

QUALITY DECISION-MAKING PRACTICES

Their Application and Impact in the Development,
Review and Reimbursement of Medicines



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Quality decision-making practices: Their application and impact in the development, review and reimbursement of medicines

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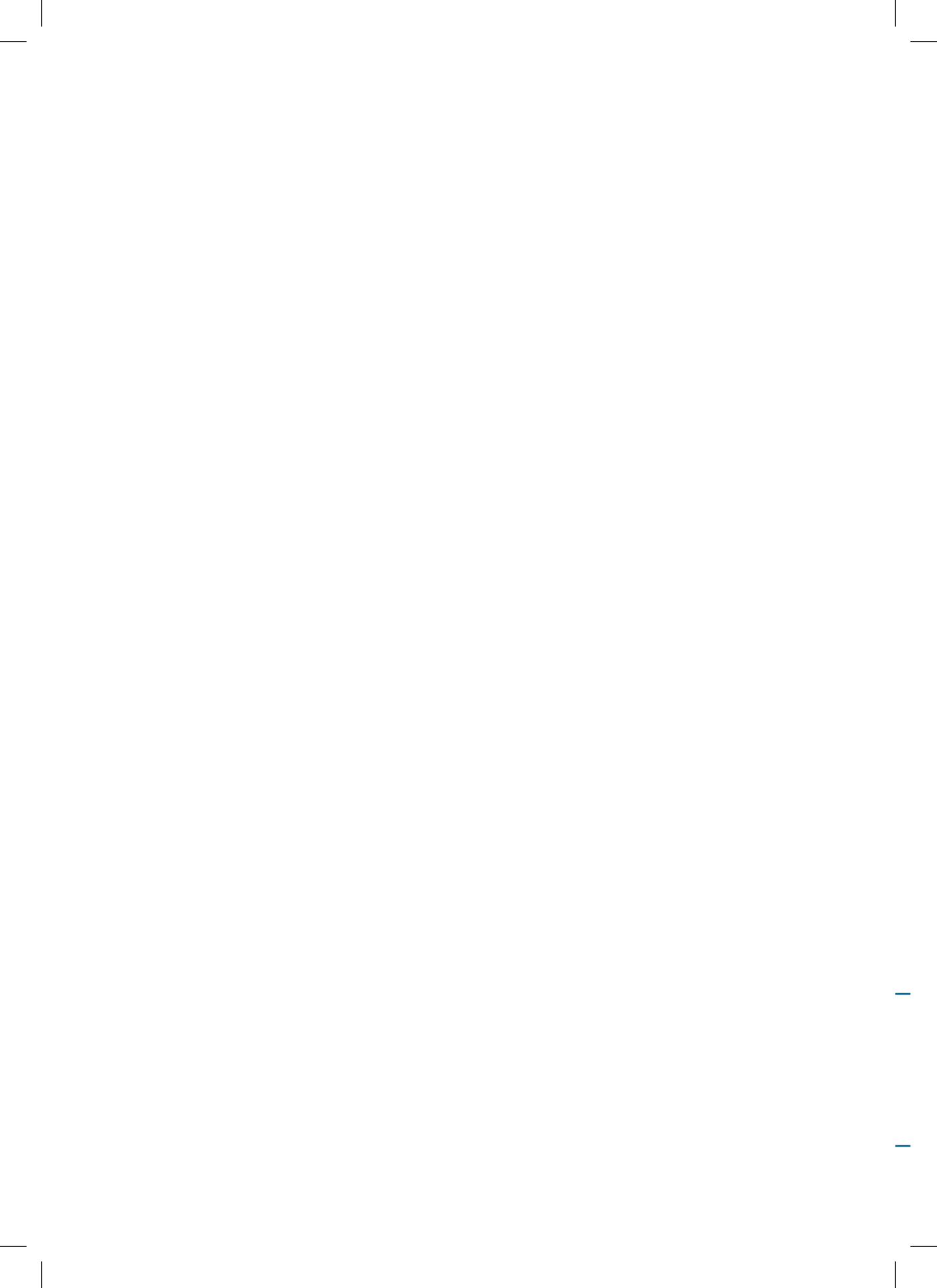
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CHAPTER 1

INTRODUCTION

"An enhanced awareness and understanding of how to identify and apply quality decision-making practices will facilitate decision-making approaches and subsequently may enable improved practices for both the individual and the organisation."



Dr Neil McAuslane

Director,
Centre for Innovation in Regulatory Science



At a 2004 CIRS Workshop on building quality into regulatory dossiers and the review process, Professor Larry Phillips of the London School of Economics gave a thought-provoking presentation on the philosophy, principles and practice of building quality into decision-making processes and how these apply in the pharmaceutical environment. He introduced his topic by commenting that many people find it hard to believe that there can be a “science of decision-making”. Indeed, there is such a science and it is based on a coherent theory about how to make better decisions.¹

Contrary to expectations, a quality decision and a decision-making process should not be tested by looking at the outcomes and consequences. In an uncertain world, it is perfectly possible to make a good decision that has poor consequences and equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally result in better outcomes. At the CIRS Workshop in 2011 in Kuala Lumpur, “Evolving the regulatory review process: What are the features that enable a transparent, timely, predictable and good-quality review?” it was discussed and agreed that delinking the regulatory review process from the process of making decisions should be explored. It was acknowledged that although the quality of decision making is of equal importance to the quality of review, process and procedure, methods for enhancing and measuring that quality had yet to be outlined.²

Over the past decade, both companies and agencies realised that a structured systematic framework was required in the area of benefit-risk assessment³ and the overarching elements of a framework for benefit-risk assessment have been well articulated, resulting in there being commonality in the steps taken by both agencies and companies to assess a medicine’s benefit-risk profile.⁴ Companies and agencies have now embedded this framework into their decision-making processes as a key tool to both inform the discussion around benefit risk-assessment and also to ensure that quality is being built into that decision process.

In addition to decisions surrounding benefit-risk, other decisions made by pharmaceutical companies, regulatory authorities and now health technology assessment (HTA) agencies throughout the life cycle of medicines are critical for ensuring that safe and effective medicines become available in a timely and efficient manner. Accordingly, as organisations seek to improve their efficiency and effectiveness, they should also routinely measure the quality of their decision-making process.⁵ Despite this need, there is a paucity of research and insight into how to build quality into decision making in medicines’ research and development both at the individual and organisational levels.⁶ The science of decision making

in companies has been largely confined to the prioritisation of assets to develop, whilst for agencies, the main focus over the last ten years has been to build quality into the review process by developing what are collectively known as good review practices and which have now been articulated by the World Health Organization (WHO) in a Guideline.⁷

In 2012, the Centre for Innovation in Regulatory Science (CIRS) initiated a study in collaboration with Cardiff University using a standardised approach including qualitative and quantitative techniques in order to develop and validate an instrument, the Quality of Decision-Making Orientation Scheme (QoDoS), for assessing the quality of decision making in medicines' development and the regulatory review.⁸

CIRS subsequently began a programme that aims to develop the principles of a quality decision framework and to identify markers and practices that build quality into decision making within drug development, the regulatory review and reimbursement. One of the objectives of this programme is to use QoDoS to assess the quality of decision-making processes and to evaluate the level of incorporation of the quality decision-making practices within companies and regulatory and HTA agencies. Indeed, ten quality decision-making practices (QDMPs) have been identified from the work undertaken and are discussed in more detail in Chapter 8. An enhanced awareness and understanding of how to identify and apply quality decision-making practices will facilitate decision-making approaches and subsequently may enable improved practices for both the individual and the organisation.

These quality decision-making practices go beyond just the implementation of a benefit-risk framework and represent a formal approach to quality decision making within an organisation. A number of common features have been identified as characteristics of a good-quality decision: having creative implementable options; having meaningful, reliable information upon which to base a decision; identifying clear values and trade-offs for each supportive element; using logically correct reasoning; and making a commitment to action. It should be determined if these are recognised or implemented as part of a company's or agency's decision making. However, decision making within companies and agencies is also in large part influenced by organisational processes and procedures. Therefore, there is a need to ensure that processes within companies are structured so as to enable consistency around making good-quality decisions.

This book compiles the presentations and syndicate discussions from a Workshop that brought together representatives from international pharmaceutical companies

and regulatory authorities from Europe, US, Canada and Australia and HTA agencies from Europe and Canada along with experts in the science of decision making. The sessions focused on why measuring decision making is important as well as on discussing the outcome of the pilot studies and surveys that CIRS has conducted with these organisations to measure the quality of their decision-making processes. In addition, as the benefit-risk framework is now becoming the cornerstone of building quality into the critical decisions within companies and agencies, there were also presentations on understanding and identifying how the benefit-risk decision framework is being built into the broader decision-making process.

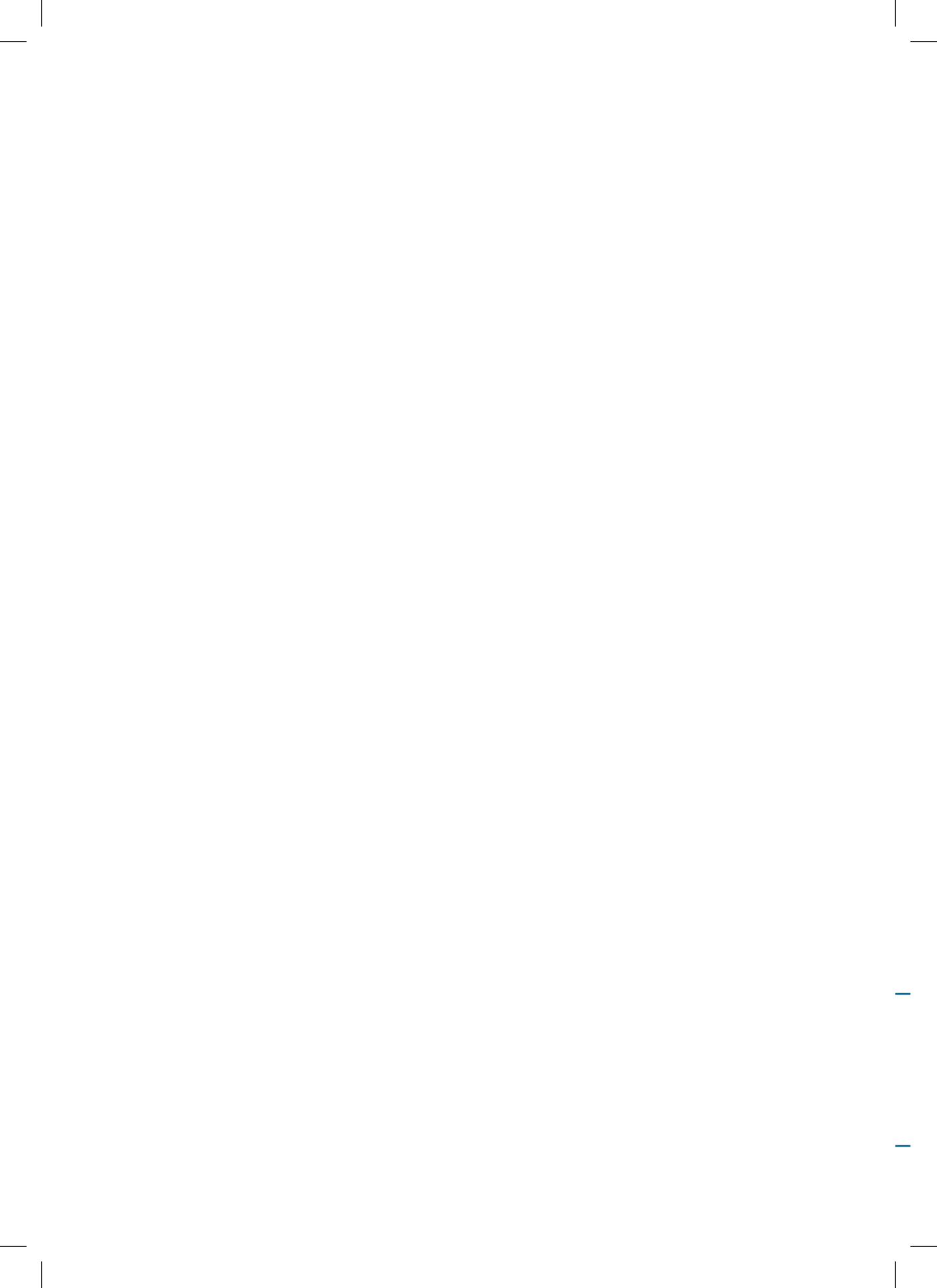
This collection of summaries described in the subsequent chapters will underscore the importance of building quality into decision making and why there is a need for stakeholders not only to be aware of what are good practices and how biases can influence the decision process, but also the need for companies and agencies to actively measure their decision-making processes. It also provides an understanding on how each of the stakeholders can embed the principles, markers and practices of a quality decision framework within their own and their organisation's decision making.

It is hoped that this book will increase the awareness as well as the practices of quality decision making and be of value to all stakeholders involved in the development, regulatory review and the reimbursement of medicines.

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CHAPTER 2

BUILDING QUALITY INTO DECISION MAKING: A REGULATORY AUTHORITY PERSPECTIVE

“Quality decision making is important to make sure that safe, effective and high-quality medicines are approved for the market, it enables a comprehensive assessment of risks, benefits and uncertainties and builds confidence in the regulatory system.”



