, recreational, ethical). A consistent risk attitude across all domains, i.e., seeking, averse or neutral, was not observed among the assessors. This is in keeping with other studies where low correlations between risk attitudes in different situations has increased awareness that there are situational determinants which may interact with personality traits to dictate behaviour[61]. However, with regard to the consistency of the perception of risk, the current results are different than reported by Weber *et al.(*2002) where the authors found that laypeople may chose to engage or not engage in a type of behaviour but they were very consistent in their perceptions of risk. In our group of respondents, there was no such consistency in the perceived risk attitude and moreover the results showed a negative correlation between perception and risk

attitude in all domains except social. This would indicate that in general life, the riskier an activity is perceived by assessors, the less likely they would engage in that activity, i.e., their actions with regards to activities is to some degree determined by their perceptions. This discovery then begs the question of what are the factors that influence the risk perception of medicinal products among the assessors.

This question was first evaluated by gathering responses on several rating scales for 28 types of medicinal products. The results highlight a methodological issue common to risk perception research. The use of broadly defined hazards such as grouping several medicinal products under one subheading e.g., cholesterol products or biotechnology products, does not in our opinion provide sufficient information for experts to make a real assessment. Products within the same group may pose different problems in terms of the risks or the benefits and because assessors are accustomed to reviewing very specific data with regard to medicines, this unspecified list may not allow them to rate the products with any precision. This may explain why, with the exception of the risk and seriousness of harm, the results of the correlation analysis between the scales used to measure the 28 types of medicinal products showed no consistent pattern.

A more targeted evaluation of the factors influencing assessors' risk perception of medicinal products was by asking them to rate a mock 'clinical dossier' on eight dimensions and then relating their responses to individual disposition and situational context, that is, the impact of gender, years in regulatory role and the specific medicinal product. The results of this evaluation are in line with those of Sjoberg 2002, where 4 factors (dread, new risk, involuntary risk, and tampering with nature) were found to explain the variability of the risk perception of a group of nuclear experts. Among our group of experts, two components were found to explain 59% of the variability, Seriousness of Harm and Scientific Evidence. The two dimensional plot of the components in Figure 7 show how the dimensions we measured are correlated in the mind of the assessors. When the dread or the worry of the harm from patient exposure to the product, the magnitude of the exposure and ethical concerns are high, then benefit and risk acceptability is low. Similarly, when the precision of the science is high, then issues concerning the newness of the risk are considered low. Surprisingly, only the Seriousness of Harm component was a significant predictor of individual risk perception. This is an important finding given that ideally in their role as regulators, the objective data, the precision of the science or the lack thereof and the attending uncertainties would be expected to be very relevant to how the drug is perceived. One possible explanation may be that in judging the risks associated with the products, assessors believed that the science was well known, not unfamiliar, and therefore there was low or no variability in their responses for these dimensions.

In order to test our hypothesis of the influence of the assessor's 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 product. The extended regression model, which included the main effects of the Seriousness of Harm component, three medicinal products and individual characteristics of gender and years in regulatory role, explained 54% of the variability between assessors. Several important points emerge from these results: variability among assessors is not only explained by an inverse relationship between benefits and risks but also through the interplay of years of regulatory experience, gender and by the context, that is, the specific product under review. The interaction terms in the model adds to the complexity of the relationship between risk perception and individual and situational characteristics but the following picture seems to emerge. Assessors with 5 or more years of experience are more risk averse than junior assessors, that is, they reported higher risk scores. Female assessors seem to report a lower perception of risks, that is they are less risk averse than male assessors. However this result requires further empirical evidence as the difference between the genders was only statistically significant for the cardiology product.

It may be useful to provide some speculation as to the connection between the general risk attitude, the observed negative correlation between risk perception and risk attitude along with the results of the 'mock' dossier. At first glance, risk attitude does not seem to be a personality trait that is stable and can be used to predict the behaviour of an individual within any situation. The results did not show a clear relationship

between general risk attitude (seeking, neutral, averse) as measured by DOSPERT and judgment on the risk perception of the drug in the mock 'dossier' although there is some evidence that those classified as risk seekers saw the drug they reviewed as less risky. However, the results from the DOPSERT scale do show that assessors are perceived risk averse, consequently in situations where assessors perceive a drug to be risky, and it is shown in our results that this perception is mediated by personality traits (gender, regulatory experience), but perhaps more so by situational factors (medicinal product, dread or worry of the harm, magnitude of the exposure and ethical concerns), they may adopt a perceived risk averse attitude. This risk averse attitude may in turn be reflected in their discussions with their colleagues, possibly leading to a more negative assessment in the Day 80 assessment report. As a result assessors may resort to requiring additional data from the Market Application Holder (MAH) as they try to adjust their perception.

The important point to raise here is that additional data from the MAH may not necessarily address the concerns of the assessors if those concerns are predominantly based on individual predisposition towards risk. The results of an internal review of assessors' compliance with the instructions provided in the EMA template/guidance for the Day 80 assessment report can be considered further evidence of the important role the component labelled as 'Seriousness of Harm', plays in the risk perception among assessors. In their assessment of the uncertainties for the benefits and the risks of a product, the worry of the potential harm to the patient seems preeminent as assessors are very compliant in listing the uncertainties but have great difficulty in being explicit about the impact of the uncertainties. For example, they express concerns regarding carcinogenicity, or '*major concerns regarding the dose finding methodology*' however they have difficulty to say what data they are using to support the impact this has on the benefit/risk balance[62]. This information remains implicit and therefore the rational for the regulatory judgment is not communicated in a transparent way. Assessors' compliance with the template guidance has improved following a training workshop provided by the EMA however the impact of the uncertainties for both the benefits and the risks remain one of the least complied with item.

5. Limitations and further research

There were several limitations both in the design of the study which should be highlighted and may provide scope for further research.

While 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. In addition, the observed relationship between the benefit dimension and the risk dimension for the mock 'dossier' may have been influenced by the wording of the questionnaire in that the question measuring the benefit dimension 'how beneficial do you consider this product to be?' may not have been interpreted solely as a question on efficacy but may have been interpreted as general balancing of efficacy and safety. The questionnaire, covering all three 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. For example, by not directing the assessor to assess specific ethical issues in relation to the product, we do not know what ethical dilemma(s) were considered. In addition, assessors only reviewed the dossier matching their area of expertise and while this is consistent with the internal organization of many NCAs, that is, clinical experts focus on the clinical data, our study created an artificial environment in that discussion between clinical, safety and non-clinical assessors, a vital part of the review process, did not occur. Future research in this area should include larger number of assessors using an expanded list of dimensions which may reveal other important components, provide greater granularity of the dimensions and may 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 requires further research as differences in this study 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.

6. Conclusions and recommendations

The EMA in its role as the central agency coordinating the activities of the National Competent Agencies in 27 European countries provided a unique opportunity via the Benefit-Risk Methodology Project to examine the processes currently in use for judging the benefit-risk balance of medicinal products. PrOACT-URL (Problem, Objectives, Alternatives, Consequences and Trade-offs) is the qualitative framework that is shown to be most comprehensive and theoretically able to encompass decisions dominated by conflicting objectives[63]. PrOACT provides a generic problem structure, which is adaptable to benefit-risk decision making by regulators and the '-URL' encompasses the **u**ncertainty, the **r**isk tolerance of the decision makers and **l**inkage to other decisions.

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 clinical data submitted by the product manufacturer and determining the probability of harm and magnitude, but in doing so assessors' belief systems and values are also engaged, giving rise to variability among assessors and contributing to divergent opinions. The picture that has emerged from the study is that assessors are perceived risk averse, that is, the more risky an activity was perceived, the less likely they were to engage in it; that the variability of risk perception among the assessors is dependent on the perception of the seriousness of the harm to the patient, which is in turn predicted by how worried they feel about the potential harms, the number of people this will affect and whether the data presents, for that assessor, an ethical dilemma. Furthermore, when these dimensions are high (worry of the harms, magnitude, ethics), a rule of thumb reaction prevails and the product may be viewed negatively and considered as providing less benefit. Lastly, risk perception may also be dependent on an important interplay between regulatory experience, gender and the medicinal product; senior assessors perceive higher risk than junior assessors, male assessors perceive higher risks than female assessors but this may depend on the product.

We do not conclude from these results that assessors, in preparing their assessment reports, are guided solely by their risk attitude or the high risk equates to low benefit heuristic, only that it exists. Over the course of the 210 days of a product review, an assessor's perception is very likely mediated by group discussion; gathering additional data from the product manufacturer and through discussions with colleagues who may be more or less senior; have similar or divergent attitudes towards risk seeking or risk aversion; or share a similar ethical viewpoint. The final outcome presented to the world is the result of a group effort, but for the individual assessor her/his final view of the drug may be an adjustment from an initial starting point along her/his risk perception continuum.

The evidence of assessor variability, use of a heuristic 'risk is the opposite of benefit', and the interplay of individual characteristics such as gender and years of regulatory experience on perceived risk lends 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. It is vital that when trying to arrive at a decision that assessors understand their own level of risk tolerance, as well as that of others when the decision is made within a group and strive to support the decision with quantitative data. In light of our results, the 'R' representing risk tolerance in the PROACT-URL model is particularly important. The implementation of decision-making support tools could support the regulatory process by: adding transparency; increasing consistency; and improving the current process of group discussion to balance individual attitudes towards risk.

To this end, our recommendations are that a tool be developed to guide assessors in understanding their risk attitude with regard to medicinal products. To strengthen the connection with 'practice', a possibility is

to re-frame 7 of the questions in the Drug Risk Perception scale (see Table 2) and, on the basis of the Component Analysis results (see Figure 7), develop a Drug Risk Perception Plot which could locate each individual on a 2-dimensional space provisionally labelled "Seriousness of Harm" (the x-axis) and "Scientific Evidence" (the y-axis).

The x axis is composed by q3, q4, q7 and the reverse of q8 and q2.

The y axis is composed by q5 and reverse of q6.

