The human dimension in the assessment of medicines

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DISCUSSION AND CONCLUSIONS

If we know all our numbers are likely to be crude, and behave that way, we may even behave sensibly. At least we will have an escape route to follow when we discover we have made a wrong decision. If our numbers are too firm, or if we believe they are firm when they are not, I am afraid we may bully ourselves into doing bad things, efficiently.

Marvin A. Schniederman, 1980

GENERAL DISCUSSION

The aspiration to have reflective and consequently democratic institutions of science as outlined by Beck, Wynne and others has not been realized. After two decades of advocating the need for such a model to govern interactions between scientists and laypeople, social scientists are beginning to wonder if they have overpromised on what could be delivered [1]. This thesis is based on the premise that such a model is still achievable if misconceptions of expert infallibility and non-expert incomprehensibility are debunked and new methodologies for supporting such interactions are allowed to flourish within our scientific institutions. In the concluding sections below, the results of empirical studies conducted among expert and non-expert groups within the field of the regulation of medicines are discussed, and an argument is made for creating a more transparent and democratic regulatory process.

Descriptive Approaches to Decision Making within the European Medicines Agency: *Are European Medical Assessors Uni-dimensional or Multi-dimensional Evaluators of Risk?*

Research in the field of risk perception has promoted an idea that experts focus only on the probability of harm and magnitude when evaluating risk, that is, experts are not swayed, as are laypeople, by cultural values, emotions or use heuristics when assessing risk [2-4]. One of the most voluble critics of this oversimplified approach to the risk perception of experts is Sjoberg [5-8]. In his investigation, he critiqued the type of expert used in the early studies of Slovic et al. The main thrust of his critique that is, only few experts responded to questions of judgement on hazards that were outside their area of expertise and the methods used to analyse the qualitative characteristics of the hazards were analysed across hazards and not across individuals. In a review of choice experiments conducted between 1959 and 1986 among 'experts' in several fields, Morgan and Henrion concluded that '*the [limited] experimental evidence provides no basis for believing that the problems of cognitive bias that can arise in the elicitation of expert subjective judgement are necessarily any less serious than those that have been documented with non-expert subjects*'. They concluded that '*until [other] studies are performed, one can only proceed with care, simultaneously remembering that elicited expert judgements may be seriously flawed, but are often the only game in town*'[9].

Four questions regarding the subjectivity of expert judgment were posed at the beginning of this thesis:

- Are there benefits or risk dimensions of a drug that predict the risk perception of an assessor?
- Do medical assessors have a consistent risk attitude, that is, risk-seeking, risk-neutral or risk-averse?

- Is there a relationship between the risk perception of a drug and individual characteristics, such as personality traits or the general risk attitude of an assessor?
- Do medical assessors exhibit congruency in their views of the benefits and risks of a drug?

The first question was evaluated by gathering responses on several rating scales for 28 types of medicinal products and is reported in Chapter 2.1 The results highlight a methodological issue common to risk perception research. The use of broadly defined hazards, such as cholesterol products or biotechnology products, does not in our opinion provide sufficient information for experts to make a real assessment. However, the results do point to some differences in risk perception by gender, professional qualifications (MD, PhD, other) and years of regulatory experience. While these differences were not seen across all 28 products, it does indicate the need for further exploration of the influence of individual characteristics within this group.

A more targeted evaluation of the factors influencing assessors' risk perception of medicinal products is also reported in Chapter 2.1. In this section of the, the psychometric paradigm made famous by Paul Slovic was applied among the assessors and revealed a mental map of benefits and risks quite similar to that of laypeople. Using the Principal Component Analysis (PCA) methodology, the components seriousness of harm and scientific evidence were found to explain 59% of the variability among assessors. The two-dimensional plot of the components (Figure 5 in Chapter 2.1) shows how the dimensions are correlated in the minds 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. In a regression analysis predicting the risk dimension scores, 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.

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 (Chapter 2.1). 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 add to the complexity of the relationship between risk perception and individual and situational

characteristics, but the following picture seems to emerge. Assessors with five 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.

The hypothesis that assessors may have a predisposition for a particular risk attitude was evaluated within the five domains of the Domain-Specific Risk-Taking (DOSPERT) scale (Chapter 2.2). 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 in which low correlations between risk attitudes in different situations has increased awareness that there are situational determinants that may interact with personality traits to dictate behaviour [10]. However, with regard to the consistency of the perception of risk, the results among the assessors are different than those reported by Weber and others where the authors found that laypeople may choose to engage or not engage in a type of behaviour but were very consistent in their perceptions of risk [11]. 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 the social domain. This would indicate that in general life, the riskier an activity is perceived to be by assessors, the less likely it is they would engage in that activity; that is, their actions with regards to activities is to some degree determined by their perceptions. In a comparison between the results of Weber's study and the current results, it would appear that assessors are more sensitive to their risk perceptions than laypeople.