Adj Prof John H Skerritt

Deputy Secretary for Health Products Regulation
Australian Department of Health



Introduction

One of the fundamentals to quality decision making by regulators is the existence of a structured and explicit benefit-risk framework. This is an area where CIRS has contributed significantly over many years and some regulators have documented similar principles to those developed by CIRS in their regulatory guidance documents. However, neither quality decision-making principles nor a usable definition of what “quality” means in this context are typically enshrined or specified in legislation; for example, in Australia, Section 25 of the *Therapeutic Goods Act 1989* simply states that in consideration of therapeutic goods (in this case prescription medicines), the decision maker must only determine “whether the quality, safety and efficacy of the goods, for the purposes for which they are to be used, have been satisfactorily established”.

Why are quality decisions important?

At the highest level, quality decision making is important to make sure that safe, effective and high-quality medicines are approved for the market. In the pre-market evaluation process, it enables a comprehensive assessment of risks, benefits and uncertainties. Just as importantly, quality decision making builds confidence in the regulatory system by external stakeholders such as industry, healthcare professionals and consumers. It is one of the factors that encourage the development of new medicines and regulatory submissions locally. Finally, having transparent and quality decision-making principles underpins fairness and natural justice for industry and health consumers. It is equally important to think through both the principles and the processes on which decisions are made in building quality into regulatory decision making.

What principles should regulatory agencies consider?

It is critical that all decisions are made in accordance with the law; that is, the laws and sets of regulations that define the current regulatory framework. Basing individual regulatory decisions on sound science is important, but this does not overrule the application of the legal/regulatory framework. Making this distinction between what may seem logical from scientific principles but which is not consistent with legislation or regulation can be challenging for product evaluators who have come through a science, engineering or medical career path rather than being trained in law.

So the starting point must be the Act /Regulations under which medicines are regulated in each jurisdiction. The legislation and/or regulations usually identifies the factors that can be considered in making decisions to varying degrees; for

example, these are described in much more detail for the US Food and Drug Administration (US FDA) in the range of enabling Acts such as the Food and Drug Administration Safety and Innovation Act of 2012 and the US Code of Federal Regulations than they are in the Australian Therapeutic Goods Administration's (TGA) legislation and regulation.

Equally important is the scope of authority; that is, who can make decisions and limitations on authority. In many countries, regulatory decisions are made by "delegates" of a single decision maker such as the national Secretary for Health. But real differences between regulators do exist regarding who is the decision maker (e.g., staff member versus a committee or another body) and the issues that can be considered in making decisions by law. For example, the US FDA has clearer powers to consider the abuse and diversion propensity of new medicines or dose forms in their consideration of these products for market authorisation than some other regulators.

What principles should regulatory agencies consider?

Building processes that enable procedures to be both fair and to be seen to be fair by others is critical. A range of public law values typically apply to the consistency, impartiality, accountability and transparency of both the final regulatory decision and the regulatory process. The transparency of regulatory processes is particularly critical. Apart from publishing decisions that have been made on the approval or rejection of individual medicines, several regulatory agencies also publish a detailed statement of reasons for those decisions, such as the European and Australian Public Assessment Reports. Regulators also typically publish safety reviews of products and some regulators such as European Medicines Agency (EMA) and Health Canada publish information on new medicine submissions as they are received, prior to their evaluation.

A second factor in quality decision making is allowing for applicants to have the clear right of review of the original decision by the regulator. The reasons for specific regulatory decisions usually have to be given in most countries. Several avenues of appeal of a decision often exist, including judicial and/or merits review, common law tort actions or remedies for defective administration such as ombudsman hearings. For example, in Australia, a "person" (typically the company applying for market authorisation of a medicine) may, by notice given in writing to the Minister of Health and with a set timeframe request reconsideration of the initial decision made by the TGA, for example, on an application for market authorisation for a medicine. The appellant must describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set

out the reasons why reconsideration is requested. In practice, the reconsideration of the decision by the Minister is made by his/her delegate – namely a senior official at TGA who was not involved in the original decision and who is at least as senior as the official who made the original decision. A request for reconsideration of an initial decision will result in one of the following outcomes: confirmation of the initial decision; revocation of the initial decision; revocation and substitution of the initial decision with a new decision or the remission of the initial decision to the original decision maker for reconsideration.

In Australia, there is also a further right to review this decision. An application may be made to the Administrative Appeals Tribunal (AAT) for a review of the Minister's decision. The Tribunal is an administrative body that reviews a wide range of decisions made by Australian Government ministers, departments, agencies and some other tribunals. The AAT takes a fresh look at a decision and, based on all the evidence before the AAT, decides the 'best or preferable decision' in the circumstances. Whereas the AAT provides a "merits" review process, affected parties may also appeal at any time to the Australian Federal Court on the grounds of the legality of a decision made by TGA – in other words, whether correct processes were followed under the Therapeutic Goods Act and Regulations and other Australian laws rather than the outcome (or "merits") of the decision itself. It is important for regulators to publicly promote the availability of the range of these review channels, both in individual decision letters to applicants and regulators' websites; for example, www.tga.gov.au/sites/default/files/guidance-requesting-reconsideration-initial-decision.pdf

Application of the law can be challenging in cases where the law may not have kept up with the science. In these cases the law still applies, even if the specific technology was not even anticipated at the time of the regulation's promulgation. Some examples where regulators globally are addressing how to better manage safety and performance issues for new technologies, but to avoid hindering innovation include biosimilar products, personalised medicine, direct-to-consumer genetic testing, 3D-printed medical devices and smartphone software with medical applications (apps).

Has a structured, documented approach been followed?

Having a consistent approach to the regulatory review of new medicines is an important element of quality and consistent decision making. The FDA and EMA have both published structured frameworks.¹⁻³ CIRS has been extensively involved in the development of such frameworks and the frameworks have been tested with

various regulators and are not reviewed further in this chapter. Bujar and colleagues have reviewed the development of a validated instrument to identify best practices (and potential biases) that may affect individuals and their organisations, as well as to assess differences in decision-making behaviours between pharmaceutical companies and regulatory agencies.^{4,5} Even if formal risk-benefit templates have not been used, regulators will invariably use guidance documents including international guidelines such as those of the World Health Organization (WHO)⁶ and templates for component/ module evaluations.

What processes does TGA use to build quality into decision making in the evaluation of new medicines?

TGA include internal and external administrative processes, benchmarking processes with decisions of global regulators as well as ensuring that medical and scientific evaluations are carried out by suitably trained and qualified staff. While several administrative parts contribute to the review of a new prescription medicine, different medical officers carry out the detailed dossier evaluation and act as final decision maker. In addition, external advisory committees provide critical input to the quality of the final decision through their consultation on a range of clinical and patient factors around the proposed decision.

A critical evaluation of the design of clinical trial studies that have been considered in a market authorisation application for quality is important. In the past, FDA and many other regulators consistently required at least two sufficiently powered and well-controlled trials in their submissions,⁷ although the limitations of randomised controlled trials have been known for some time, especially when it comes to inadequate prediction of the subsequent effectiveness of particular medicines in routine clinical experience.⁸ However, in the period from 1999-2014, 75 unique indications were granted by FDA and EMA (combined) without the requirement for data from randomised controlled trials.⁹

An important part of quality assurance in the review process is to determine whether the applicant deliberately or inadvertently excluded the results of negative trials in the submission. It should also be established if appropriate patients were enrolled. For example, a company may seek approval of a particular indication for a wide or unrestricted age range, but the age range of patients who were enrolled in the pivotal trials was quite narrow.

A common challenge that decision makers face is when a new medicine may have had a statistically significant effect in a pivotal trial but there is some doubt as to whether the effect is clinically significant.¹⁰ This is especially relevant where

the endpoint is a secondary one or an effect on a biomarker. To this point, only some cancer medicines that have been approved on the basis of a surrogate endpoint had an overall survival benefit.¹¹ A further challenge is determining the relevance of trial data relating to impacts on physiological and biochemical endpoints compared with measures of patient quality of life or other measures of effectiveness.¹² Undertaking thorough peer reviews of the evaluations of both the clinical and non-clinical modules is valuable in these cases as well as an examination of the conclusions reached by other regulators. Increasingly, international regulators are forming communities of practice to discuss on an in confidence basis, new submissions in areas such as oncology and paediatrics.

Predictability in the timelines and milestones of the medicines review process is also an important part of quality in review. Where market authorisation applications are successful, it also assists companies with planning for applications for reimbursement and for product launch. In a recent study of six major regulatory agencies by CIRS, Australia had the most consistent and predictable median approval timeframes.¹³ However, the introduction of some new pathways for priority review and provisional approval pathways alongside maintenance of a “standard” pathway will necessarily increase the diversity in review timeframes in Australia for different types of submissions.

Quality in medicines evaluation goes further than just issues to do with evaluation of the dossier itself. In good manufacturing practice (GMP) inspections of medicines manufacturing facilities, which is a key part of the decision-making process for permitting market authorisation of a new product, having appropriately qualified specialist inspectors is fundamental. Elements such as clarifying inspection interpretations through both revision of standard operating procedures (SOPs) and training of new inspectors, having technical forums to review interpretation of GMP guidances (in particular, for emerging or combination technologies) and the establishment of a multidisciplinary inspection report review panel prior to the finalisation of those reports that identified critical deficiencies are all important.

In quality decision making across the broader medicine life cycle, organisational separation of pharmacovigilance decision making from market authorisation decision making is important. This can avoid the potential for conflict of interest if staff were placed in the position of making decisions on a product for which they had earlier led initial market authorisation. It is also important that there be an assessment of “plausible causality” of adverse events, noting that many regulators deliberately focus on the assessment of adverse events that were not previously widely known for the particular product. The “denominator” (size of population

using the medicine) should be estimated if possible so that the frequency of the potential adverse event can be estimated. A range of other approaches are increasingly used by regulators such as mining of big administrative health datasets, external sources (such as information from other regulators, medical literature), internal peer review of adverse event signals and cases and external pharmacovigilance advisory committees.

The medicine market authorisation decision-making process

Medicine regulators typically make thousands of decisions each year and the responsibilities for decision making differ for different types of products. Usually, decisions on new prescription medicine applications are made at a more senior level and/or with the advice of a committee compared with the myriad of decisions on product variation, product labelling or generic medicines market authorisation that are made by a range of staff.

Decision models differ between countries, but unlike medicine funding or reimbursement decisions, which involve a commitment of government funding, regulatory decisions on medicine market authorisation are usually made by a senior medical official. Committees are involved in the decision-making process in two broad senses. Either they make a formal recommendation whether or not to approve a product for market authorisation (and an individual effectively “rubber stamps” the decision) or the committee may be asked to provide input on contentious issues and advise the decision maker in the regulatory authority, rather than the committee making an overall recommendation on acceptance or rejection of the submission.

Committees and decision making

Having well-functioning external advisory committees is an important part of quality decision making in medicine regulation,^{14, 15} particularly for small- and medium-sized regulatory authorities, as they provide specialised clinical expertise that would usually not be available within the staff of the regulatory agency. This is increasingly important as new therapies become more specialised such as in oncology and rare disease treatment. At the other extreme, the “real world” experience of physicians in general practice and of patient representatives on committees is just as valuable as specialist advice. Other committee members may also provide skills; for example, in specialised biostatistics and population pharmacokinetics, that may not be available within the regulatory agency.

Transparency of committee decision making and having formal and robust processes to manage conflicts of interest among committee members is also very important.

While advisory committee voting patterns are usually predictive of the final decision made by the regulatory decision maker, committees do have a number of potential drawbacks.^{16,17} Members are typically only part-time appointees and so are much less informed on the detailed regulatory context than an evaluator who may have spent months considering a submission. In addition, clinical or academic members of committees may not always consider issues from a regulatory or population health standpoint (that is, through a systematic analysis of benefits/harms/uncertainty).

There are other factors that could apply to any type of committee. For example, an authoritative member with professional standing in the field can hold sway or alternatively, a poorly informed but strongly opinionated member can unduly influence others. Newer committee members may feel reluctant in presenting a differing view about a product, if they follow in the agenda an internationally recognised expert in the committee discussion. Even within committees (such as some of US FDA) that formally vote on product submissions, influences of this type may persist, as secret ballots are usually not used on these regulatory advisory committees. It is also unclear whether an impact on debate and decision making is created by holding advisory committee meetings in public versus in private.

Possible hurdles to quality decision making

A number of national regulatory systems rely on the decision of an individual, often a senior medical officer. The different clinical backgrounds and perspectives of the decision makers and varying emphasis on population versus individual patient benefits could influence consistency and quality of decisions. Also, recognition of uncertainty can sometimes be inappropriately conflated with harms of a product. Assessing uncertainties will become more important in the future as regulators receive more dossiers with only earlier stage trial data for priority review or provisional approval. Development of guidance documents and internal review protocols that have a clearer description of harms versus uncertainties and that clearly communicate information through public assessment reports can go some way to clarifying the difference between uncertainty and harms of products. It is also important for regulators to formally require the implementation of post-market commitments by the industry sponsors of these products.