These questions could be asked *in advance* of the data intensive assessment exercise, as a way to gauge and make explicit the assessor's 'prior belief' in the drug, which then is updated in light of the data presented in the dossier. This would make explicit one's individual view of the drug, and could even be a factor taken into account to create a team with different prior beliefs and to encourage a well-rounded and balanced discussion.

7. Appendix A

Domain-specific risk-taking (adult) scale – risk taking

For each of the following statements, please indicate the likelihood that you would engage in the described activity or behaviour if you were to find yourself in that situation. Provide a rating from Extremely Unlikely to Extremely Likely, using the following scale:

1	2	3	4	5	6	7
Extremely Unlikely	Moderately Unlikely	Somewhat Unlikely	Not Sure	Somewhat Likely	Moderately Likely	Extremely Likely

Admitting that your tastes are different from those of a friend. (S)

Going camping in the wilderness. (R)

Betting a day's income at the horse races. (F/G)

Investing 10% of your annual income in a moderate growth mutual fund. (F/I)

Drinking heavily at a social function. (H/S)

Taking some questionable deductions on your income tax return. (E)

Disagreeing with an authority figure on a major issue. (S)

Betting a day's income at a high-stake poker game. (F/G)

Having an affair with a married man/woman. (E)

Passing off somebody else's work as your own. (E)

Going down a ski run that is beyond your ability. (R)

Investing 5% of your annual income in a very speculative stock. (F/I)

Going whitewater rafting at high water in the spring. (R)

Betting a day's income on the outcome of a sporting event (F/G)

Engaging in unprotected sex. (H/S)

Revealing a friend's secret to someone else. (E)

Driving a car without wearing a seat belt. (H/S)

Investing 10% of your annual income in a new business venture. (F/I)

Taking a skydiving class. (R)

Riding a motorcycle without a helmet. (H/S)

Choosing a career that you truly enjoy over a more secure one. (S)

Speaking your mind about an unpopular issue in a meeting at work. (S)

Sunbathing without sunscreen. (H/S)

Bungee jumping off a tall bridge. (R)

Piloting a small plane. (R)

Walking home alone at night in an unsafe area of town. (H/S)

Moving to a city far away from your extended family. (S)

Starting a new career in your mid-thirties. (S)

Leaving your young children alone at home while running an errand. (E)

Not returning a wallet you found that contains $200. (E)

Note. E = Ethical, F = Financial, H/S = Health/Safety, R = Recreational, and S = Social.

Domain-Specific Risk-Taking (Adult) Scale – Risk Perceptions

People often see some risk in situations that contain uncertainty about what the outcome or consequences will be and for which there is the possibility of negative consequences. However, riskiness is a very personal and intuitive notion, and we are interested in your gut level assessment of how risky each situation or behaviour is.

For each of the above statements, please indicate how risky you perceive each situation. Provide a rating from *Not at all Risky* to *Extremely Risky*, using the following scale:

1	2	3	4	5	6	7
Not at all Risky	Slightly Risky	Somewhat Risky	Moderately Risky	Risky	Very Risky	Extremely Risky

Blais, A-R. and E. U. Weber. 2006. "A Domain-specific Risk-taking (DOSPERT) Scale for Adult Populations." Judgment and Decision Making, *1*, pp33-47.

Appendix B

List of 28 types of medicinal products

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

Adapted (excluding HRT, Botox injections, allergy products) from Slovic, P., Peters, E., Grana, J., et al., (2007) Risk Perception of Prescription Products: Results of a National Survey. Drug Information Journal, *vol. 41, pp. 81–100.*

Appendix C

I am someone who is…

Big five inventory of personality traits	
Is talkative	Tends to be lazy
Tends to find fault with others	Is emotionally stable, not easily upset
Does a thorough job	Is inventive
Is depressed, blue	Has an assertive personality
Is original, comes up with new ideas	Can be cold, aloof
Is reserved	Perseveres until the task is finished
Is helpful and unselfish with others	Can be moody
Can be somewhat careless	Values artistic aesthetic experiences
Is relaxed, handles stress well	Is sometimes shy, inhibited
Is curious about many different things	Is considerate and kind to almost everyone
Is full of energy	Does things efficiently
Starts quarrels with others	Remains calm is almost every situation
Is a reliable worker	Prefers work that is routine
Can be tense	Is outgoing sociable
Is ingenious, a deep thinker	Is sometimes rude to others
Generates a lot of enthusiasm	Makes plans and follows through with them
Has a forgiving nature	Gets nervous easily
Tends to be disorganized	Likes to reflect, play with ideas
Worries a lot	Has few artistic interests
Has an active imagination	Likes to cooperate with others
Tends to be quiet	Is easily distracted
Is generally trusting	Is sophisticated in art, music , or literature

John, O. P., Donahue, E. M., & Kentle, R. L. (1991). The Big Five Inventory--Versions 4a and 54. Berkeley, CA: University of California, Berkeley, Institute of Personality and Social Research.

8. Appendix D

Table 3. Demographic characteristics of the study population

Variable	Characteristic	Frequency	
Gender	Male	38	
	Female	37	
Age	Between 20 and 29	1	
	Between 30 and 39	22	
	Between 40 and 49	30	
	Between 50 and 59	18	
	Over 60	3	
Professional qualifications	MD	27	
	MD/PhD	11	
	PhD	19	
	PhD/Pharm	3	
	Pharmacist	10	
	Other	5	
Role in NCA	CHMP member	6	
	Internal Assessor	57	
	External Assessor	9	
	Other	3	
Time in role by country	**Country**	**<5 years**	**5+ years**
	France	2	8
	Spain	4	3
	The Netherlands	8	3
	United Kingdom	4	6
	Germany	3	7
	Austria	9	1
	Italy	10	0
	Portugal	1	3
	Ireland	0	3

Table 4. Categories by Risk Taking and Risk Perception within each Domain

Domain	Risk seeking		Risk neutral		Risk averse	
Risk Taking	*Row N=75*	*%*	*Row N=75*	*%*	*Row N=75*	*%*
Social	19	25.3	46	61.3	10	13.3
Financial	14	18.7	47	62.7	14	18.7
Health/Safety	9	12.0	57	71.0	9	12.0
Recreational	12	16.0	51	68.0	12	16.0
Ethical	14	18.7	53	70.7	8	10.7
Risk perception						
	Row N=75	*%*	*Row N=75*	*%*	*Row N=75*	*%*
Social	9	12.0	53	70.7	13	17.3
Financial	13	17.3	48	64.0	14	18.7
Health/Safety	14	18.7	50	66.7	11	14.7
Recreational	13	17.3	46	61.3	16	21.3
Ethical	13	17.3	49	65.3	13	17.3

Table 5. Categories across Domains by General Risk Attitude and Perceived Risk Attitude

	General risk attitude		Perceived risk attitude	
	N=75	%	N=75	%
Seeking	2	2.5	2	2.5
Seeking neutral	26	32.5	28	35.0
Neutral	12	15.0	14	17.5
Neutral averse	24	30.0	25	31.2
Averse	0	0	2	2.5
Mixed	11	13.8	4	5.0

Table 6. Correlation coefficients for Mean Risk Taking score and Mean Risk Perception score by Domain

Domain		
	Spearman Rho	*Significance (0.05)*
Social	-.149	.203

Domain		
Financial	**-.343**	**.003**
Health/Safety	**-.357**	**.002**
Recreational	**-.470**	**.000**
Ethical	**-.350**	**.002**

Table 7. Differences in Risk Perception Score between countries (Krusall Wallis test)

National Agency		Health /Safety perception score			Recreational perception score		
	N=75	Mean rank	Chi Sq	Sig.	Mean rank	Chi Sq	Sig.
France	10	54.05	19.341	**0.013**	43.45	18.115	**0.02**
Spain	7	58.43			57.71		
The Netherlands	11	28.41			33.09		
United Kingdom	10	41.45			27.75		
Germany	10	28.60			29.5		
Austria	10	32.65			34.75		
Italy	10	30.00			44.65		
Portugal	4	46.00			57.88		
Ireland	3	25.67			16.50		

Table 8. Differences in Recreational Risk Taking and Recreational Perception by Gender (Mann Whitney test)

Gender	Recreational risk taking					Recreational perception			
	N=75	Mean rank	Sum of ranks	Mann Whitney U	Sig.	Mean rank	Sum of ranks	Mann Whitney U	Sig.
Male	38	43.62	1657.5	489.5	**0.023**	32.01	1216.5	461	**0.01**
Female	37	32.23	1192.5			44.15	1633.5		

Table 9. Correlation between Ethical risk taking and other risk taking domains and risk perception domains

Domain	Ethical risk taking correlation coefficient (n=75)	
	Spearman rho	*Significance (0.05)*
Risk taking		
Social	.047	.690
Financial	**.282**	**.014**
Health/Safety	**.479**	**.000**
Recreational	.220	.058
Risk perception		
Social	-.098	.403
Financial	-.129	.269
Health/Safety	-.101	.387
Recreational	-.134	.250

Table 10. Correlation between Ethical Perception and Other Risk Taking and Risk Perception Domains

Domain	Ethical perception correlation coefficient (n=75)	
	Spearman rho	*Significance (0.05)*
Risk taking		
Social	-.001	.995
Financial	.064	.587
Health/Safety	-.154	.188
Recreational	-.009	.941
Risk perception		
Social	**.448**	**.000**
Financial	**.227**	**.050**
Health/Safety	**.451**	**.000**
Recreational	**.498**	**.000**

Table 11. Frequencies of responses on the risk scale for 28 types of medicinal products