In order to complete the picture of the mental map of assessors with regards to benefits and risks, Chapter 2.3 measured the degree of consensus within the group for the main benefits and risks associated with the drug they were asked to review. A critique of the approach used in the European Medicines Agency Benefit Risk (EMA BR) Project in Work Package 1 was that the assessors were asked to state generally what was a benefit and what was a risk. It is difficult to see how assessors could provide congruent responses when asked the question about benefits and risks in such a general way. The benefits and risks of a drug are in many cases specific to the drug under review; therefore, an assessment of the congruency or incongruence of assessors can only be made if they are reviewing the same information. Given 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, it is clear that the appetite for risk differs between experts [12]. The field of risk regulation in

medicines is no different. Between 1998 and 2011, there were 60 applications where regulators reviewing the same data arrived at divergent conclusions [13]. From 1995 to 2010, of a sample of 325 non-generic medicinal products approved by the FDA, four 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 from 1995 to 2010, seven had a 'not approved' status from the FDA at the time of the EMA opinion [13]. 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 US, depending on one's viewpoint. The existence of these divergent viewpoints is again borne out in the results of Chapter 2.3 in which there was some but not overwhelming consistency among assessors for risks and low consistency for the main benefits. It can be argued that the individual characteristics (gender, experience, personality traits and risk attitudes) reported in Chapter 2.1 and Chapters 2.2 influence the perceptions of the assessors, as is known to occur with laypeople, leading to lack of congruency in their perception of both the benefits and the risks of a specific drug.

It may be useful to provide some discussion as to the connection between Chapter 2.1-2.3, that is, the general risk attitude and the observed negative correlation between risk perception and risk attitude, along with the results of the 'mock' dossier. At first glance, general risk attitude does not seem to be a personality trait that is stable or that can be used to predict the behaviour of an individual in 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 to be 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 and 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/positive assessment in the Day 80 and subsequent assessment reports.

Prescriptive Approaches to Decision-Making within the European Medicines Agency

Determining the benefit–risk balance of a drug is a complex task and requires the evaluations and synthesis of the 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 not

as good at synthesizing multiple valuations [14, 15], and in order to simplify complex problems there is a reliance on various heuristic methods that can often lead to biases in judgments[16, 17].

In 2009, based on the findings of an audit identifying 'poor understanding of how regulatory decisions are made', the EMA in collaboration with the Committee for Medicinal Products for Human Use (CHMP), launched a three-year research initiative with the aim of improving the consistency, transparency and communication of the benefit–risk assessment in CHMP assessment reports. Five (later six) countries sponsored the project by providing members to form a steering committee to oversee the deliverables of the project [18]. Five (5) work packages (WPs) were planned, of which three have already been completed and the relevant reports adopted [1]. This thesis was conducted under the auspices of the EMA BR Project, and some of the results are reported here.

Chapter 3.1 presents the output of the EMA BR Project at the time of publication, including an illustration of a quantitative model, multi-criteria decision analysis (MCDA), applied to regulatory decision-making. In answer to the question posed in the chapter title, the field studies among the six participating agencies showed that a quantitative approach can be used in supporting the drug assessment process; whether it is desirable would depend on the agencies gaining additional experience with the concepts inherent to such models. At the end of the three-year project, the EMA had adopted the four-fold model shown in Table 1, Chapter 3.1 and concluded that the use of a qualitative framework such as proposed in Table 2 could be integrated into the current assessment and required further exploration. However, the application of an MCDA model, while allowing for greater precision of the decision with its focus on eliciting value judgments and weights from key decision makers and allowing for sensitivity analysis, was considered to be more appropriate in cases of new and complex situations. To date, no MCDA model has been used to support a regulatory decision.

The main drawback of a wider/fuller acceptance of the use of such a model has several elements: the continued intractability of the system despite the acknowledgement that the process of benefit–risk assessment remains implicit and shrouded in mystery; a

1 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)

poor understanding of the methodology, that is, elicited values and weights as inputs for the model appear to be 'too' subjective and the practical difficulties of conducting a decision conference for each new drug application. The EMA and the CHMP have instead continued to explore the use of the PROACT-URL framework, with the Effects Table as the tangible output. The Effects Table is appealing in that it is a compact presentation of salient findings of the clinical data, is simple to build and communicate, achieves a certain level of transparency and can be integrated into current regulatory processes. While the Effects Table achieves some of the goals of the EMA Benefit Risk Methodology project, it is limited in several respects; it does not provide for managing the inherent uncertainty in the clinical parameters, there is no transparency of the regulators' preferences and it has limited or no capacity to appropriately summarize data from multiple studies.