Several authors have identified a number of biases that can be manifested among regulatory decision makers.^{4, 5, 18-20} These include:

- › “Action-oriented” biases – which may lead to a failure to sufficiently analyse data given work and time pressures
- › Interest biases – “emotional” attachment; for example, where the reviewer has previously conducted research on the same medicine class or has had

significant treatment successes or failures with their patients with other medicines for the same condition

- › Pattern recognition biases – where the reviewer seeks information that reinforces positives – such as where similar medicines have been approved already for the same indication
- › Stability biases – inertia from a decision maker in the presence of uncertainty – where there is a view that it would always be possible for the applicant to provide more data to the regulator

A range of external inputs, some of which are formally required by most governments, can also build quality into the decision-making process. In Australia, apart from product-specific advisory committees there are formal stakeholder forums to advise on regulatory processes and policies such as an industry-TGA Regulatory Affairs Working Group and a TGA-Industry Consultative Committee. TGA undertakes formal public consultations on new guidance documents and proposed regulation changes and the external auditors (the Australian National Audit Office) undertake relatively regular compliance and performance audits on the regulatory framework and processes.

Some newer challenges to quality decision making

With the greater numbers of electronic Common Technical Dossier (e-CTD) submissions to smaller and medium sized regulatory agencies, it is anticipated that the “submission lag time” will decrease in coming years. This increases the likelihood of near-simultaneous but divergent decisions emerging from different regulators. Under this scenario, the communication of clear reasons for the regulatory decision made in each case becomes even more important.

Much has been written elsewhere about the changing nature of clinical trial designs. The changing nature of designs also challenges regulators. It is, for example, harder for regulators to specify data quality requirements in submissions that are based on “adaptive” trial designs, which are complex. Different statistical analytical approaches may also be required because of loss of powering of the control arm as the trial proceeded. Even with “traditional” trial designs, the necessarily smaller sample size in trials for medicines for rare diseases proposes a challenge. Naci and colleagues have contended that only a minority of medicines that have undertaken facilitated review by FDA have been through randomised trials,²¹ yet several of these medicines have become part of the standard of care for particular conditions.

The data for oncology medicines submissions in particular has changed in recent years. Cancers are being redefined away from “organ-based” definitions and

secondary endpoints/biomarkers are increasingly submitted in regulatory dossiers as measures of efficacy in their treatment. Many companies use a process of “rolling” submissions for extension of indications and so it can be difficult to determine when the most appropriate time should be for “locking” the data in a submission. New types of therapies being developed for oncology provide an additional challenge over the longer-standing small-molecule and monoclonal antibody approaches. These include bi-specific antibodies and multi-drug delivery proteins; macrophage, dendritic or natural killer cell stimulators and viral vector treatments, chimeric antigen receptor T-cell (CART) and targeted therapy/immunotherapy combinations.

The wider use of “real-world data” is in vogue, but this also poses several data quality challenges for medicine regulators. Systematic collection of efficacy or effectiveness data may stop once the medicine receives market authorisation or government or insurer reimbursement as the incentives to collect data may be limited. Real-world data are also dispersed through hospitals, private practices, insurers and patients and are often of variable quality. The validity of many data sets may be hard to confirm and the data sources poorly connected.

The relationship between quality decision making and trust

Trust in how regulatory decision makers and their advisory committees address particular issues that come up during market authorisation underlies the integrity of the regulatory system. For example, some of the issues our decision makers and committees have had to address in recent months relate to the quality of the data before them, which impacts the quality of the decision they can then make.

These include:

- › Extrapolation from a related but different indication
- › Approval for chronic use of a medicine based on data from trials of under 3 months duration and where there is longer term data – how should data from open-label long-term extension trials be treated?
- › Are the warning statements in the product label adequate?
- › Should approval for adolescent or paediatric populations be granted, if it is based largely on data from adult populations?
- › Is a single phase 2 or 3 trial good enough (or are two such trials needed to be confident in the efficacy of the new medicines)?
- › Is the proposed dose for the new medicine really evidence based?
- › If the medicine is to be approved on the basis of a secondary endpoint, should testing for a biomarker be mandated with use of the medicine?
- › Should prescribing of a medicine with particular risks be limited to specialist physicians?

Improving pre-submission processes and avoiding the need to require companies to resubmit data in response to reviewers' questions that have been triggered by issues such as these, may have the most significant impact of overall approval times.²²

Transparency and trust are also closely related. There have been major changes in community expectations of government over the last 20 years. Regulators now publish business plans, annual reports and senior officials testify before their parliaments on regulatory issues. There is now greater publication by regulators of:

- › Information on product cancellations and reasons for their cancellation
- › GMP inspection information and reports
- › Enforcement information, such as advertising complaints
- › Information on recently approved medicines
- › Information on new prescription medicines that are currently under review as well as information on positive and negative decisions for medicines
- › Access to (patient de-identified) clinical trial data
- › Reporting against key performance indicators and information on business performance such as approval times, number of products approved and compliance information

Other less tangible elements of trust are just as important. These include the importance of open regulator-industry relationships with clear and positive expectations from both parties; confidence that the regulator has a good pharmacovigilance system and regulation and self-regulation of inappropriate medicine advertising. Consumer education on the importance and benefits of new medicines to the community and the role of the regulator in evaluating medicines and in monitoring safety is also important.

How quality decision processes can help manage uncertainty

Australia is implementing two new processes in 2017 and 2018, both of which increase uncertainty. These are the priority review of a complete medicines dossier within 150 working days and a provisional approval pathway making use of early data on safety and efficacy, where the potential benefits from immediate availability of the medicine outweighs the uncertainty. The eligibility criteria for both pathways include that the medicine must be for a serious condition, represent a major therapeutic advance and a comparison against existing therapeutic alternatives is undertaken. However, provisional approval will be based on consideration of "promising evidence from early clinical data" and provisional approval, if given, would lapse after 2 years (with a maximum of two 2-year extensions being possible).

Industry product sponsors will be required to collect and submit more safety and efficacy data to TGA and may be able to apply for full registration if the data meets requirements for full registration.

There are a number of schemes in place internationally for accelerated and/or conditional regulatory approval of medicines.^{23,24} These schemes have had significant impact in making novel medicines accessible to certain patient groups somewhat earlier than otherwise.²⁵⁻²⁷ Several studies have, however, questioned whether the medicines that had been approved through facilitated pathways were more efficacious than those approved through standard pathways.²⁸ In a review of US FDA approvals, it was noted that only 10 of 123 controlled studies published after approval of the particular medicine confirmed superior efficacy for the approved indication.²⁹ Conditional or provisional approval schemes are based on an assumption that reliable new data on benefits and harms will be available soon after conditional approval.³⁰ However, it may be hard to gather such data and there are challenges in removing a medicine once it is on the market.³¹ Medicines approved through various FDA expedited pathways also required a higher frequency of label-related safety changes after their approval than medicines approved through standard pathways.³² A number of other studies have reported that post-marketing commitments for medicines on these pathways were not met and were often dogged by poor recruitment of patients.²⁹ Banzi and colleagues noted that while EMA required medicine manufacturers to provide more data for about three quarters of conditionally approved medicines between 2006 and 2016, there were both ethical and logistical challenges to allowing patient randomisation in the requested study to follow up performance of a new medicine after licensing.³³ This is especially a challenge for medicines for rare diseases or conditions.³⁴

Strengthening the pharmacovigilance of new medicines will be a critical element in support of the quality of provisional and priority approval schemes. In Australia we are implementing new activities, such as a pharmacovigilance inspection program and a “black triangle” scheme for the product and consumer information on these and some other medicines. We are also enhancing existing pharmacovigilance through a risk management plan compliance monitoring program, reforming the product information and modernising our IT systems for adverse event signal identification and management.

Conclusions

A range of policies and processes are in place to support quality regulatory decision making at most well-established medicines regulatory authorities, but improvements are always possible.³⁵ Regulators differ in their use of structured frameworks³⁷ but

all have various forms of internal quality assurance for decision making and usually processes established by law for the internal and external review of decisions. There are many advantages to using committees to access external specialist advice, especially for small- and medium-sized regulatory authorities, but committees can still suffer from some of the same biases and broader shortcomings of individual decision makers. It is also questionable whether either regulators or the regulated industry adequately learn from their failures, notwithstanding some detailed analyses of the failure. For example, the US FDA recently published results obtained with medicine candidates that showed promise in phase II but failed in phase III. Of these, 14 failed for lack of efficacy, 1 for safety concerns and 7 for both reasons (benefit/harms issues).³⁷

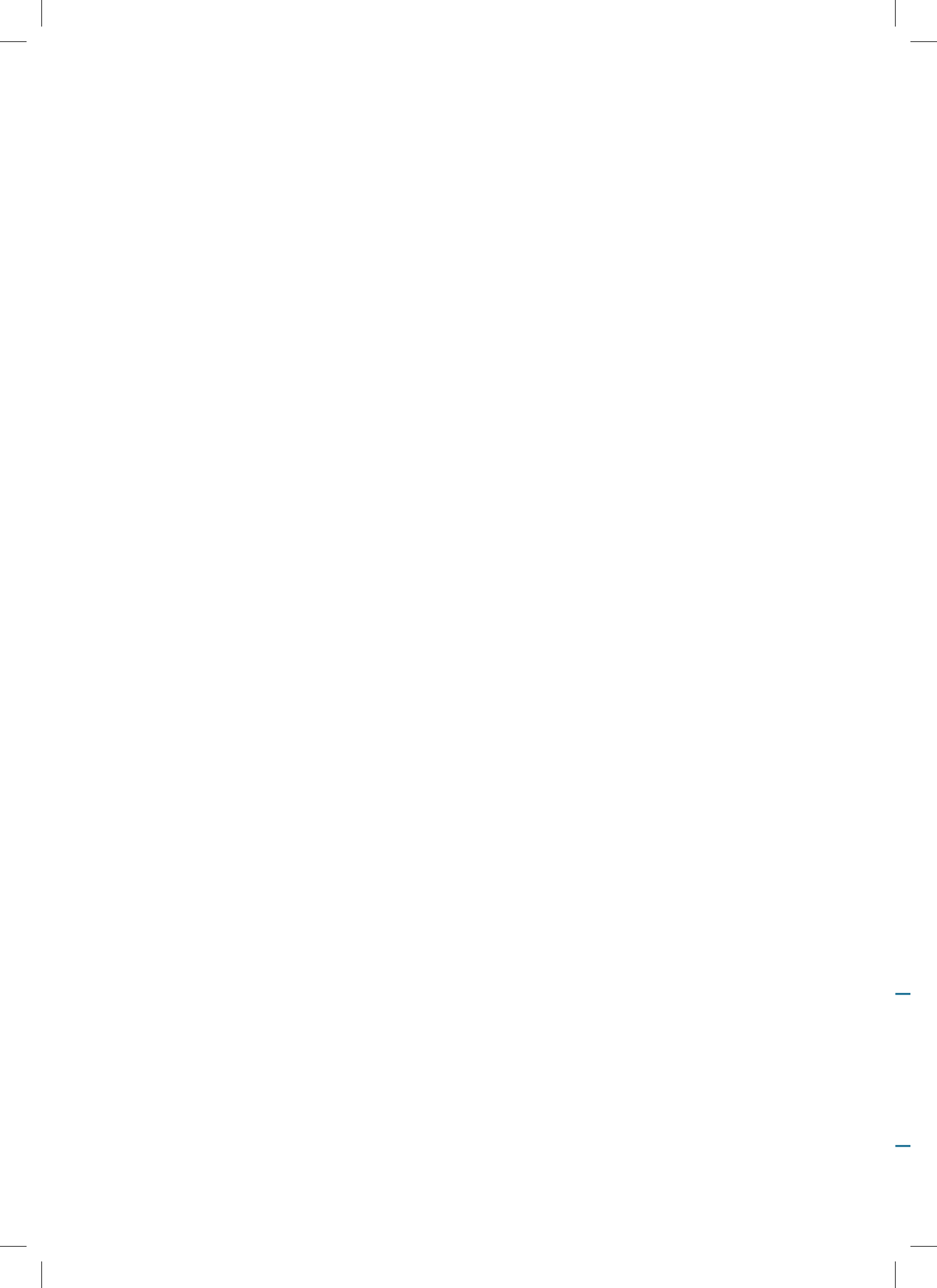
There is global pressure by patients, clinicians and industry for faster medicines approvals especially where there is a clear unmet clinical need. It is important that additional processes for maintaining the quality of decisions in the face of increased uncertainty are implemented, noting that some options for improving decision quality could slow or increase the cost of decision making. Arguments have been made for more flexible approaches to the assessment of benefit and risk during the medicinal product lifecycle, to accommodate these new models.³⁸ It will be interesting to see if with the passage of time, whether the implementation of provisional licensing of medicines by regulators has made it easier to reverse an initial decision (and thus correct a particular original “poor quality” decision) on efficacy or safety grounds.

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CHAPTER 3

DECISION QUALITY – THE IMPORTANCE OF MEASURING THE PROCESS AS WELL AS THE OUTCOME

“The requirements for decision quality may seem like common sense but common sense is not common practice.”