	1 Not at all risky		2		3		4		5		6		7 Extremely risky	
	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Acne (Risk)	1	1,3%	24	32,0%	15	20,0%	21	28,0%	13	17,3%	0	,0%	1	1,3%
AIDS (Risk)	1	1,3%	3	4,0%	15	20,0%	18	24,0%	21	28,0%	16	21,3%	1	1,3%
Alzheimer's (Risk)	2	2,7%	15	20,0%	26	34,7%	14	18,7%	16	21,3%	2	2,7%	0	,0%
Antibiotic (Risk)	1	1,3%	19	25,3%	27	36,0%	20	26,7%	5	6,7%	2	2,7%	1	1,3%
NSAIDS (Risk)	0	,0%	9	12,0%	27	36,0%	16	21,3%	18	24,0%	5	6,7%	0	,0%
Anxiety (Risk)	0	,0%	5	6,7%	18	24,0%	25	33,3%	18	24,0%	8	10,7%	1	1,3%
Arthritis (Risk)	0	,0%	6	8,0%	18	24,0%	23	30,7%	23	30,7%	4	5,3%	1	1,3%
Aspirin (Risk)	1	1,3%	20	26,7%	22	29,3%	20	26,7%	8	10,7%	4	5,3%	0	,0%
Asthma (Risk)	1	1,3%	15	20,0%	34	45,3%	19	25,3%	5	6,7%	1	1,3%	0	,0%
Biotechnology (Risk)	0	,0%	9	12,0%	18	24,0%	16	21,3%	21	28,0%	9	12,0%	2	2,7%
Birth control (Risk)	3	4,0%	33	44,0%	20	26,7%	14	18,7%	2	2,7%	3	4,0%	0	,0%
Blood pressure (Risk)	1	1,3%	22	29,3%	24	32,0%	17	22,7%	7	9,3%	4	5,3%	0	,0%
Cholesterol (Risk)	0	,0%	24	32,0%	26	34,7%	19	25,3%	6	8,0%	0	,0%	0	,0%
Depression (Risk)	0	,0%	4	5,3%	16	21,3%	30	40,0%	17	22,7%	7	9,3%	1	1,3%

	1 Not at all risky		2		3		4		5		6		7 Extremely risky	
Diet Pills (Risk)	0	,0%	7	9,3%	12	16,0%	19	25,3%	22	29,3%	13	17,3%	2	2,7%
Epilepsy (Risk)	0	,0%	9	12,0%	22	29,3%	25	33,3%	8	10,7%	11	14,7%	0	,0%
Erectile dysfunction (Risk)	3	4,0%	12	16,0%	19	25,3%	21	28,0%	14	18,7%	5	6,7%	1	1,3%
Herbal Meds (Risk)	2	2,7%	23	30,7%	19	25,3%	17	22,7%	9	12,0%	2	2,7%	3	4,0%
Insulin (Risk)	3	4,0%	19	25,3%	19	25,3%	18	24,0%	12	16,0%	3	4,0%	1	1,3%
Laxatives (Risk)	4	5,3%	26	34,7%	19	25,3%	12	16,0%	11	14,7%	3	4,0%	0	,0%
Nicotine patches (Risk)	17	22,7%	32	42,7%	17	22,7%	4	5,3%	4	5,3%	1	1,3%	0	,0%
Oncology (Risk)	0	,0%	0	,0%	4	5,3%	9	12,0%	15	20,0%	30	40,0%	17	22,7%
Osteoporosis (Risk)	1	1,3%	8	10,7%	27	36,0%	19	25,3%	19	25,3%	1	1,3%	0	,0%
Sleeping pills (Risk)	1	1,3%	5	6,7%	18	24,0%	15	20,0%	19	25,3%	11	14,7%	6	8,0%
Smallpox (Risk)	4	5,3%	35	46,7%	12	16,0%	13	17,3%	8	10,7%	2	2,7%	1	1,3%
Ulcers (Risk)	3	4,0%	32	42,7%	23	30,7%	11	14,7%	6	8,0%	0	,0%	0	,0%
Vaccines (Risk)	3	4,0%	35	46,7%	17	22,7%	13	17,3%	3	4,0%	3	4,0%	1	1,3%
Vitamin pills (Risk)	23	30,7%	39	52,0%	6	8,0%	6	8,0%	1	1,3%	0	,0%	0	,0%

Table 12. Frequencies of responses for benefit scale for 28 types of medicinal products

	1 Not at all beneficial		2		3		4		5		6		7 Extremely beneficial	
	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Acne (Benefit)	1	1,3%	6	8,0%	20	26,7%	23	30,7%	20	26,7%	4	5,3%	1	1,3%
AIDS (Benefit)	0	,0%	0	,0%	1	1,4%	2	2,7%	10	13,5%	25	33,8%	36	48,6%
Alzheimer's (Benefit)	5	6,8%	11	14,9%	11	14,9%	15	20,3%	15	20,3%	9	12,2%	8	10,8%
Antibiotic (Benefit)	0	,0%	0	,0%	3	4,0%	2	2,7%	7	9,3%	30	40,0%	33	44,0%
NSAIDS (Benefit)	0	,0%	0	,0%	5	6,7%	17	22,7%	22	29,3%	25	33,3%	6	8,0%
Anxiety (Benefit)	0	,0%	4	5,3%	13	17,3%	20	26,7%	26	34,7%	10	13,3%	2	2,7%
Arthritis (Benefit)	0	,0%	0	,0%	8	10,7%	13	17,3%	27	36,0%	14	18,7%	13	17,3%
Asthma (Benefit)	0	,0%	0	,0%	2	2,7%	3	4,0%	20	26,7%	24	32,0%	26	34,7%
Biotechnology (Benefit)	0	,0%	1	1,3%	6	8,0%	19	25,3%	20	26,7%	23	30,7%	6	8,0%
Birth control pills (Benefit)	0	,0%	1	1,3%	1	1,3%	10	13,3%	14	18,7%	28	37,3%	21	28,0%
Blood pressure (Benefit)	0	,0%	0	,0%	1	1,3%	6	8,0%	16	21,3%	30	40,0%	22	29,3%
Cholesterol (Benefit)	1	1,3%	2	2,7%	7	9,3%	9	12,0%	20	26,7%	27	36,0%	9	12,0%

	1 Not at all beneficial		2		3		4		5		6		7 Extremely beneficial	
Depression (Benefit)	0	,0%	2	2,7%	8	10,8%	17	23,0%	24	32,4%	17	23,0%	6	8,1%
Diet pills (Benefit)	14	18,9%	32	43,2%	20	27,0%	7	9,5%	1	1,4%	0	,0%	0	,0%
Epilepsy (Benefit)	0	,0%	0	,0%	1	1,3%	5	6,7%	16	21,3%	28	37,3%	25	33,3%
Erectile dysfunction (Benefit)	2	2,7%	7	9,3%	19	25,3%	20	26,7%	16	21,3%	9	12,0%	2	2,7%
Herbal Meds (Benefit)	19	25,3%	21	28,0%	26	34,7%	6	8,0%	2	2,7%	1	1,3%	0	,0%
Insulin (Benefit)	0	,0%	1	1,3%	2	2,7%	0	,0%	4	5,3%	21	28,0%	47	62,7%
Laxatives (Benefit)	0	,0%	17	22,7%	22	29,3%	18	24,0%	13	17,3%	3	4,0%	2	2,7%
Nicotine patches (Benefit)	6	8,0%	13	17,3%	15	20,0%	20	26,7%	15	20,0%	5	6,7%	1	1,3%
Oncology (Benefit)	0	,0%	2	2,7%	4	5,3%	7	9,3%	16	21,3%	22	29,3%	24	32,0%
Osteoporosis (Benefit)	0	,0%	5	6,7%	9	12,0%	21	28,0%	20	26,7%	14	18,7%	6	8,0%
Sleeping pills (Benefit)	2	2,7%	6	8,0%	27	36,0%	23	30,7%	14	18,7%	3	4,0%	0	,0%
Smallpox (Benefit)	2	2,7%	5	6,7%	3	4,0%	9	12,0%	10	13,3%	16	21,3%	30	40,0%
Ulcers (Benefit)	0	,0%	0	,0%	4	5,3%	7	9,3%	19	25,3%	30	40,0%	15	20,0%
Vaccines (Benefit)	1	1,3%	0	,0%	0	,0%	5	6,7%	7	9,3%	26	34,7%	36	48,0%

	1 Not at all beneficial		2		3		4		5		6		7 Extremely beneficial	
Vitamin pills (Benefit)	15	20,3%	30	40,5%	15	20,3%	6	8,1%	7	9,5%	1	1,4%	0	,0%

Table 13. Frequencies of responses for the seriousness of harm scale for 28 types of medicinal products

	1 No harm at all		2		3		4		5		6		7 Severe harm	
	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Acne (Serious)	2	2,7%	7	9,3%	21	28,0%	20	26,7%	9	12,0%	10	13,3%	6	8,0%
AIDS (Serious)	2	2,7%	1	1,3%	4	5,3%	15	20,0%	18	24,0%	28	37,3%	7	9,3%
Alzheimer's (	0	,0%	0	,0%	22	29,3%	24	32,0%	11	14,7%	14	18,7%	4	5,3%
Antibiotic (Serious)	1	1,3%	3	4,0%	19	25,3%	18	24,0%	16	21,3%	12	16,0%	6	8,0%
NSAIDS (Serious)	1	1,3%	1	1,3%	14	18,7%	18	24,0%	19	25,3%	18	24,0%	4	5,3%
Anxiety (Serious)	0	,0%	3	4,0%	8	10,7%	20	26,7%	26	34,7%	14	18,7%	4	5,3%
Arthritis (Serious)	0	,0%	0	,0%	7	9,3%	26	34,7%	24	32,0%	14	18,7%	4	5,3%
Aspirin (Serious)	1	1,3%	2	2,7%	13	17,3%	17	22,7%	23	30,7%	13	17,3%	6	8,0%
Asthma (Serious)	0	,0%	2	2,7%	7	9,3%	28	37,3%	21	28,0%	13	17,3%	4	5,3%
Biotechnology (Serious)	0	,0%	1	1,3%	5	6,7%	17	22,7%	18	24,0%	22	29,3%	12	16,0%
Birth control pills (Serious)	4	5,3%	5	6,7%	12	16,0%	15	20,0%	17	22,7%	16	21,3%	6	8,0%
Blood pressure (Serious)	1	1,3%	3	4,0%	13	17,3%	20	26,7%	19	25,3%	16	21,3%	3	4,0%
Cholesterol (Serious)	1	1,3%	5	6,7%	16	21,3%	17	22,7%	25	33,3%	8	10,7%	3	4,0%