In 1998, the Council for International Organizations of Medical Sciences (CIOMS) Working Group IV published a landmark document that presented a standardised methodology for reassessing the established benefit–risk relationship of a marketed drug when a new safety problem arises [19]. However, after 15 years, a substantial part of the vision of the CIOMS Working Group IV remains unachieved, most notably '*including metrics for weighting the relative severity /seriousness of different adverse drug reactions (…), [the] use of formal decision theory in the decision-making process.*' While it is encouraging that with the Effects Table some progress has been made towards the use of a structured framework to aid decision making, it cannot be said that much has changed since the EMA 2004 audit of the assessment process.

Measuring Regulator and Patient Preferences using the MACBETH Approach: Hitting the Notes and Playing the music?

In 2006, Brian Wynne wrote of the continued public mistrust of scientific institutions and stated that the institutions had failed to engage with the public and with social scientists in the building of reflexive institutions [20]. In his essay, Wynne criticises science policy institutions for engaging the public at a procedural level but missing the chance for reflexive dialogue, that is, hitting the notes but missing the music. In the area of regulatory decision making for medicines, several patient-focused initiatives have been launched that appear to support Wynne's criticism. Since 2006, the EMA has initiated several patient-focused strategies: a standing working party with patient representatives and consumers; inclusion of patient representatives' input for scientific and other advisory groups and permanent non-voting patient representatives on some committees. While laudable, none of these strategies allows for full participation in the decision process, thus failing to achieve meaningful public involvement. In the US, the fifth authorization of the FDA PDUFA encourages the inclusion of the patient perspective

in drug development by issuing guidance on the use of patient-reported outcomes (PROs) in drug development and by collaboration with the Critical Path Institute and industry to form the PRO Consortium, with the aim of developing robust symptom-measurement tools [21]. Additional initiatives under PDUFA V include the Patient Participation in Medical Product Discussions and the Patient-Focused Drug Development program [22, 23]. Both initiatives seek to involve patients either as employees of the FDA providing their expertise from the patient perspective or as participants in disease-specific 'town hall' meetings.

In both regulatory agencies, the emphasis to date (prior to PDUFA V) has focused on a one-way dialogue, with the expertise resting firmly among the regulators. Recent evidence from the FDA shows new emphasis on gathering input from patients and acknowledges the need to shift to a two-way dialogue. During the FDA CDRH Patient Preferences Initiative Workshop in September 2013, the following methodological challenges were raised: what to measure, how to measure and when to measure [24]. PRO instruments have for many years been the means of engaging patients; however, while useful for measuring the patients' experiences after receiving the intervention (medicine or device), PROs do not indicate what the patients' preferences are (based on current knowledge) or would be (if the knowledge changes). Determining patient preferences therefore requires new questions to be asked of patients, but what are the questions and how to ask them? This is succinctly summed in the transcript of the FDA CDRH 2013 workshop: '*The methods matter. How do you ask a question? You obviously don't want to ask a leading question of the patient. You don't want to ask the healthcare equivalent of "when did you stop beating your wife?" You really want to ask [the patient] what is most important to [them]. What risks are you willing to take? And do you understand the risks? Can we provide more information to put those risks in context so you can really give us an honest and considered opinion about what you are looking for in your clinical options?*'

Chapters 4.1 and 4.2 present the results of a study, conducted among multiple sclerosis patients, medical assessors and CHMP members, where a novel approach for the elicitation of preferences was used. The Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH) approach, as described in Chapter 4.1 is a multi-criteria analytic model that presents an important advance over current methods used to collect preferences. It meets the criteria advocated in Chapter 3.1 of '*logical soundness, comprehensiveness, acceptability of results, practicality and usefulness*'[25]. Restructured for the purpose of this thesis with a user-friendly interface and made available as an online questionnaire, preferences can now be captured via MACBETH across a wide geographic area, can be deployed at different timepoints during the lifecycle of a drug, can be used to elicit preferences among patients and regulators and can provide transparent granular

results of patients' value judgments and subsequent treatment choices. As shown in Chapter 4.1, the capture of individual risk profiles (risk attitudes) can allow for further statistical analysis that may identify different risk profiles among subgroups of patients. Chapter 4.2 showed that from the results of this model regulators could gain insight into the patient perspective in several ways: knowledge of what group of patients would be willing to undertake a given level of risk for a given level of benefit, at what point the risk profile of the regulators deviates from those of the patients, which of the drug alternatives on the market would the majority of patients be willing to choose and at what level of increased risk does the patients' choice pattern differ from their own.