Dr Carl Spetzler

Cofounder, Chairman and CEO
Strategic Decisions Group



Introduction

In terms of strategies and business decisions, those made between the regulatory and the corporate world before they get to the regulatory world, are critical for ensuring timely availability of needed patient treatments. These decisions are often complex and uncertain, calling for deliberation and focus on quality. This chapter will focus on how to make the decision process better as well as on the importance of measuring the process as well as the outcome on the journey to achieve decision quality (DQ).¹

There is no universal best process or set of steps to follow in making good decisions. The process has to be tailored to the decision situation – more specifically to its magnitude, complexity, content challenges, inherent difficulties and likely decision traps. Of note, however, any good decision process recognises DQ as its measurable destination.

Before addressing what must be done to achieve DQ, it is helpful to step back and consider that at a very simple level, all decisions first have to be declared (Figure 3.1). Decisions do not come ready to be made. You have to shape them and declare what is the decision you should be making; that must be made. Let me illustrate what I mean. Recently, my wife said to me: “It’s time to paint and carpet our house.” In agreement, I replied: “You know, in six months we’re going to be empty nesters. We have a playroom that we don’t need any longer, and there is also that tiny kitchen you don’t like. Maybe we should do a little remodelling.” My wife loved that idea and soon we started talking about the remodelling we wanted to do, not only to the kitchen but to the bedrooms as well. We even hired an architect to help us design the amenities we wanted. Before long we realised what the substantial price would be if we were to do all the remodelling we wanted. We then asked each other: “Should we look at houses for sale that already have what we want?” and “How far away should we look for houses?” We actually found an area we really liked; only to discover no houses were for sale. However, we discovered lots were available to buy. This new information resulted in us asking the other whether we should build on a lot, instead of holding out to buy a house. Then my wife asked me: “How long are you going to keep working in this area, Carl?” and “When are you going to retire?” and finally: “What are we going to do with the rest of our lives?” As you can see, my wife’s simple painting and carpeting statement morphed into subsequent statements and questions from both of us, all leading to the specific problem or opportunity we needed to be tackling and making a decision.

In essence, at a very simple level, all decisions come to us like this – like a bunch of spaghetti, all in a bowl to tease apart and find out exactly where they fit. The part of finding where they fit is called “declaration.” It is the act of declaring the need for a decision that triggers all that follows. Whether a decision is forced upon us or is of our own invention, or whether it is motivated by crisis or opportunity, declaring the need for a decision directs attention to a situation where a deliberate choice should be made and that declaration initiates a decision process.

The destination of DQ

All decisions have one thing in common – the best choice creates the most potential for what you truly want. To find that best choice, you need to reach DQ and you must recognise it as the destination when you get there. You cannot reach DQ if you are unable to visualise or describe it. Nor can you say you have achieved it with any confidence, if you cannot recognise it when it is achieved. This means you have to evaluate decisions against the six requirements of DQ and recognise when further improvement of each requirement is worth the time or effort (Figure 3.2).

Figure 3.1. The journey to get to decision quality (DQ) requires a process – and begins when someone declares a decision must be made.

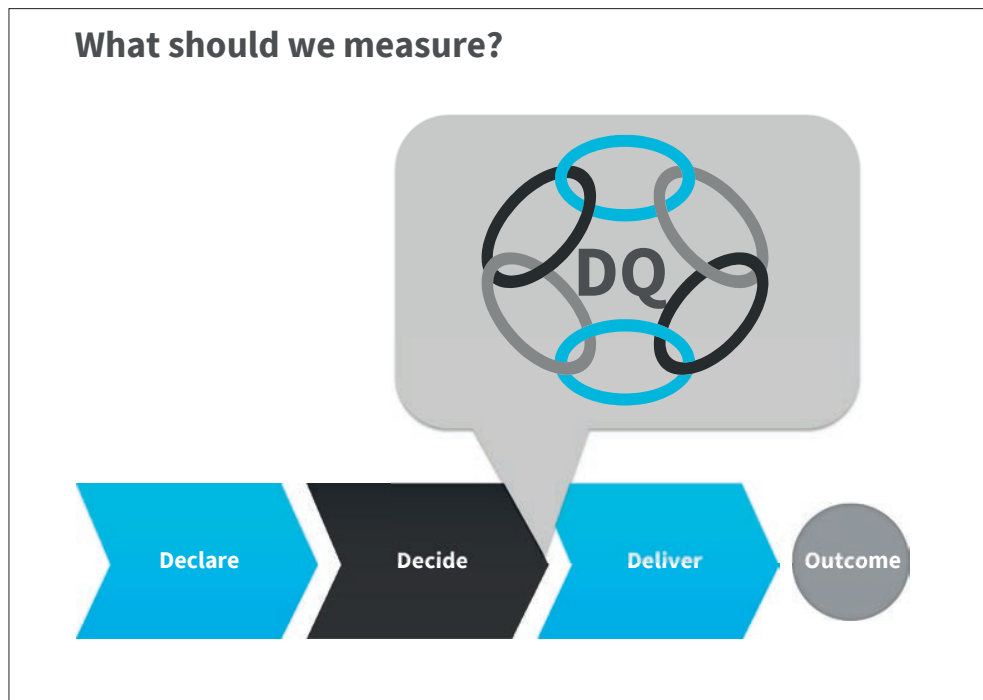
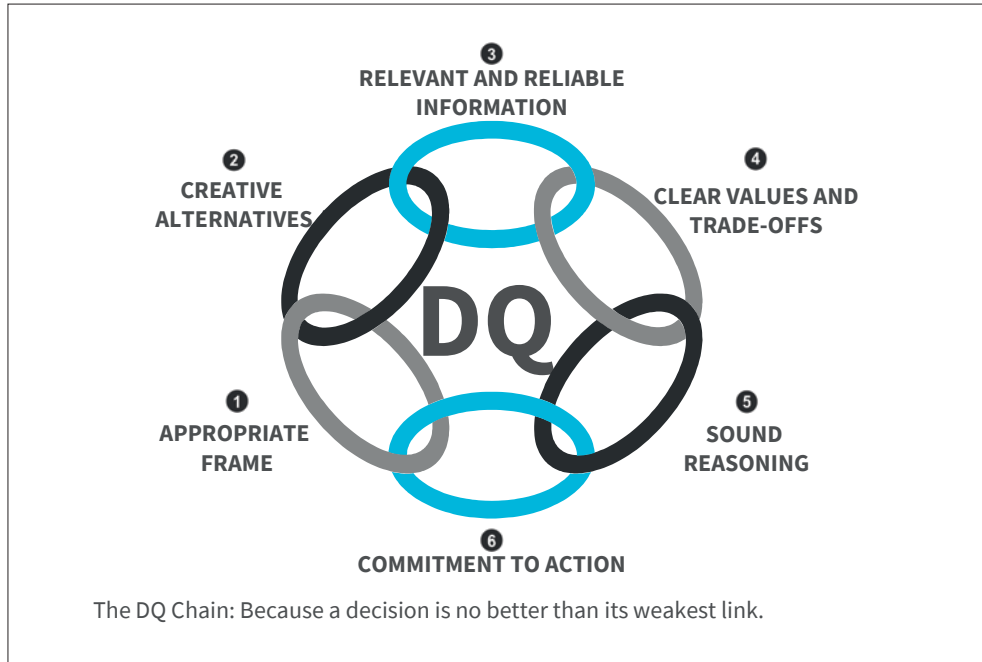


Figure 3.2. To reach DQ you must meet the six requirements of a good decision.



The six requirements for a good decision are: (1) an appropriate frame, (2) creative alternatives, (3) relevant and reliable information, (4) clear values and trade-offs, (5) sound reasoning, and (6) commitment to action. To judge the quality of any decision before you act, each requirement must be met and addressed with quality. We represent it as a chain, because a decision is no better than its weakest link.

The **frame** specifies the problem or opportunity you are tackling, including what is to be decided. It has three components: (1) your *purpose* in making the decision; (2) the *scope* of what will be included and excluded; and (3) your *perspective* including your point of view, how you want to approach the decision, what conversations will be needed, and with whom. Agreement on framing is essential, especially when more than one party is involved in decision making. Of note, there is no single best or right frame for any decision. What is important is to find the frame that is most appropriate for the situation. If you get the frame wrong, you will be solving the wrong problem or not addressing the opportunity in the correct way.

The next three links are: **alternatives** – defining what you can do; **information** – capturing what you know and believe (but cannot control), and **values** – representing what you want and hope to achieve. Together, these three elements form your

decision basis. The three elements of the decision basis are combined using *sound reasoning*, which guides you to the best choice (the alternative that gets you the most of what you want and in light of what you know). With sound reasoning, you reach clarity of intention and are ready for the final element – *commitment to action*.

While it may seem like common sense to have the six requirements for DQ described, the truth is the human mind is not wired to achieve DQ without a systematic effort and common sense is not a common practice, especially when decisions are complex and uncertain and involve multiple parties with different interests.

From a regulatory perspective, asking: “What is the decision I should be making?” is not a simple question. Today, you have a plethora of short- and long-term alternatives to respond to that go beyond the simple yes/no. Further, in the regulatory world, where an advocacy approval process is generally used, the question “On what decision should I be focusing?” is particularly challenging. It is a question, however, that is important to be asked, because you have to know what decision you are making. It defines the range within which you have creative and compelling alternatives. It defines constraints. It defines what is possible. Yes, regulators are often constrained into yes/no or very specific paths, but even within that frame, generating and having creative alternatives on the table is key because a decision cannot be better than the best alternative. It is interesting to note, that many organisations fail to create a rich set of alternatives and simply debate whether to accept or reject a proposal. The problem with this approach is that people frequently latch on to ideas that are easily accessible, familiar or aligned directly with their experiences.

In understanding potential outcomes for alternatives, the information for alternatives is a combination of analysis, rigor, technology and judgement. Data are about the past and present – requiring additional judgement to anticipate future consequences. What we know about the future is uncertain and therefore needs to be described with possibilities and probabilities. Questions like: “What might happen?” and “How likely is it to happen?” are difficult and often compound. To produce reliable judgements about future outcomes and probabilities you have to gather facts, study trends and interview experts while avoiding distortions from biases and decision traps. In the decision context, values or preferences, describe what you want. When one alternative provides everything desired, the choice among alternatives is not difficult. *Trade-offs* must be made when alternatives do not provide everything desired. You must then decide how much of one value you are willing to give up in order to receive more of another.

In most cases, commitment to action is attained by involving the right people in the decision efforts. The *right* people must include individuals who have the authority and resources to commit to the decision and to make it stick (the decision makers) and those who will be asked to execute the decided-upon actions (the implementers). In business, decision makers are frequently not the implementers and much of a decision's value can be lost in the handoff to implementers. In your work leading to the decision, you must always consider the resource requirements and challenges for implementation.

Define the quality of the decision when you make it

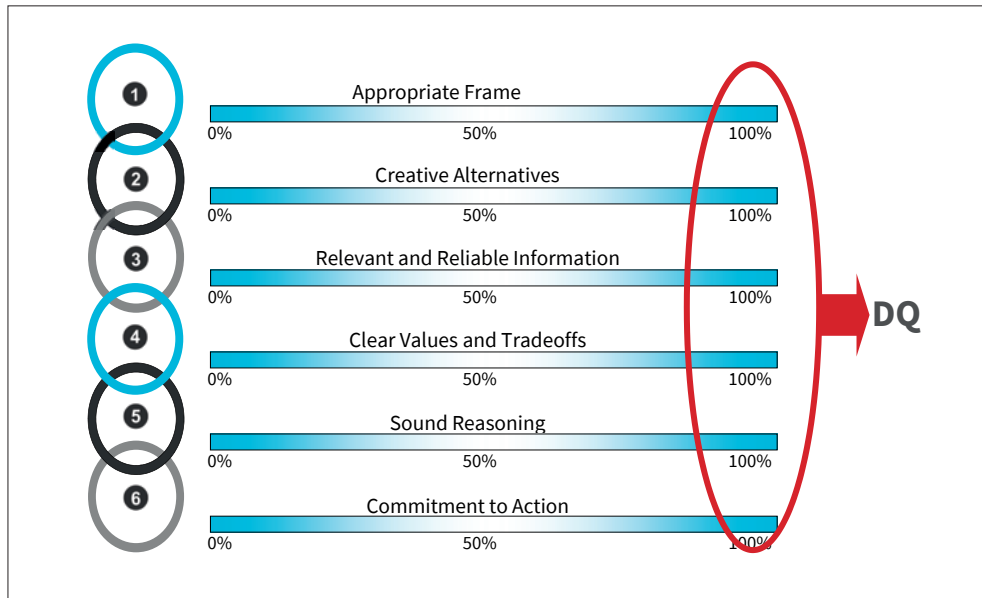
The virtue of the six requirements of DQ is that they can be used to judge the quality of the decision at the time it is made. There is no need to wait six months or six years to assess its outcome before declaring the decision's quality. By meeting the six requirements you know at the time of the decision you made a high-quality choice. You cannot simply say: "I did all the right steps." You have got to be able to judge the decision itself, not just how you got to that decision. When you ask, "How good is this decision if we make it now?" the answer has to be a very big part of your process. The piece missing in the process just may be in the material and the research and that is a piece that has to go right. Sometimes, the six requirements are drawn as a slider scale and we define decision quality as when you have reached 100% on each of the requirements. However, 100% is not perfection. It is when it is not worth doing more or delaying the decision to improve the specific requirements of DQ (Figure 3.3).