	1 No harm at all		2		3		4		5		6		7 Severe harm	
Depression (Serious)	0	,0%	1	1,3%	3	4,0%	22	29,3%	28	37,3%	16	21,3%	5	6,7%
Diet pills (Serious)	2	2,7%	5	6,7%	13	17,3%	20	26,7%	17	22,7%	10	13,3%	8	10,7%
Epilepsy (Serious)	0	,0%	0	,0%	4	5,3%	16	21,3%	26	34,7%	21	28,0%	8	10,7%
Erectile dysfunction (Serious)	1	1,3%	1	1,3%	8	10,7%	19	25,3%	22	29,3%	16	21,3%	8	10,7%
Herbal Meds (Serious)	5	6,7%	17	22,7%	20	26,7%	17	22,7%	8	10,7%	4	5,3%	4	5,3%
Insulin (Serious)	1	1,3%	5	6,7%	4	5,3%	7	9,3%	12	16,0%	22	29,3%	24	32,0%
Laxatives (Serious)	2	2,7%	14	18,7%	23	30,7%	21	28,0%	11	14,7%	3	4,0%	1	1,3%
Nicotine patches (Serious)	4	5,3%	26	34,7%	24	32,0%	14	18,7%	4	5,3%	1	1,3%	2	2,7%
Oncology (Serious)	1	1,3%	0	,0%	0	,0%	3	4,0%	8	10,7%	32	42,7%	31	41,3%
Osteoporosis (Serious)	1	1,3%	5	6,7%	15	20,0%	32	42,7%	15	20,0%	6	8,0%	1	1,3%
Sleeping pills (Serious)	1	1,3%	1	1,3%	12	16,0%	8	10,7%	18	24,0%	23	30,7%	12	16,0%
Smallpox (Serious)	0	,0%	11	14,7%	10	13,3%	15	20,0%	13	17,3%	12	16,0%	14	18,7%
Ulcers (Serious)	1	1,3%	6	8,0%	20	26,7%	20	26,7%	15	20,0%	11	14,7%	2	2,7%

	1 No harm at all		2		3		4		5		6		7 Severe harm	
Vaccines (Serious)	3	4,0%	7	9,3%	12	16,0%	11	14,7%	14	18,7%	14	18,7%	14	18,7%
Vitamin pills (Serious)	12	16,0%	36	48,0%	12	16,0%	10	13,3%	2	2,7%	1	1,3%	2	2,7%

Table 14. Frequencies of responses for knowledge of harm scale for 28 types of medicinal products

	1 Risks unknown		2		3		4		5		6		7 Risks known precisely	
	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Acne Meds (Knowledge)	3	4,1%	8	10,8%	18	24,3%	15	20,3%	14	18,9%	11	14,9%	5	6,8%
AIDS (Knowledge)	13	17,3%	18	24,0%	16	21,3%	12	16,0%	11	14,7%	4	5,3%	1	1,3%
Alzheimer's (Knowledge)	1	1,4%	1	1,4%	10	13,5%	20	27,0%	19	25,7%	18	24,3%	5	6,8%
Antibiotic (Knowledge)	2	2,7%	14	18,7%	12	16,0%	17	22,7%	18	24,0%	11	14,7%	1	1,3%
NSAIDS (Knowledge)	0	,0%	7	9,3%	15	20,0%	16	21,3%	18	24,0%	15	20,0%	4	5,3%
Anxiety (Knowledge)	1	1,3%	3	4,0%	13	17,3%	23	30,7%	19	25,3%	14	18,7%	2	2,7%
Arthritis (Knowledge)	1	1,4%	7	9,5%	19	25,7%	22	29,7%	16	21,6%	7	9,5%	2	2,7%
Aspirin (Knowledge)	4	5,3%	11	14,7%	13	17,3%	12	16,0%	15	20,0%	15	20,0%	5	6,7%
Asthma (Knowledge)	6	8,1%	13	17,6%	21	28,4%	18	24,3%	11	14,9%	3	4,1%	2	2,7%
Biotechnology	2	2,7%	5	6,7%	9	12,0%	15	20,0%	17	22,7%	17	22,7%	10	13,3%

	1 Risks unknown		2		3		4		5		6		7 Risks known precisely	
(Knowledge)														
Birth control pills (Knowledge)	6	8,0%	11	14,7%	14	18,7%	11	14,7%	16	21,3%	15	20,0%	2	2,7%
Blood pressure (Knowledge)	4	5,3%	11	14,7%	10	13,3%	25	33,3%	21	28,0%	4	5,3%	0	,0%
Cholesterol (Knowledge)	2	2,7%	14	18,9%	12	16,2%	20	27,0%	14	18,9%	10	13,5%	2	2,7%
Depression (Knowledge)	4	5,3%	4	5,3%	17	22,7%	20	26,7%	13	17,3%	17	22,7%	0	,0%
Diet products (Knowledge)	1	1,3%	7	9,3%	4	5,3%	10	13,3%	14	18,7%	24	32,0%	15	20,0%
Epilepsy (Knowledge)	7	9,3%	16	21,3%	22	29,3%	14	18,7%	8	10,7%	8	10,7%	0	,0%
Erectile dysfunction (Knowledge)	3	4,1%	4	5,4%	7	9,5%	19	25,7%	22	29,7%	15	20,3%	4	5,4%
Herbal Meds (Knowledge)	6	8,0%	6	8,0%	1	1,3%	6	8,0%	7	9,3%	22	29,3%	27	36,0%
Insulin (Knowledge)	24	32,4%	24	32,4%	9	12,2%	4	5,4%	6	8,1%	5	6,8%	2	2,7%
Laxatives (Knowledge)	3	4,0%	9	12,0%	6	8,0%	12	16,0%	21	28,0%	16	21,3%	8	10,7%

	1 Risks unknown		2		3		4		5		6		7 Risks known precisely	
Nicotine Patches (Knowledge)	5	6,7%	4	5,3%	10	13,3%	18	24,0%	11	14,7%	22	29,3%	5	6,7%
Oncology (Knowledge)	16	21,3%	23	30,7%	10	13,3%	10	13,3%	10	13,3%	3	4,0%	3	4,0%
Osteoporosis (Knowledge)	3	4,1%	7	9,5%	14	18,9%	16	21,6%	16	21,6%	12	16,2%	6	8,1%
Sleeping pills (Knowledge)	4	5,4%	7	9,5%	21	28,4%	14	18,9%	12	16,2%	14	18,9%	2	2,7%
Smallpox (Knowledge)	5	6,7%	11	14,7%	9	12,0%	15	20,0%	13	17,3%	12	16,0%	10	13,3%
Ulcers (Knowledge)	2	2,7%	9	12,0%	13	17,3%	26	34,7%	10	13,3%	13	17,3%	2	2,7%
Vaccines (Knowledge)	4	5.3%	10	13.3%	14	18.7%	20	26.7%	9	12.0%	10	13.3%	8	10.7%
Vitamin (Knowledge)	7	9,5%	9	12,2%	5	6,8%	8	10,8%	10	13,5%	11	14,9%	24	32,4%

Table 15. Means and medians of 4 perception scales for 28 types of medicinal products (means >4 are highlighted by author)

Name of medicinal drug	Risk perception		Benefit perception		Seriousness of harm		Knowledge of those exposed	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Diet products	4.37	4.00	2.31	2.00	4.43	4.00	5.15	6.00
Cholesterol products	3.09	3.00	5.16	5.00	4.28	4.00	3.92	4.00
Laxatives	3.12	3.00	3.59	3.00	3.51	3.00	4.59	5.00
Nicotine replacement	2.32	2.00	3.59	4.00	2.99	3.00	4.49	5.00
Sleeping pills	4.37	4.00	3.67	4.00	5.11	5.00	3.99	4.00
Herbal medicines	3.35	3.00	2.39	2.00	3.45	3.00	5.35	6.00
Ulcer products	2.80	3.00	5.60	6.00	4.11	4.00	4.07	4.00
Alzheimer's disease Products	3.44	3.00	4.12	4.00	4.39	4.00	4.74	5.00
Blood pressure products	3.25	3.00	5.88	6.00	4.51	5.00	3.80	4.00
Vaccines	2.88	2.00	6.19	6.00	4.65	5.00	4.09	4.00
Asthma products	3.20	3.00	5.92	6.00	4.64	5.00	3.43	4.00
Biotechnology products	4.12	4.00	5.01	5.00	5.21	5.00	4.75	5.00
Vitamin pills	1.97	2.00	2.50	2.00	2.53	2.00	4.81	5.00
Smallpox vaccination	2.95	2.00	5.51	6.00	4.63	5.00	4.28	4.00
Epilepsy products	3.87	4.00	5.95	6.00	5.17	5.00	3.32	3.00
AIDS products	4.43	5.00	6.26	6.00	5.11	5.00	3.08	3.00
Aspirin	3.35	3.00	5.05	5.00	4.63	5.00	4.17	4.00
Insulin	3.40	3.00	6.44	7.00	5.48	6.00	2.55	2.00
Acne products	3.33	3.00	3.95	4.00	4.08	4.00	4.11	4.00
Erectile dysfunction products	3.67	4.00	4.01	4.00	4.87	5.00	4.54	5.00
Oncology products	5.63	6.00	5.65	6.00	6.16	6.00	2.95	2.00
Osteoporosis products	3.67	4.00	4.63	5.00	4.03	4.00	4.28	4.00

Name of medicinal drug	Risk perception		Benefit perception		Seriousness of harm		Knowledge of those exposed	
Arthritis products	4.05	4.00	5.15	5.00	4.76	5.00	4.00	4.00
Depression products	4.13	4.00	4.86	5.00	4.93	5.00	4.13	4.00
NSAID	3.77	4.00	5.13	5.00	4.64	5.00	4.41	4.00
Anxiety products	4.12	4.00	4.41	5.00	4.69	5.00	4.41	4.00
Antibiotic products	3.25	3.00	6.17	6.00	4.40	4.00	3.96	4.00
Birth control pills	2.84	3.00	5.73	6.00	4.44	5.00	3.97	4.00