Borrowing from the six-step process recommended by Ethan Basch for patient-centred drug development, Table 1 below outlines the what, who and when for inclusion of patient preferences in the regulatory process.

Lessons Learned and Future Avenues for Research

The EMA in its role as the central agency coordinating the regulatory activities of the 31 Member States of the European Union provided a unique opportunity via the Benefit–Risk Methodology Project to examine the processes currently in use for assessing the benefit–risk balance of medicinal products. Regulatory evaluation of medicinal products involves determining the balance between the benefits promised by the product and the attending potential harms. Assessors review the objective clinical data submitted by the product manufacturer and determine the probability of harm and the magnitude of such harm, but in doing so it is the premise of this thesis that assessors' belief systems and values are engaged, giving rise to variability among assessors and contributing to divergent opinions. The evidence of assessor variability, use of the heuristic 'risk is the opposite of benefit' and the interplay of individual characteristics such as gender and years of regulatory experience regarding 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. Further studies of risk perception among medical assessors should include a larger number of assessors using an expanded list of dimensions that may reveal other important components, provide greater granularity of the dimensions and explain a larger proportion of the variability between assessors. The application of the MACBETH tool to regulatory decision making opens many avenues for research regarding the stability of patient preferences, the timing of the collection of preferences and the comparison of value judgments to standard utility measurements.

I conclude this thesis by highlighting a ready counterargument to the risk perception results among assessors, that is, in preparing their assessment reports, assessors are

Table 1. Key steps toward patient-centred drug development

Step	Responsible Party	Phase of Drug Development	Strategies
Identify patient-centred outcomes through direct patient feedback	Drug developer	Before pivotal trials	Prioritize patient-centred outcomes planning at earliest stages of drug development; conduct literature review, qualitative research (focus groups, interviews); [...] enable early collaboration with clinical outcome team and decision theory experts
Discuss plans for measuring and analysing feedback at structured meeting between drug development team and regulatory authorities	Drug developer and regulatory agency	Throughout drug development lifecycle, starting during early-phase trials	Formalize meetings between developers and regulators discussing and prioritizing endpoints meaningful to patients with open communication, specific recommendations from regulators, collaborative selection of outcomes and measurement strategies, elucidation of relationships between patient [preferences] and other endpoints
Evaluate outcomes using established qualitative and quantitative methods	Drug developer	Before pivotal trials	Complete before pivotal trial design to ensure appropriate selection of key and exploratory patient-centred endpoints[...]
Include [patient preferences] and other patient-centred outcomes in pivotal trials with protocol-specific plans for statistical analysis as well as minimizing and handling missing data	Drug developer	Pivotal trials	Dedicate statistical power for analysis of selected key [preferences] endpoints with support from exploratory endpoints; use electronic data capture or web-based data capture with backup data-collection strategies
Engage patient representatives of the target population	Drug developer and regulatory agency	Throughout drug-development lifecycle	Use formalized approaches to obtain patient input on study inclusion criteria, outcomes, measures, endpoint design, comparators, strategies for accruing and retaining participants, plans for dissemination and implementation
Include results from [patient preferences] in drug label to help patients and providers with decision making	Regulatory agency	Regulatory review	Create pathway for information about patient preferences to be included in labels; facilitate qualification of existing patient preference measures; [...]

Adapted with permission from (Basch, E. (2013). Toward Patient-Centered Drug Development in Oncology. *N Engl J Med 369*, 397-400), Copyright Massachusetts Medical Society [26].

not guided solely by their risk attitudes, personality traits or the high risk/low benefit heuristic. Over the course of the 210 days of a product review, an assessor's perception is very likely mediated by group discussion, by gathering additional data from the product manufacturer and by discussions with colleagues who may be more or less senior, who have similar or divergent attitudes towards risk seeking or risk aversion or who share similar ethical viewpoints. The final outcome presented to the world is therefore the result of a group effort. However, as stated by March, reliance on the so called 'bottoms up approach' in organizations to lead us to truth in decision making is tantamount to ignoring the elephant in the room, that is, '*decisions in organizations involve an ecology of actors trying to act rationally with limited knowledge and preference coherence; trying to discover and execute proper behaviour in ambiguous situations; and trying to discover, construct and communicate interpretations of a confusing world*' [27]. There is no guarantee of a truly rational choice whether within organisations or without. The best that can be hoped for is to achieve openness concerning the choices that are made and to include in the decision process all who wish to participate. The implementation of decision-making tools in the regulatory process can support this vision by adding transparency, increasing consistency and improving the current process by making it inclusive rather than exclusive.

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