Beware when you ask: "How are you doing?"

When you have gone through the whole process and you ask, "How are you doing on this?" you often find big gaps and bias for action on the individual dimensions. A group may be ready to move forward with a decision but find they have some big gaps on one or more requirements, in the example in Figure 3.4, the gap is information. People believe that if they agree around the table, it is a good decision. (When tested against decision quality later on they say, "How could we have missed this?") In group decision making, you have to understand gaps and do something about them. First, you need pull it back and say, "We are not ready to act." Second, you need to start filling the gaps.

Comfort zone bias is when people do what they know how to do, rather than what is needed to make a strong, high-quality decision. You overcome the comfort zone bias by figuring out where there are gaps. Let us say the gap is with alternatives. Your process then becomes primarily a creative process to generate alternatives instead of gathering a great deal more data. Maybe we are awash in

Figure 3.3. When it is not worth additional effort or delay to improve quality, you have reached 100%.



a sea of information, but we just have not done the reasoning and modelling and understanding of the consequences. This becomes more of an analytical effort. In essence, the specific gaps define where you should put your attention to improve the quality of the decision.

The role of leadership is assembling the right people to make quality decisions. Once you know how to recognise DQ, you need an effective and efficient process to get there and that process involves many things including structured interactions between decision maker and decision staff (Figure 3.5). Of note, productive discussions result when multiple parties are involved in the decision process and difference in judgement are present.

Typically, in the corporate world, you define a decision body, usually called *decision boards*. You could also think of this body to be like the regulator, but most regulators ask for advocated positions rather than alternatives. In terms of quality decision making, the decision maker rather than decision support or work must own the answer. The decision maker has to be able to say, "I have a quality decision. We meet the six requirements to the level that in my judgement provides a high-quality frame. We have the right alternatives and the information to be able to make the decision and we are getting the most of what we want in choosing the alternatives."

Figure 3.4. Measure the quality of each element. The 100% point for a given situation is where additional work is not worth the effort.

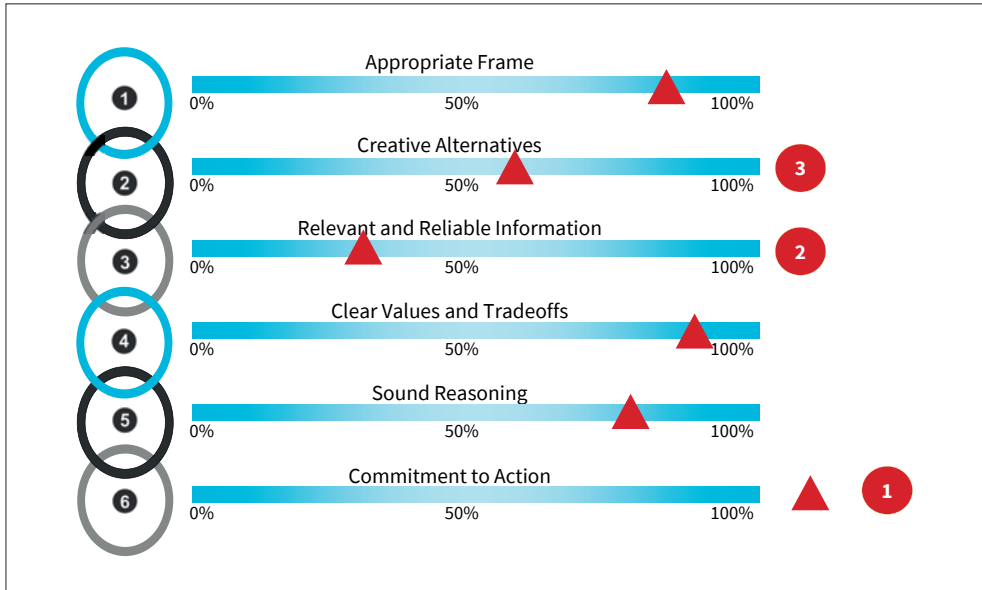
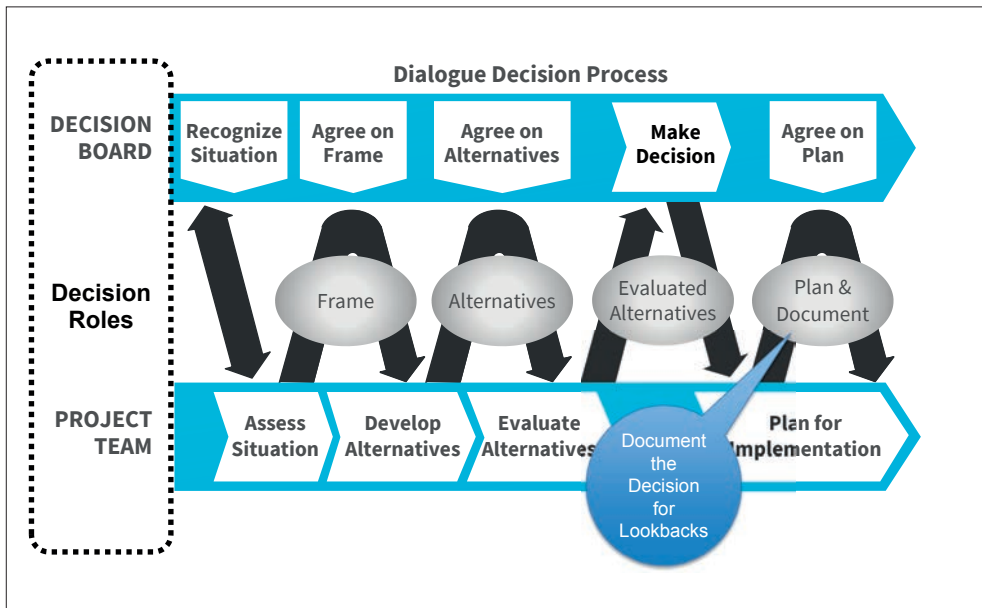


Figure 3.5. Decision quality is achieved through structured interactions between decision maker and staff.



Once you are in advocacy mode, you are no longer in a decision-quality mode

The most common decision process, even within corporations and organisations, is an advocacy decision process. What this means is that you are asking somebody to sell you an answer. Once you are in advocacy mode, you are no longer in a decision-quality mode and you cannot get the best choice out of an advocacy decision process. Advocacy suppresses alternatives. Advocacy forces confirming evidence bias and means selective attention to what supports your position. Once in advocacy mode, you are really in a sales mode and it becomes a people competition.

When you want quality in a decision, you want the alternatives to compete, not the people. From the decision board's perspective, when you are making a decision, you want to have multiple alternatives in front of you and you want to figure out which of these alternatives beats the others in terms of understanding the full consequences in risk, uncertainty and return. For each of the alternatives one will show up better. If you can make this happen, then it is not the advocate selling it, it is you trying to help look at which of these things gives us the most value for our investment in some way.

The regulatory situation, by structure and by nature is one where most of the decision quality on the corporate side will already have been created. The big decisions regarding the label of the drug: what are we going to do, what are we going to ask for, how do we position the data, how do we select it to support, are all handled in an advocacy mode. It is hard to establish trust in this mode and this results in a great deal of value left on the table for society.

The role outcomes play in the measuring of decision quality

Always think of decisions and outcomes as separate because when you make decisions in an uncertain world, you cannot fully control the outcomes. When looking back from an outcome to a decision, the only thing you can really tell is if you had a good outcome or a bad outcome. For example, a person drives home from an event having had too much to drink and gets home safely. It was not a good decision to drive but it did result in a good outcome. Hindsight bias is strong, and once you have hindsight, it is hard to put yourself back into understanding what decisions should have been made with what you knew at the time, or could have known at the time.

In understanding how we use outcomes in terms of evaluating decisions, you need to understand the importance of documenting the decision and the decision quality at the time of the decision. Ask yourself, if you were going to look back two years from now, what about this decision file answers the questions: "Did we make a decision that was good?" and "What can we learn about the things about which we had some questions?" This kind of documentation is different from what people usually do. What is usually documented is the approval and the working process. There is usually no documentation answering the question: "If we are going to look back in the future, what would we need to know to be able to learn about making better decisions?"

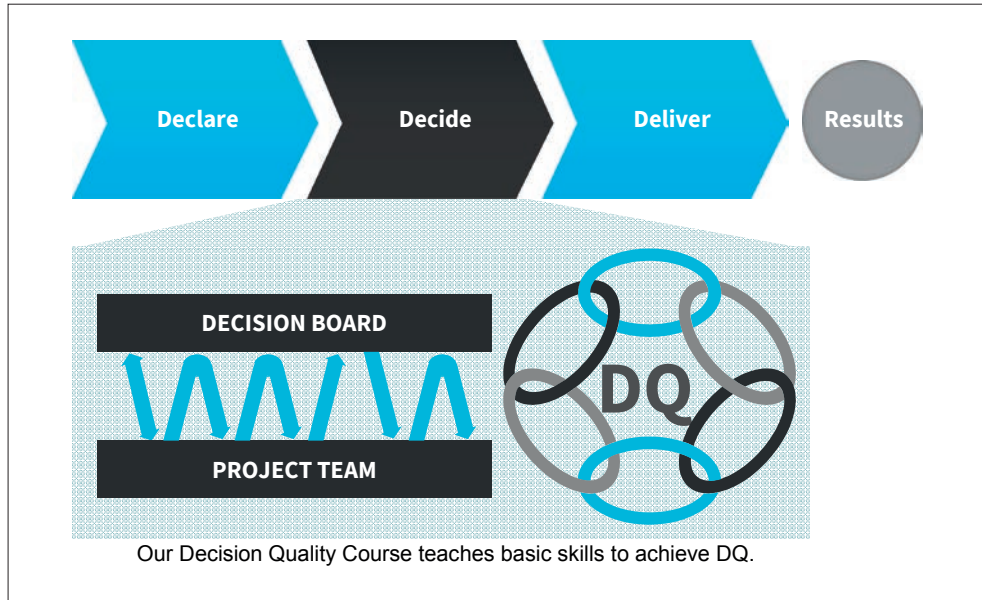
The reason you want to look back is because that is the way you learn and improve the whole decision process. It is not for blaming, although in the regulatory world, you might need to go back and ask: "Who made the mistake and how should they be punished?" In the end, what you are trying to show in documentation is: "We made the best decision we could then. Here is what we thought about the uncertainties. Here is what we thought were the driving factors."

This kind of learning process often gets applied in pharmaceutical decision making, where people make big bets, usually at the beginning of phase three, where suddenly the investment required increases greatly. Looking back is powerful if you take a decision quality perspective. You always want to ask: "Did we do what we needed to do in terms of the six requirements of DQ?" To focus on quality decision making, there are really two pieces to the decision process. One is how we get there, but more important even than how we get there, is that we arrive at a quality decision and we know how to judge it when there.

Decision failures are caused when people fail to achieve 100% in one or more of the six requirements (Figure 3.6). For example, if you did not come up with the right frame, you would have done a good job solving the wrong problem. If a decision maker did not use reliable information, that decision would exemplify a "garbage in, garbage out" decision. Regarding alignment and commitment to action, remember, there is a big difference between clarity and actually doing it. In the regulatory world, that is usually not the problem. When you say "yes," people are ready to move. However, inside corporate decision making, you can have great clarity and nothing might move for months. Making sure you get true alignment and commitment to action must be part of the decision because a decision is not made until the committed action is actually defined and is moving.

Some principles of DQ are already adopted in parts of the pharmaceutical industry such as clarity of roles and including uncertainty. The idea of defining decision quality and using this as another metric will result in greater awareness and actions

Figure 3.6. A focus on DQ with an effective decision process avoids most decision failures.

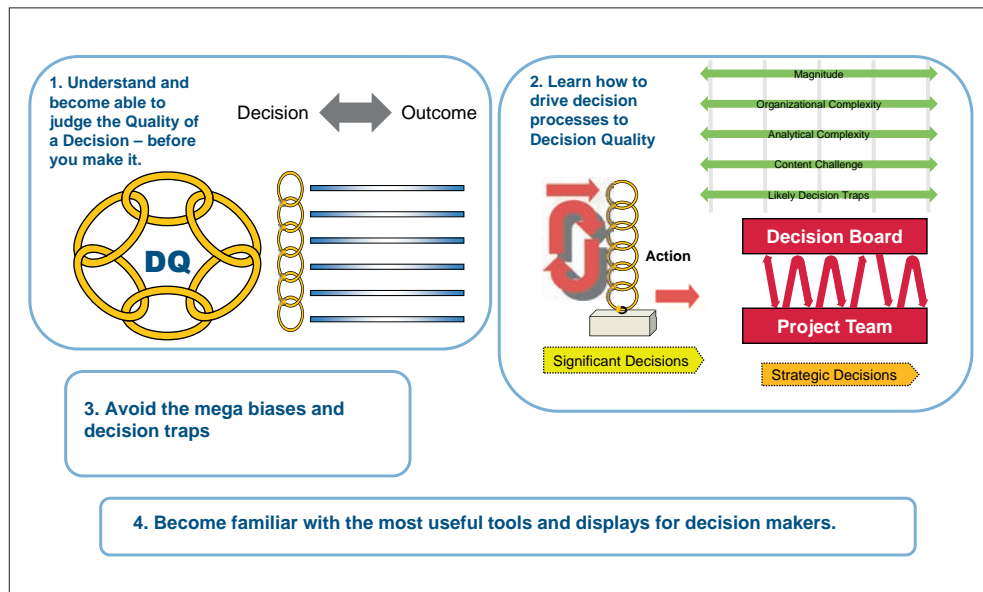


or prevention of actions that will help avoid most decision failures and traps on the journey to DQ.