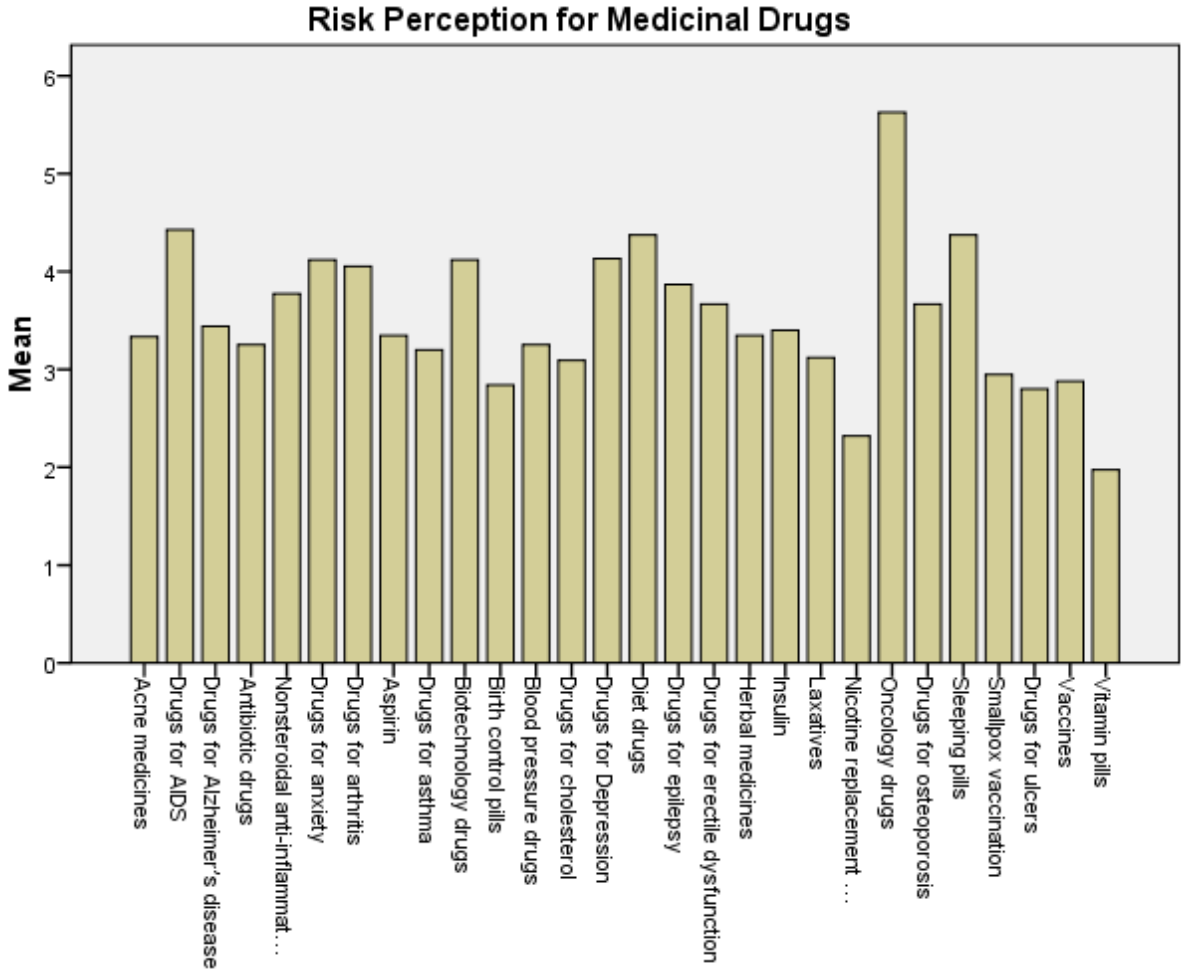

Figure 1. Expert ranking of risk perception of 28 types of medicinal products

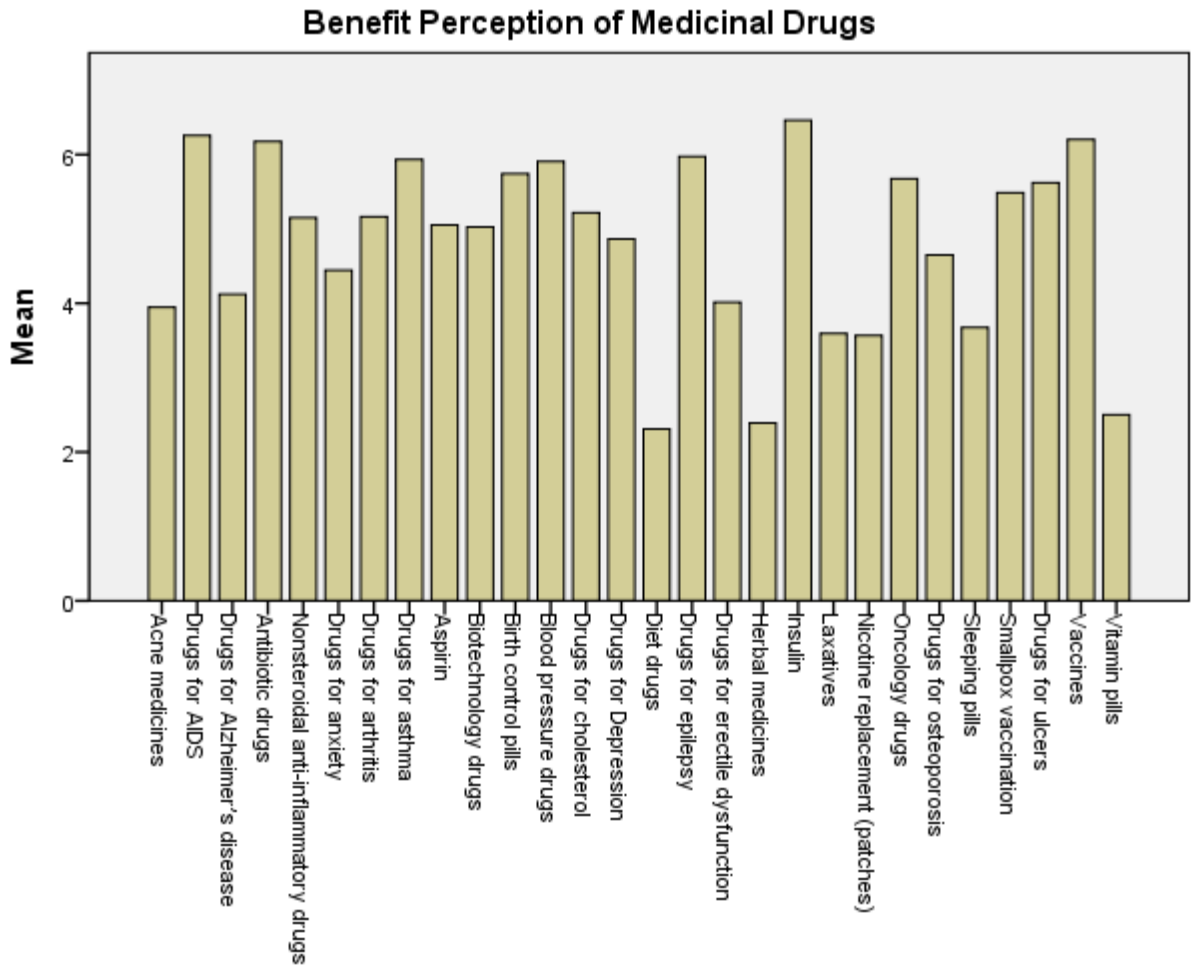

Figure 2. Expert ranking on the benefit perception of 28 types of medicinal products

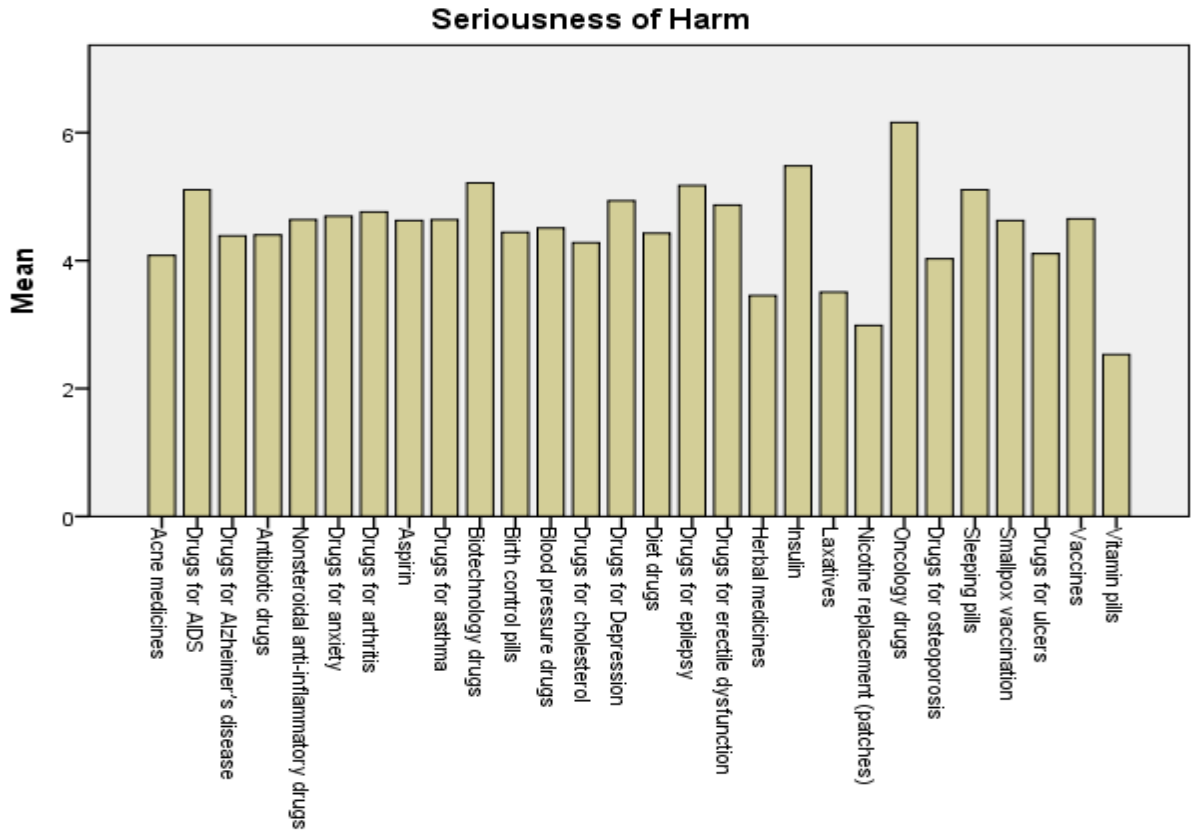

Figure 3. Expert ranking on the seriousness of harm for 28 types of medicinal products