The truth is that when decision makers and individuals understand the importance of reaching quality in each of the six requirements, they feel meeting those requirements is a decision-making right and should be demanded as part of the decision process (Figure 3.7). For them, to be in a position where they can make a good decision, they know they deserve a good frame and significantly different alternatives or they cannot be in a position to reach a powerful, correct conclusion and make a decision. From a decision-maker's perspective, these are indeed needs and rights to be thought about. From a decision support perspective, these needs and rights are required to be able to position the decision maker to make a good choice.

Today, the biggest adopters of decision quality capabilities and principles are those individuals or organisations making a "big bet" with decisions made under conditions of uncertainty, typically in the pharmaceutical, oil and gas and high-tech sectors. Of note, Pfizer recently and Lilly a year ago, won the Raiffa-Howard award for organisational decision quality. These organisations have achieved DQ in specific decisions, and also have achieved DQ in significant organisational domains, in particular in their development portfolios.

Figure 3.7. Decision makers need to have a basic understanding of the DQ framework and to develop the skills to demand DQ.



The DQ framework forms the core knowledge of a large and growing group of decision professionals who assist leaders around the world with strategic decisions. Building DQ enables measurable value creation and its framework can be learned, implemented and measured. Become familiar with how DQ helps you navigate the complexity of uncertainty of significant and strategic choices. Develop the skillset to achieve DQ and avoid mega biases and big decision traps. Most importantly, familiarise yourself with the useful tools available that will help you drive process to DQ.

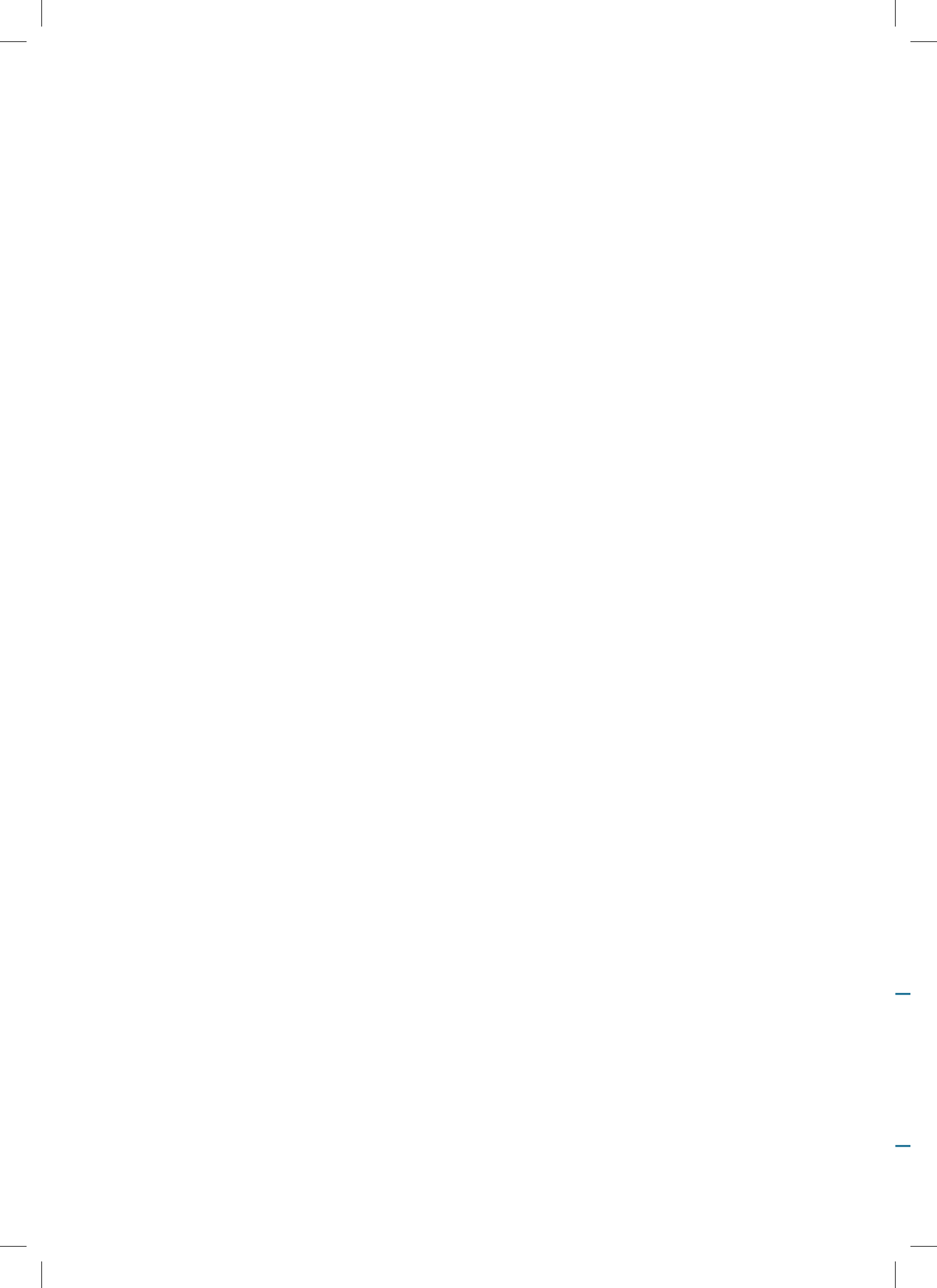
Note

The decision quality chain was created in the mid-1980s by Strategic Decisions Group (SDG). The chain and the Dialogue Decision Process were presented by Carl Spetzler and Vince Barabba at the Planning Forum International Conference in Toronto, Canada on April 30, 1991 (materials available as a download from the SDG website). The chain and process were published in book form in 1998 as *The Smart Organization* by David Matheson and Jim Matheson, then colleagues at SDG. The book focuses on DQ particularly in the context of R&D-intensive organizations. See David Matheson and Jim Matheson, *The Smart Organization: Creating Value through Strategic R&D* (Boston: Harvard Business School Press, 1998).

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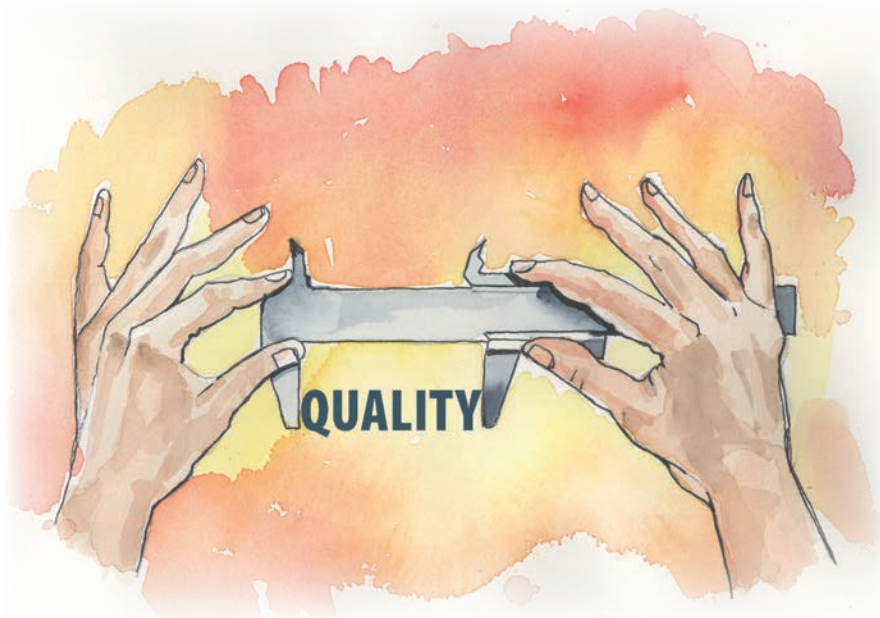


CHAPTER 4

KEY ISSUES FOR STAKEHOLDERS IN THEIR DECISION-MAKING PROCESSES IN THE DEVELOPMENT, REGULATORY REVIEW AND REIMBURSEMENT OF MEDICINES

“The value of quality decision making is not only just for the decision (and its implications), but to the effectiveness of teams, better productivity between teams and leadership, and to ensure a level of trust across the broader organisation as well as between various stakeholders”

Participant comment from regulatory questionnaire



Magdalena Bujar

Project Manager

Centre for Innovation in Regulatory Science



Introduction

The science and art of decision making is well established, but this topic is still largely unexplored in the area of medicines' development, regulatory review and reimbursement.¹ Moreover, it has been recognised by researchers in this field that "what gets measured gets done" and therefore organisations that seek to improve their decisions should also routinely measure the quality of their decision making.² Nevertheless, it is important to note that decisions made under conditions of uncertainty, such as those made throughout the lifecycle of medicines, should be judged by the quality of the decision-making process, not just by the quality of the outcomes. Although a good process may not always guarantee a favourable outcome, such as achieving regulatory approval and reimbursement of a medicine on the market, organisations can increase the probability of positive outcomes by having more structured decision-making processes, being aware of cognitive biases and by establishing an organisational culture of constructive debate.³ Pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies already concentrate on the generation and analysis of medical, social, economic and ethical data, but it is not always clear how the decisions, which require judgement and interpretation, are made around the information.⁴ Nevertheless, organisations involved throughout the lifecycle of medicines should not ignore the human factor in the making of important decisions, as this is key to ensure trust and transparency in the development and review of medicines. Consequently, a study was initiated by the Centre for Innovation in Regulatory Science to address the research gap in quality decision making during the lifecycle of medicines, where the aim was to provide insight into the decision-making practices, processes and perspectives behind regulatory and reimbursement decision making. Interestingly, almost all the participants who took part in the study described below agreed that their organisation's decision making could be improved.

Study method and approach

This study was carried out in two parts, first in 2015 in regulatory agencies and regulatory company departments,⁵ followed by a 2017 study in HTA agencies and health outcomes company departments. As many decisions are made within these organisations on a daily basis, the study was anchored to specific high-level decisions, as outlined below. The objectives were to evaluate the decision-making processes, the use of frameworks and formal assessments as well as the perceived occurrence of biases during:

1. Regulatory decision making
 - › Pharmaceutical company decision to submit a dossier to a regulatory agency
 - › Regulatory agency review decision to approve or reject a medicine

2. HTA decision making

- › Pharmaceutical company process for evidence generation to support reimbursement of medicines
- › HTA agency appraisal decision-making process to recommend reimbursement of medicines

Questionnaires on reimbursement decision making were sent to 16 HTA agencies in Australia, Europe, Canada and Latin America and 24 multinational companies. The responses were compared with published results of questionnaires sent to 25 companies and 14 regulatory agencies in Australia, Asia, Europe and North America.⁵

Results

An average response rate of approximately 65% was received from the four groups, which suggested interest in this topic. Overall, for the regulatory questionnaire, responses were received from 10 out of 14 regulatory agencies (71%) in Australia, Canada, Singapore, the US, the European Medicines Agency and national agencies from the European member states (Denmark, France, Sweden, and United Kingdom using the national procedure; and the Netherlands using the centralised procedure); as well as 17 out of 25 major international pharmaceutical companies (68%). On the other hand, for the reimbursement questionnaire, responses were received from 11 out of 16 HTA agencies (69%) in Australia, Belgium, Brazil, Canada (national and Quebec), England, Netherlands, Poland, Scotland, Spain (Basque region) and Sweden; as well as from 12 out of the 24 companies (50%), where 1 company declined to respond due to the inability to meet the deadline and 11 (46%) gave positive responses which were used in the analysis.

The key results are presented under the following subheadings:

1. Decision-making processes
2. Frameworks and practices
3. Biases in decision making
4. Measures for quality decision-making process
5. Challenges and solutions

1. Decision-making processes

The following process characteristics were evaluated across the companies and agencies for the respective decision-making processes: use of committees (defined as a formal or informal decision-making group); types of decision-making processes (consensus; majority vote or one individual makes the decision based on committee recommendation) and types of decision-making systems (qualitative, which is

based on expert or management opinion; quantitative primarily based on data and computing or mixed) (Figure 4.1).

Some similarities were identified between the decision-making processes of pharmaceutical companies, regulatory authorities and HTA agencies, such as the use of committees, having a primarily mixed (qualitative/quantitative) internal decision-making system. Nevertheless, the results indicate differences, as companies and agencies use diverse processes to arrive at the final decision, either through consensus, majority vote or an individual making the decision. This may be due to the difference in the purpose of the decision made by an agency as opposed to a company, as well as to other factors such as differences in scope, political pressures or cultural differences between the various organisations.