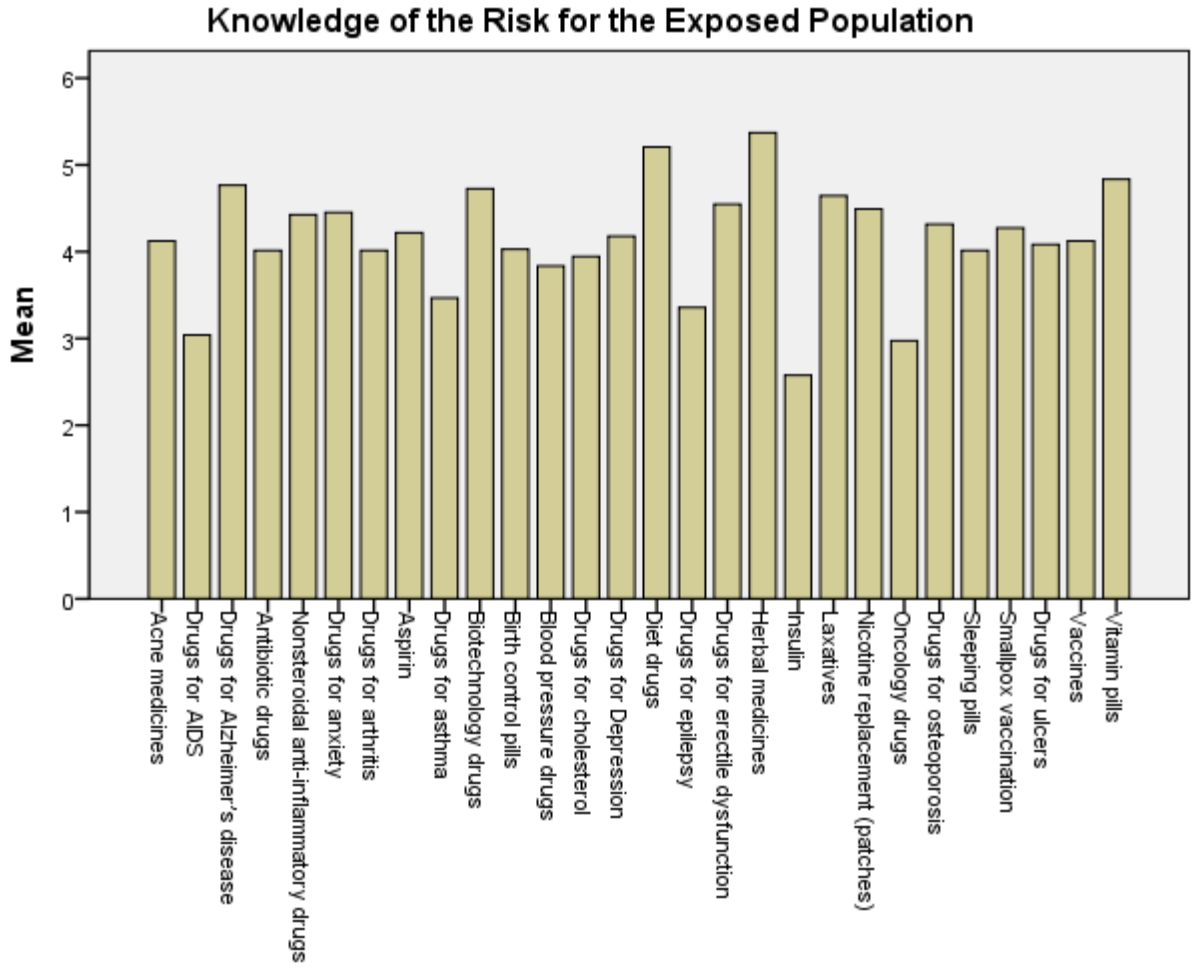

Figure 4. Expert ranking on the knowledge of the risk for those exposed for 28 types of medicinal products

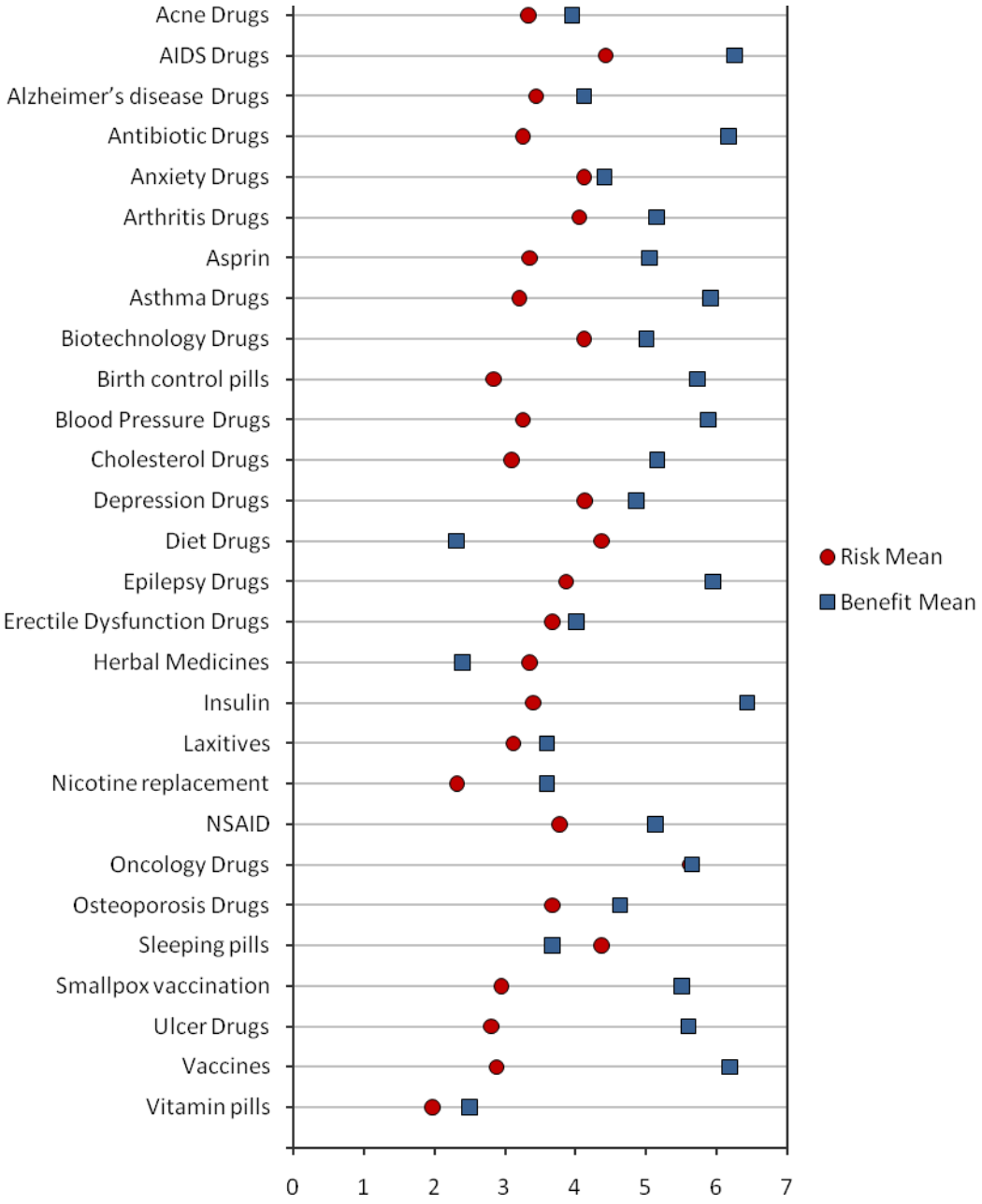

Figure 5. Plot of the means for risk and benefit judgment of 28 types of medicinal products

Table16. Correlations for risk and benefit perception of 28 types of medicinal products

Drug products	Risk and benefit correlation coefficient (n=75)	
	Spearman rho	*Significance (0.05)*
Acne products	.168	.150
AIDS products	**-.256**	**.028**
Alzheimer's disease products	**.266**	**.022**
Antibiotic products	-.146	.212
Anxiety products	.011	.927
Arthritis products	.013	.915
Aspirin	-.019	.873
Asthma products	-.206	.076
Biotechnology products	**.265**	**.022**
Birth control pills	**-.270**	**.019**
Blood pressure products	-.190	.103
Cholesterol products	-.104	.377
Depression products	.054	.646
Diet products	-.180	.276
Epilepsy products	.125	.287
Erectile dysfunction products	.057	.628
Herbal medicines	-.111	.343
Insulin	**-.234**	**.044**
Laxatives	.291	.059
Nicotine replacement	.010	.093
NSAID	.029	.802
Oncology products	-.143	.222

Drug products	Risk and benefit correlation coefficient (n=75)	
Osteoporosis products	-.035	.763
Sleeping pills	-.088	.351
Smallpox vaccination	-.199	.087
Ulcer products	**-.236**	**.041**
Vaccines	**-.303**	**.001**
Vitamins	.136	.247

Table 17. Correlations for risk and seriousness of harm perception of 28 types of medicinal products