2. Frameworks and practices

Second, the study evaluated the use of frameworks to structure the decision-making processes within companies, regulatory authorities and HTA agencies, which is perceived as key to ultimately provide more process consistency and increase the probability of better outcomes³ (Figure 4.2). The definition of a *framework* was adapted from previous research in the area of benefit-risk assessment⁶ and was defined as “a set of principles, guidelines and tools which provide

Figure 4.1. Committee, process and system characteristics for pharmaceutical companies (regulatory and health outcome departments), regulatory authorities and HTA agencies.

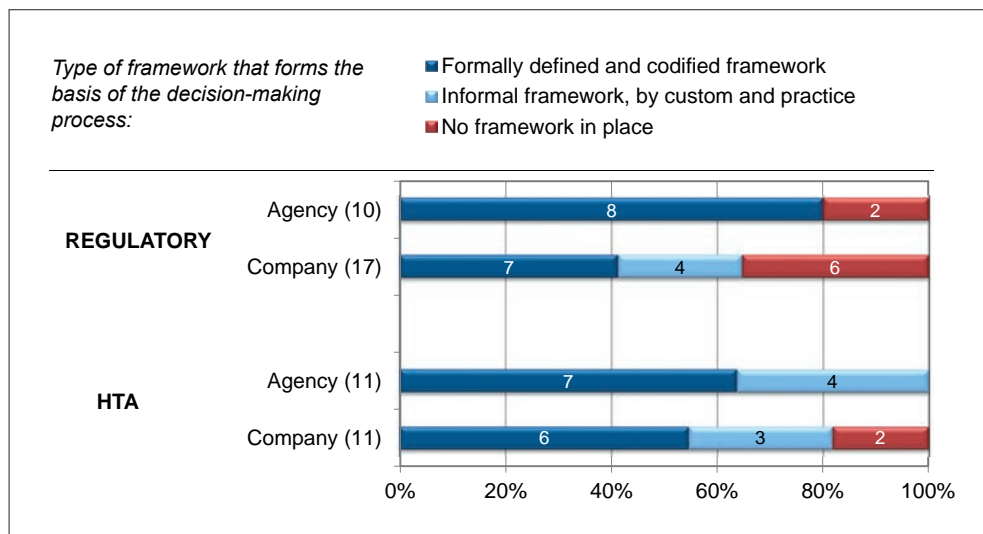
		Committee		Committee Process		Decision-making System	
		REGULATORY	HTA	REGULATORY	HTA	REGULATORY	HTA
AGENCY		9 out of 10 (90%) use a Committee (4 ad hoc)	10 out of 11 (91%) use a Committee	<ul style="list-style-type: none"> • 5 (56%) individual • 3 (33%) majority • 1 (11%) by consensus 	<ul style="list-style-type: none"> • 5 (50%) majority • 4 (40%) consensus • 1 (10%) individual 	<ul style="list-style-type: none"> • 4 (40%) mixed • 4 (40%) quantitative • 2 (20%) qualitative 	<ul style="list-style-type: none"> • 9 (82%) mixed • 1 (9%) quantitative • 1 (9%) qualitative
		All 17 (100%) use a committee	10 out of 11 (91%) use a Committee	<ul style="list-style-type: none"> • 7 (41%) consensus • 6 (35%) individual • 4 (24%) other 	<ul style="list-style-type: none"> • 4 (40%) individual • 4 (40%) consensus • 2 (20%) other 	<ul style="list-style-type: none"> • 9 (52%) quantitative • 4 (24%) mixed • 4 (24%) qualitative 	<ul style="list-style-type: none"> • 9 (82%) mixed • 2 (18%) qualitative
COMPANY							

a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision”.

The majority of agencies and companies have a framework in place that forms the basis of their respective decision-making process, but a formally defined and codified framework was not always used within organisations, particularly within companies, whereas a number of participants used an informal framework, which had never been clearly agreed but over time became practice (i.e., by “custom and practice”). The top reasons for not having a formally defined and codified framework were a lack of a validated framework being available or the benefits of a framework were not apparent as well as resource/administrative limitations.

The participants were asked to select “Quality Decision-Making Practices” (QDMPs) that were incorporated into their organisation’s decision-making framework. The QDMPs proposed for this study were previously developed based on results from semi-structured interviews with 29 key opinion leaders from agencies and companies to investigate and identify the key issues that influence decision making.⁷ The majority of companies and agencies incorporated the 10 QDMPs into their formal frameworks (Figure 4.3). QDMPs, which were least incorporated into the frameworks were QDMP 5, 7, 8 and 10 as detailed below. Companies and

Figure 4.2. Type of framework used by pharmaceutical companies, regulatory authorities and HTA agencies for the respective decision-making processes during regulatory review and reimbursement.



agencies could address and better incorporate QDMP 5 (assign values and relative importance to decision criteria) and QDMP 10 (effectively communicate the basis of the decision) within their organisational framework by making decision-making values, preferences and uncertainty more explicit and transparent to stakeholders through better communication of decision basis. QDMP7 (evaluates both internal and external influences/biases) was also incorporated by a minority of companies and agencies, which is consistent with the perception that biases systematically affect decision-making processes within companies and agencies alike; this will be discussed in more detail in the next section. Finally, QDMP 8 (perform impact analysis of the outcome) was also generally not incorporated, which may be due to the perceived narrow frame of the decisions made by companies and agencies, where, despite its importance, impact analysis may not be considered as an essential step. Nevertheless, those QDMPs which were least incorporated into agency and company frameworks were generally considered relevant by the four groups.

Figure 4.3. Quality decision-making practices (QDMPs) incorporated into organisations' formal frameworks, where (n) = number of respondents.

Quality Decision-Making Practice (QDMP)	Practice incorporated?			
	Regulatory		HTA	
	Agency (8)	Company (7)	Agency (7)	Company (6)
1. Have a systematic, structured approach to aid decision making (consistent, predictable, timely)	Practice generally incorporated			
2. Assign clear roles and responsibilities (decision makers, advisors, information providers)	Practice generally incorporated			
3. Consider uncertainty regarding the process*	Practice generally incorporated			
4. Examine alternative solutions*	Practice generally incorporated			
5. Assign values and relative importance to decision criteria	25%	57%	43%	50%
6. Re-evaluate as new information becomes available	Practice generally incorporated			
7. Evaluate both internal and external influences/biases	50%	86%	43%	33%
8. Perform impact analysis of the outcome**	38%	57%	86%	17%
9. Ensure transparency and provide a record trail	Practice generally incorporated			
10. Effectively communicate the basis of the decision**	38%	57%	86%	67%

* These two QDMPs were combined as one in the regulatory questionnaire
**These two QDMPs were combined as one in the regulatory questionnaire

3. Biases in decision making

Any decision with an element of risk is subject to universal human biases such as over-optimism and loss aversion. Key, strategic decisions are also susceptible to biases, particularly when the incentives of certain individuals are not aligned with the rest of the organisation. Consequently, the different types of cognitive biases that occur during decision making were also investigated. Four main groups of biases adapted from previous research⁸ were proposed for this study to underpin the evaluation of bias perception within companies and agencies:

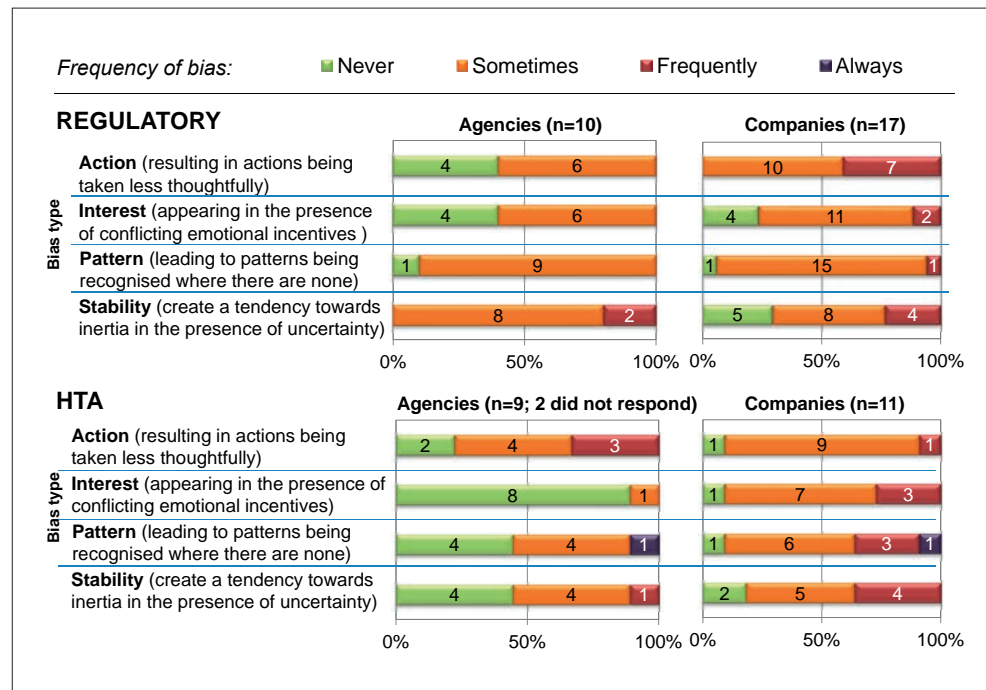
- › **Action biases**, such as gut feeling or over-optimism resulting in actions being taken less thoughtfully
- › **Interest biases**, such as misaligned individual or organisational attachments, appearing in the presence of conflicting emotional incentives
- › **Pattern-recognition biases**, such as confirmation bias that seeks out information supporting a favoured decision and ultimately leads to patterns being recognised even where there may be none
- › **Stability biases**, namely preference for the status quo in the absence of pressure to change it, thereby creating a tendency towards inertia in the presence of uncertainty

Agencies and companies considered the perceived occurrence of biases within their organization as relevant, but this varied according to the type of bias (Figure 4.4). In general, interest bias (arising in the presence of conflicting incentives) was perceived as the least influential by both HTA and regulatory agencies, which may be due to strict conflict of interest regulations within the various committees at both agencies. Action-oriented bias (e.g., overconfidence or intuition leading individuals to take action less thoughtfully) was perceived as most influential within HTA agencies and stability bias (creating a tendency towards inertia in the presence of uncertainty) within regulatory agencies. For regulatory and health outcome departments within companies, the responses were mixed, but in general, companies perceived a higher influence of biases on their decision making compared to agencies.

Nevertheless, it was suggested⁸ that organisations can reduce the impact of those biases by assessing and appropriately adjusting their decision-making processes and culture as outlined below:

- › *Counter action biases* by recognising uncertainty and discussing probability of different outcomes
- › *Counter interest biases* (individual preferences, incentives, career options) by making them explicit
- › *Counter pattern-recognition biases* by changing the angle of vision and encouraging debate

Figure 4.4. Types of biases and the perceived frequency at which they occur within pharmaceutical companies, regulatory authorities and HTA agencies during their decision making.



- › *Counter stability biases* by challenging status quo and coming up with innovative alternatives

4. Measures for quality decision-making process

The only way organisations can learn how to make better decisions is by first evaluating the quality of their decision making. Consequently, companies and agencies were asked whether there are evaluations in place to periodically measure the quality of decision making within their organisations either through: audit of the decision-making process; examination of the actual outcome compared to expected outcome or formal feedback from internal and external stakeholders. The results indicated that companies and agencies did not generally have formal assessments to measure the quality of their decision making. For the few regulatory and HTA agencies as well as company departments that undertook formal assessments of decision-making quality (19 out of 49 organisations), the majority did this by obtaining feedback from stakeholders (15) or re-evaluating the outcome (15) but only a small minority actually audited the decision-making process (11), despite this being a key measure. Consequently, more effort is needed to increase the awareness of assessing and improving the quality of the process

to increase the probability of good outcomes. The respondents were asked who conducts the various evaluations and in general, for regulatory and HTA agencies, the assessments were carried out by a mix of internal and external groups, whereas for companies the assessments were generally carried out by internal groups. Interestingly, when asked whether the respondents believe that evaluating the quality decision-making process is possible, almost all the respondents agreed this to be the case and made good suggestions for doing this (Figure 4.5).

5. Challenges and solutions

The following key challenges for quality decision making were identified by pharmaceutical companies, regulatory authorities and HTA agencies:

- › Occurrence of biases: optimism, stability and historical biases from previous decisions
- › Misalignment and competing interests
 - Internally, for example, within companies - between HTA and regulatory functions and requirements (focus primarily on registration)

Figure 4.5. Key measures proposed by pharmaceutical companies (regulatory and health outcome departments), regulatory authorities and HTA agencies for assessing the quality of decision making.