Drug products	Risk and seriousness of harm correlation coefficient (n=75)	
	Spearman rho	*Significance (0.05)*
Acne products	**.542**	**.000**
AIDS products	.223	.054
Alzheimer's disease products	**.566**	**.000**
Antibiotic products	**.282**	**.014**
Anxiety products	**.338**	**.003**
Arthritis products	**.261**	**.024**
Aspirin	**.471**	**.000**
Asthma products	**.299**	**.009**
Biotechnology products	**.396**	**.000**
Birth control pills	**.305**	**.008**
Blood pressure products	.061	.602
Cholesterol products	**.248**	**.032**
Depression products	.201	.084
Diet products	**.365**	**.001**
Epilepsy products	**.361**	**.001**
Erectile dysfunction	**.447**	**.000**

Drug products	Risk and seriousness of harm correlation coefficient (n=75)	
Products		
Herbal medicines	**.445**	**.001**
Insulin	**.238**	**.040**
Laxatives	**.378**	**.001**
Nicotine replacement	**.436**	**.001**
NSAID	**.300**	**.009**
Oncology products	**.259**	**.025**
Osteoporosis products	**.403**	**.001**
Sleeping pills	**.309**	**.007**
Smallpox vaccination	**.306**	**.008**
Ulcer products	**.490**	**.000**
Vaccines	**.273**	**.018**
Vitamins	**.244**	**.035**

Table 18. Correlations for risk and knowledge of the harm to those exposed perception of 28 types of medicinal products

Drug products	Risk and knowledge of harm correlation coefficient (n=75)	
	Spearman rho	*Significance (0.05)*
Acne products	-.063	.595
AIDS products	.116	.322
Alzheimer's disease products	.040	.733
Antibiotic products	-.069	.557
Anxiety products	.043	.716
Arthritis products	**.275**	**.018**
Aspirin	.073	.534
Asthma products	.177	.132
Biotechnology products	.043	.715
Birth control pills	-.052	.655
Blood pressure products	.120	.304
Cholesterol products	.005	.965
Depression products	.110	.349
Diet products	.099	.398
Epilepsy products	.104	.376
Erectile dysfunction products	**.313**	**.007**
Herbal medicines	-.011	.923
Insulin	.194	.098
Laxatives	-.103	.912
Nicotine replacement	.016	.890
NSAID	.048	.685
Oncology products	**-.245**	**.034**

Drug products	Risk and knowledge of harm correlation coefficient (n=75)	
Osteoporosis products	.025	.834
Sleeping pills	.024	.838
Smallpox vaccination	.051	.661
Ulcer products	-.121	.301
Vaccines	.118	.131
Vitamins	-.174	.138

Table 19. Mann-Whitney test of differences in mean score by gender (F=*Female;* ^=*higher scores)*

Medicinal drug	Statistical results			
	Mann-Whitney	Wilcoxcon W	Z	Asymp. Sig (2-tailed)
Risk				
Acne	526.500	1267.500	-1.937	.053
Diet pills	452.500	1193.500	-2.726	**.006 F^**
Erectile dysfunction	540.500	1281.500	-1.766	.077
Sleeping pills	511.000	1252.000	-2.079	**.038 F^**
Benefit				
Alzheimer's	387.500	1090.500	-3.254	**.001 F^**
Anxiety	509.000	1250.000	-2.130	**.033 F^**
Arthritis	399.500	1140.500	-3.325	**.001 F^**
Asthma	484.000	1255.000	-2.437	**.015 F^**
Biotechnology	466.000	1207.000	-2.597	**.009 F^**
Blood pressure	492.500	1233.500	-2.350	**.019 F^**
Cholesterol	502.500	1243.500	-2.203	**.028 F^**
Depression	466.000	1169.000	-2.431	**.015 F^**
Epilepsy	472.500	1213.000	-2.573	**.010 F^**
Insulin	550.000	1291.000	-1.895	.058
Oncology	404.000	1145.000	-3.283	**.001 F^**
Osteoporosis	484.500	1225.500	-2.375	**.018 F^**
Ulcers	537.000	1278.000	-1.843	.065
Seriousness				
AIDS	504.000	1245.000	-2.192	**.028 F^**
Biotechnology	537.000	1278.000	-1.810	.070
Blood pressure	485.000	1226.000	-2.370	**.018 F^**
Herbal medicines	540.000	1243.000	-1.768	.077
Sleeping pills	537.000	1278.500	-1.801	.072

Table 20. Krusall Wallis test of differences in mean score by professional qualifications (*M=Medical Doctor, Ph=PhD, P=Pharmacist, O=Other; ^=higher scores*)

Medicinal drug	**Statistical results**		
Risk	**Chi Sq.**	**Df**	**Asym. Sig.**
NSAIDS	7.372	3	.061
Cholesterol	14.298	3	**.003 O^**
Sleeping pills	6.272	3	.099
Benefit			
Oncology	7.959	3	**.047 Ph^**
Ulcers	6.834	3	.077
Vaccines	7.140	3	.068
Seriousness			
NSAIDS	8.776	3	**.032 M^**
Arthritis	9.915	3	**.019 P^**
Blood pressure	7.233	3	.065
Oncology	6.931	3	.074
Knowledge of the exposed			
Acne	13.065	3	**.004 M^**
Epilepsy	11.338	3	**.010 O^**
Oncology	8.018	3	**.046 O^**
Osteoporosis	8.512	3	**.037 O^**

Table 21. Krusall Wallis test of differences in Mean Score by Years of Regulatory Experience (*1-2yrs, 2-3yrs,3-5yrs, 5+yrs; ^=higher scores*)

Medicinal products	**Statistical results**		
Risk	**Chi Sq.**	**df**	**Asym. Sig.**
Blood pressure	13.393	4	**.010 2-3^**
Oncology	9.897	4	**.042 1-2^**
Benefit			
Herbal medicines	10.768	4	**.029 2-3^**
Seriousness			
Acne Meds	9.024	4	.061
Vitamin pills	8.199	4	.085
Knowledge of the exposed			
Asthma	14.621	4	**.004 3-5^**
Birth control pills	9.790	4	**.044 2-3^**
Blood pressure	12.780	4	**.012 2-3^**
Cholesterol	11.913	4	**.018 1-2^**
Insulin	8.246	4	.085
Osteoporosis	12.932	4	**.012 1-2^**
Ulcers	13.382	4	**.010 2-3^**

Table 22. Krusall Wallis test of differences in mean score by clinical expertise (*E=Clinical Efficacy, S=Clinical Safety,N=Non-clinical, O=Other; ^=higher scores*)

Medicinal products	**Statistical results**		
Risk	**Chi Sq.**	**df**	**Asym. Sig.**
NSAIDS	7.555	3	.056
Anxiety	10.034	3	**.018 S^**
Arthritis	9.031	3	**.029 S^**
Asthma	11.725	3	**.008 S^**
Depression	9.869	3	**.020 S^**
Epilepsy	7.916	3	**.048 S^**
Erectile dysfunction	8.526	3	**.037 S^**
Oncology	8.990	3	**.029 O^**
Osteoporosis	8.948	3	**.031 S^**
Sleeping Pills	11.216	3	**.011 S^**
Smallpox	10.962	3	**.012 S^**
Vitamin Pills	13.093	3	**.004 S^**
Benefit			
NSAIDS	8.011	3	**.046 S^**
Diet Pills	7.199	3	.068
Sleeping pills	6.525	3	.089
Seriousness			
Acne meds	8.092	3	**.044 O^**
Knowledge of the exposed			
Alzheimer's	10.209	3	**.017 O^**
Asthma	10.075	3	**.018 S^**
Insulin	12.184	3	**.007 S^**
Oncology	10.159	3	**.017 S^**

Table 23. Output of the component analysis showing eigenvalues, total variance, extracted and rotated sums of the squared loadings

Total variance explained

Component	Initial eigenvalues			Extraction sums of squared loadings			Rotation sums of squared loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2,817	40,248	40,248	2,817	40,248	40,248	2,709	38,703	38,703
2	1,319	18,849	59,098	1,319	18,849	59,098	1,428	20,394	59,098
3	,954	13,629	72,727						
4	,779	11,135	83,862						
5	,566	8,083	91,945						
6	,323	4,610	96,554						
7	,241	3,446	100,000						

Extraction Method: principal component analysis.

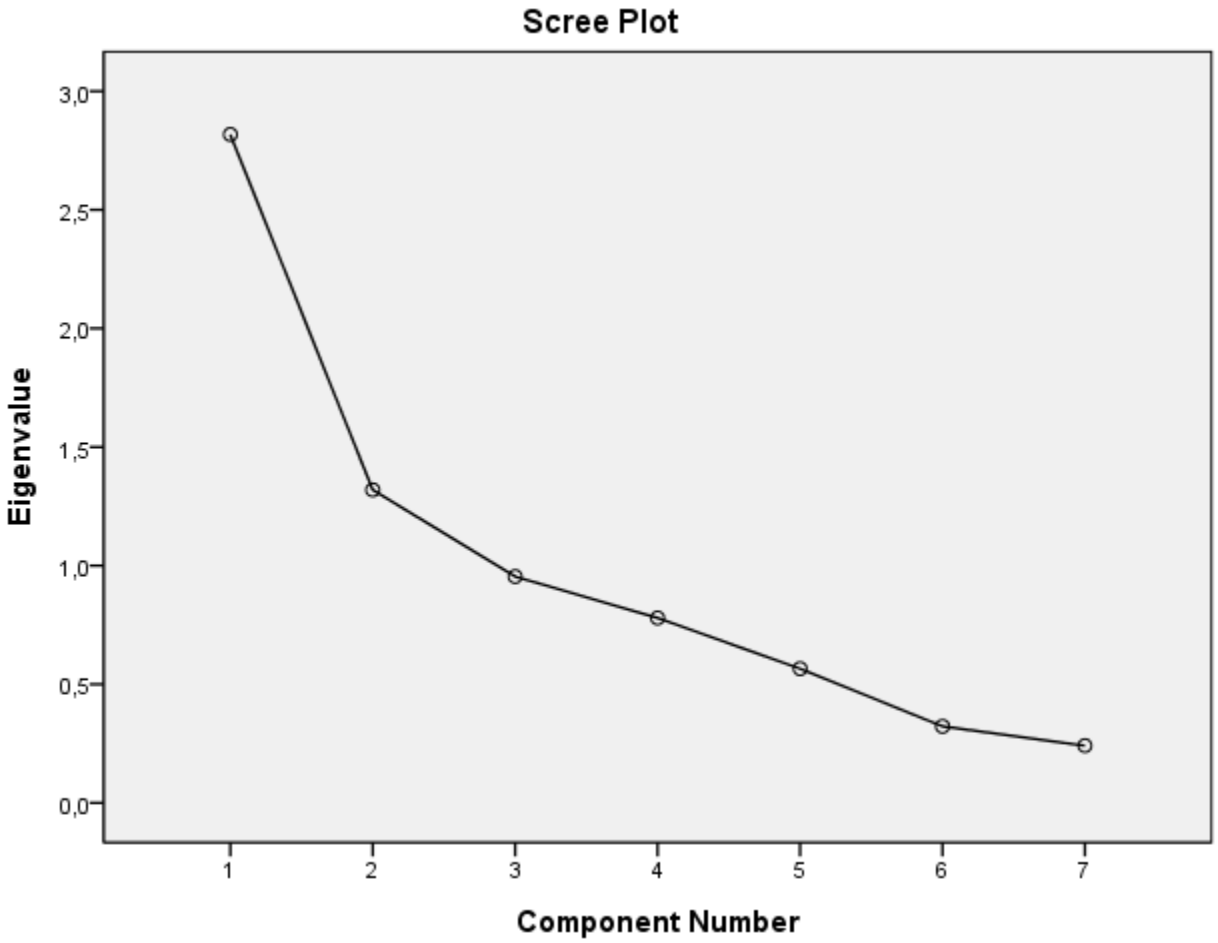

Figure 6. Scree Plot of extracted components

Table 24. Rotated component matrix

	Component	
	1	2
Benefit	-,754	,129
Magnitude	,594	,006
Dread	,735	,118
Scientific knowledge	-,237	,810
New Risk	-,083	-,822
Ethical	,673	-,224
Benefit risk balance	-,855	,125
Extraction method: principal component analysis. rotation method: varimax with kaiser normalization.		
a. Rotation converged in 3 iterations.		

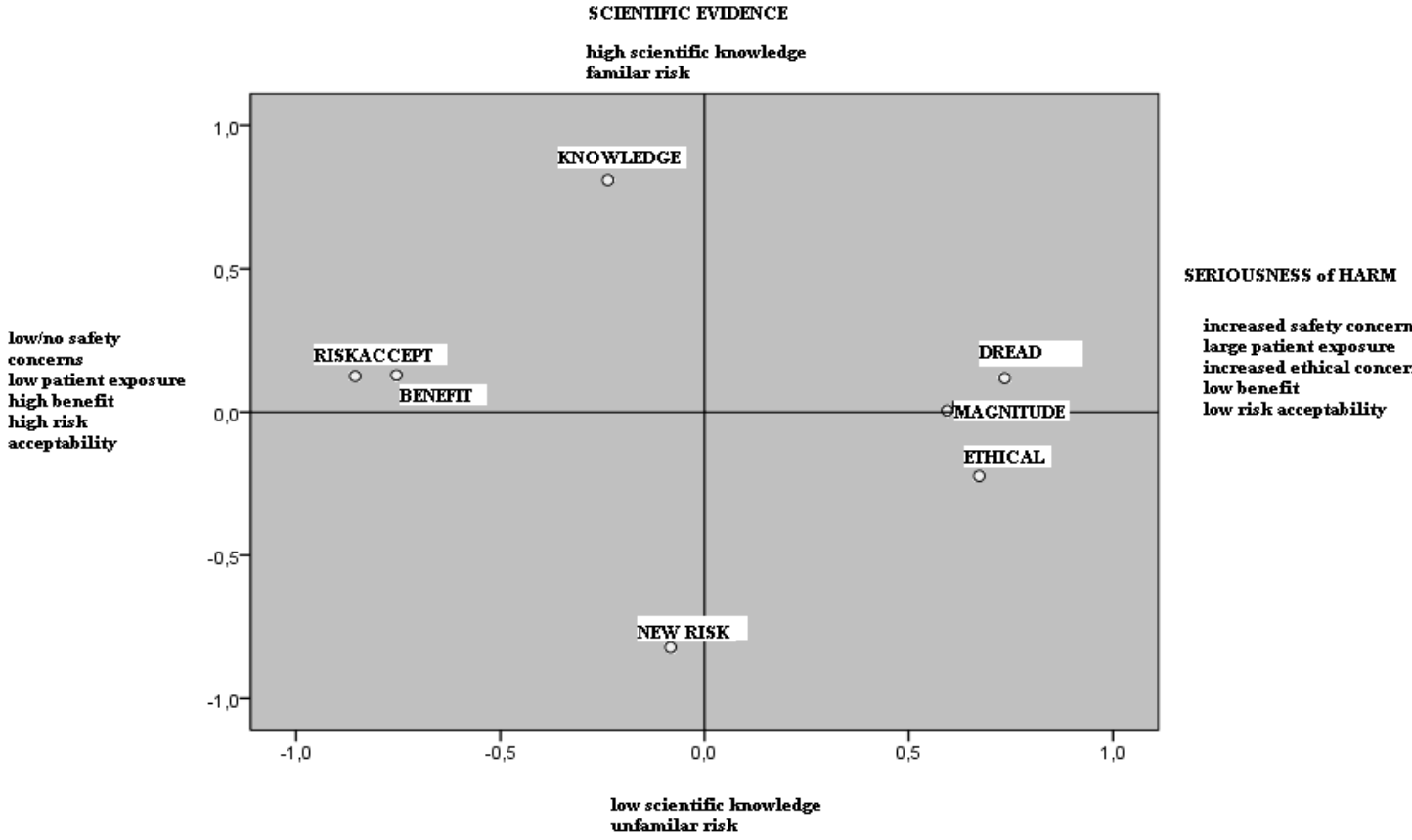

Figure 7. A plot of the components from the PCA model-seriousness of harm and scientific evidence

Figure 8. Estimated marginal means from GLM model by gender and years of regulatory experience

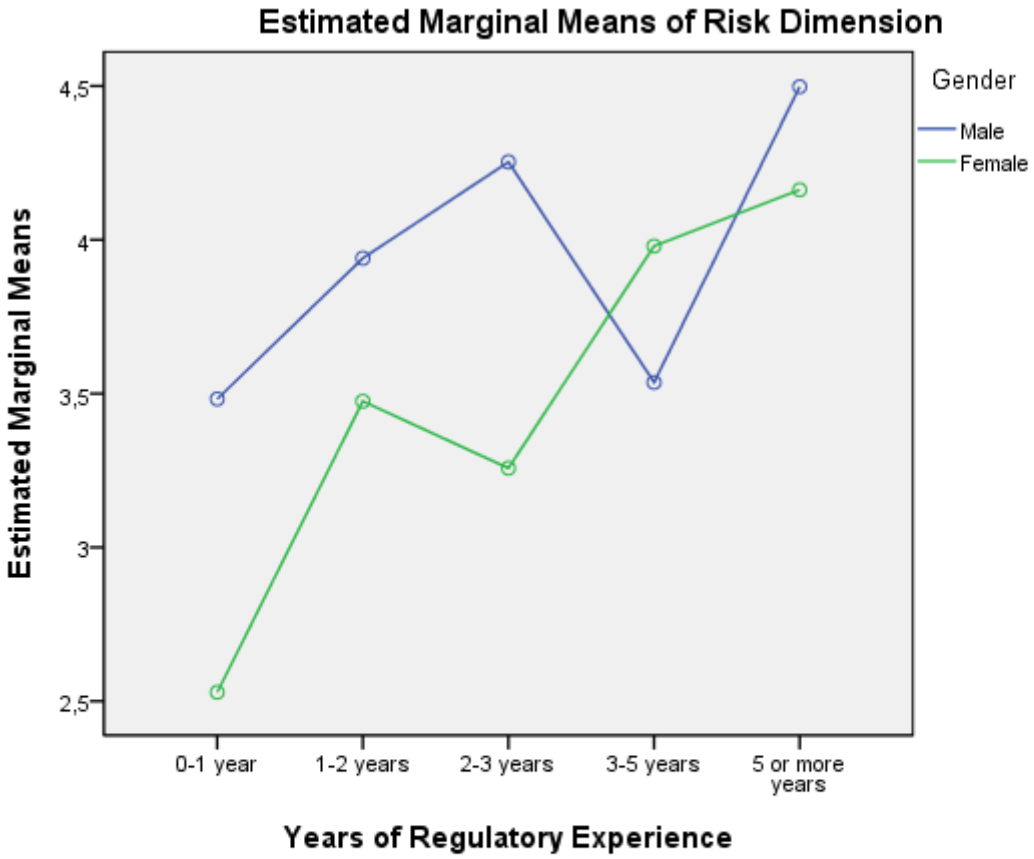

Table 25. Ordinal regression results for benefit perception and risk perception with risk attitude as predictor variable

	Estimate	Std. Error	Wald	df	Sig. (0.05)	95% CI	
Benefit perception							
Not at all beneficial	-2.394	.582	16.923	1	.000	-3.525	-1.254
Somewhat beneficial	.721	.440	2.683	1	.101	-.142	1.585
Neither beneficial nor not	1.380	.474	8.485	1	.004	.451	2.308
Beneficial	3.265	.793	16.941	1	.000	1.710	4.819
Extremely beneficial	0	0	0		0	0	0
Risk attitude							
Seeking/SeekingNeutral/Neutral	-.082	.537	0.23	1	.879	-1.134	.971
Neutral Averse/Averse	0	0	0		0	0	0
Risk perception							
Not at all risky	-4.183	.828	25.515	1	.000	-5.806	-2.560
Somewhat risky	-.989	.441	5.023	1	.025	-1.854	-.124
Neither risky nor not risky	-.224	.421	.283	1	.595	-1.049	.601
Risky	2.296	.641	12.847	1	.000	1.041	3.552
Extremely risky	0	0	0	0	0	0	0
Risk attitude							
Seeking/seeking neutral/neutral	-1.175	.524	5.033	1	.025	-2.202	-.149
neutral averse/averse	0	0	0	0	0	0	0

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