Regulatory	
Agencies (n=7)	Companies (n=17)
1. Assess adherence against validated standard or guideline for decision making	1. Assess the outcomes such as obtaining a first cycle approval, achieving a label decided at submission stage, short time to submission and approval
2. Review the consistency of the decision-making practices within an organisation	2. Receive formal feedback from internal and external stakeholder
3. Assess the degree of clarity and transparency in decision making	3. Identify signs of bias
4. Review that all evidence (positive and negative) has been considered	4. Review lessons learned including best practices and project insights
5. Formally assess internal stakeholders' evaluation practices	5. Evaluate adherence to the decision-making practices
HTA	
Agencies (n=6)	Companies: (n=7)
1. Formal assessment of the internal decision-making process including decision transparency and communication	1. External benchmarking of decision-making processes and outcomes compared to other jurisdictions
2. Incorporation of milestones and indicators into process to verify if key factors at each stage are addressed by internal stakeholders	2. Internal assessment of the decision-making process (structure; use of committees and frameworks)
3. Evaluation of HTA success compared to the evidence generated	3. Degree of participation and engagement with stakeholders
4. Analysis of the actual decision and its foundation including the evidence considered and other influencing factors	4. Formal feedback from internal and external stakeholder

- Externally, for example, relating to agency requirements and standards – local vs global; HTA vs regulatory
- › Time pressure – need to decide quickly and reluctance to start early
- › Resource constraints
- › Lack of a universal decision-making framework and practices
- › Lack of training in decision making
- › Poor assessment of uncertainty
- › Poor strength, availability or assessment of evidence
- › Lack of formal feedback regarding decision impact in place
- › Political pressure
- › Lack of trust

Finally, the various stakeholders suggested the following solutions for the above barriers:

- › Establish or implement a structured decision-making framework/method that requires values/preferences/uncertainty to be made explicit
- › Initiate a more formal review of decision-making processes, outcomes (both positive and negative) and feedback from stakeholders
- › Promote education and training regarding decision making and communication
- › Ensure transparency and information access within organisations
- › Have a robust system that focuses on evidence, including real-world evidence and facts
- › Create an environment that encourages dissenting opinions and challenging ideas
- › Incentivise internal systems to align and facilitate cross-functional collaborations (HTA-regulatory), planning and collection early in the process
- › Encourage early and frequent discussions with external stakeholders (regulatory and HTA)
- › Ensure multi-stakeholder inclusion for example, patients and payers
- › Lobby for a more predictable and harmonised environment

Conclusion

Although most participants recognised the occurrence of biases within their organisation as well as the need to improve the quality of their decision-making process, the majority do not currently perform any such formal assessments, but interestingly believe that it can and should be done. The findings of this study demonstrate the relevance of the 10 QDMPs for ensuring quality decision making by companies, regulatory authorities and HTA agencies; the need to implement these into formal decision-making frameworks within organisations and the importance

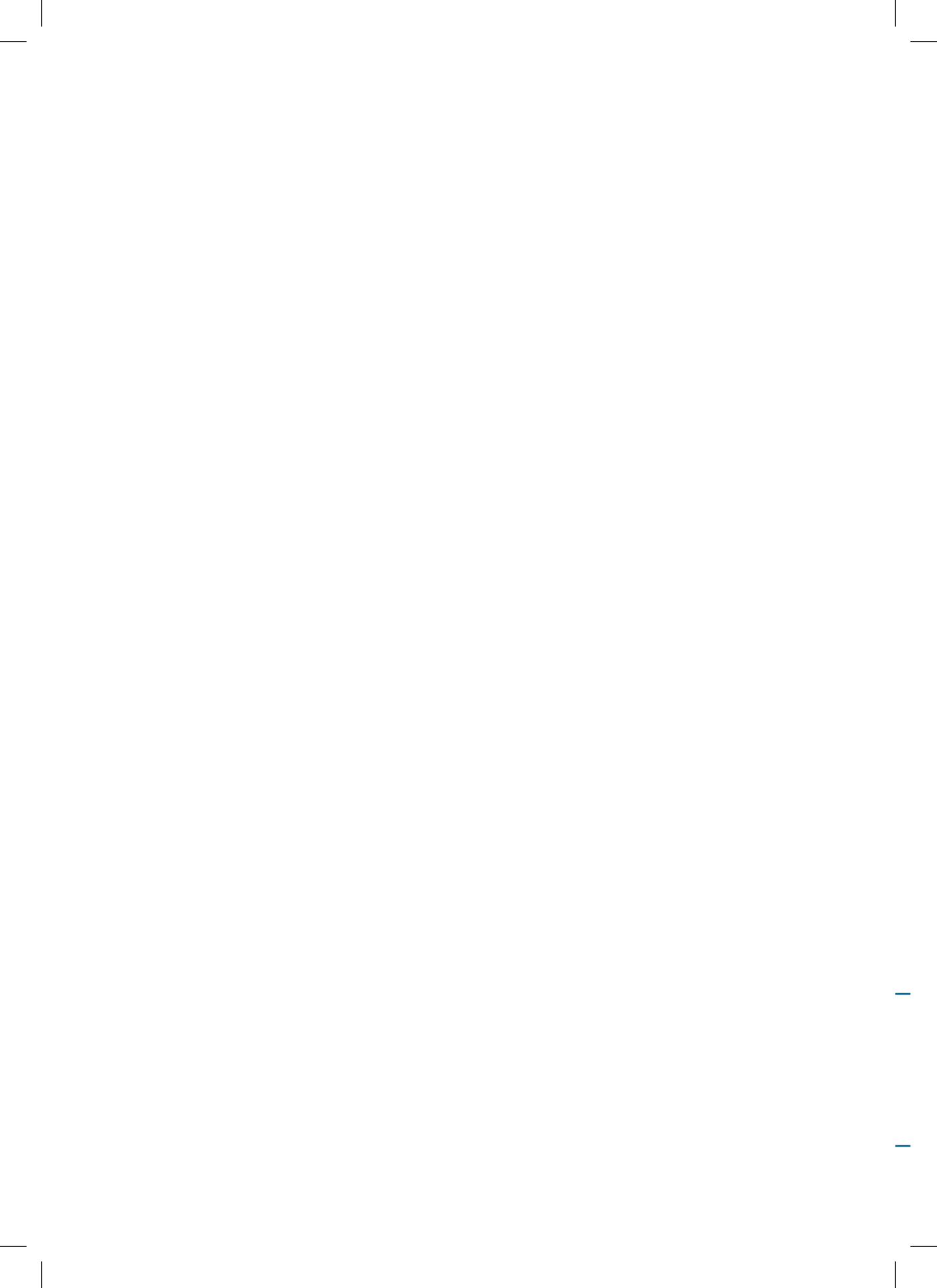
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KEY DECISION-MAKING ISSUES

of periodically evaluating the practical implementation of these practices within organisations using the most appropriate available measures.¹ Furthermore, there is a need to continue research into this topic to help increase awareness of the importance of quality decision making as well as uncover areas for improvement within companies and agencies in order to ultimately enable consistency, trust and transparency to be built into the critical decisions during the lifecycle of medicines.

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CHAPTER 5

BUILDING QUALITY INTO DECISION MAKING: A REGULATORY AUTHORITY PERSPECTIVE

“Attention to decision quality includes the need for a regulatory agency to attend to the quality of content as well as process to address critically important decisions in a timely efficient way.”



Dr Theresa Mullin

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Center for Drug Evaluation and Research US Food and Drug Administration



Introduction

Various decisions made by pharmaceutical companies, regulatory authorities and health technology assessors throughout the life cycle of medicines are critical to ensuring the availability of safe and effective medicines. It has also been noted that it is very difficult to assess the quality of such decisions in terms of outcomes or consequences and effort might be better spent focusing on building quality into the process. Some approaches and efforts that the US FDA has been undertaking to build quality into drug regulatory decision making are described, particularly those related to the review of new drug marketing applications.

Decision context: FDA assessment of drug benefits and risks

As part of its public health mission, FDA ensures that safe and effective drugs and biologics are available to American patients. To be approved for US marketing, a drug must be safe and effective for its intended use. The meaning of “safe” is not explicitly defined in the law or regulations, and recognising that all drugs have some ability to cause adverse effects, the safety of a drug is assessed by determining whether its benefits outweigh the risks. This benefit-risk assessment is the basis of the FDA’s regulatory decisions in the pre-market and post-market review process. The assessment will evaluate the evidence of safety and effectiveness submitted in a New Drug Application (NDA) or a Biologics License Application (BLA), as well as an analysis of the disease condition and available treatment options for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.

In making a benefit-risk assessment for a submitted NDA or BLA, FDA reviewers consider the medical severity of the condition and how it affects patients’ daily living across the spectrum of disease severity, and how well the patient population’s medical needs are met by currently available therapies. The assessment of drug benefit will examine the evidence of effectiveness in terms of the evidentiary standard, the clinical relevance of studied endpoints (including how well they relate to how a patient feels, functions, and survives), how measured treatment effects translate to patient benefits, and how well that can be extrapolated to the indicated population. Product risks are assessed through examination of the submitted safety database including how well this database would reflect expected use in the patient population, and examine the most important safety concerns identified. This includes aspects that inform assessment of the likelihood that identified risks could be effectively managed. The risk assessment includes consideration of potential

drug interactions, potential safety concerns based on pharmacological or non-clinical findings, and potential harm posed by any unresolved product quality issues. As part of the assessment, the reviewer must also consider how specific concerns about the product's safety profile might change in the post-market setting if the product were approved, related, for example, to changes in prescriber specialty, care setting, care management, or treated population. The limited information available at the time of the regulatory reviewer's pre-market benefit-risk assessment creates inevitable uncertainties related to all of these critical considerations.

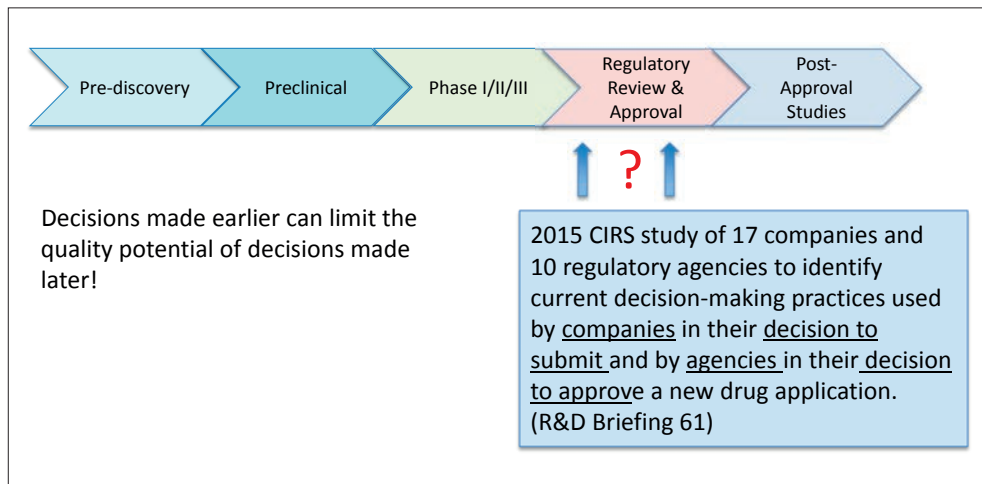
Improving quality by reduction of avoidable uncertainty

Although the submitted applications include a vast amount of information that must be sifted through and analysed in a fairly short well-defined period of time that defines the review cycle, there are typically a number of residual uncertainties that must be factored into the assessment and review decision. These sources of uncertainty can potentially reduce the quality of the risk-benefit assessment, in terms of accuracy, efficiency, timeliness and other factors.

Some of the sources of uncertainty are rather unavoidable and have to do with factors such as current understanding of the underlying science, or the limits of extrapolation from the still-limited body of evidence generated in even the best-designed clinical development programmes. Other sources of uncertainty are the result of avoidable suboptimal decisions or practices occurring "upstream" of the regulatory pre-market review at an earlier stage of drug development (Figure 5.1). Unnecessary uncertainty can be contributed by both drug developers and regulators. Regulators can reduce their contribution by establishing clear technical standards (where the science permits) that are applied in a consistent way. Timely and effective communication between companies and regulators during drug development, for example, communication related to standards and regulatory expectations, can also reduce uncertainty and improve the quality of the development programmes. Drug companies can reduce their contribution to uncertainty by taking steps to better plan drug development programmes to generate better evidence of new medicines effectiveness and safety.

The findings of a recently published CIRS study suggest support for this. In 2015 CIRS conducted a study among 17 pharmaceutical companies and 10 regulatory agencies to identify current decision-making practices used by companies in their decision to submit and by agencies in their decision to approve a new drug application. They reported that company respondents identified "poor assessment of uncertainty or strength of evidence" as one of the hurdles, and regulators identified a "reluctance to discuss uncertainties or value judgments" and "ensuring consistent review or evaluation practices" among their top hurdles to better decision-making.¹

Figure 5.1. Decisions made upstream of regulatory review and approval can contribute avoidable uncertainty that can affect decision quality.



Building in quality upstream of regulatory review

In addition to the already-recognised value of early and ongoing consultation between sponsors and regulators during drug development, some more recent work at FDA has highlighted further opportunities for building quality into development to produce better quality evidence for subsequent decision making.

Making an early effort to gain patients' perspectives

One of these opportunities involves early effort to get patients' and caregivers' perspectives on what matters most in treatment of their disease. FDA recently completed a commitment under the 2012 reauthorisation of the Prescription Drug User Fee Act (PDUFA), to hold at least 20 public meetings where each focused on a different disease area.² Referring to this as the Patient Focused Drug Development (PFDD) initiative, FDA focused each meeting on hearing from patients regarding the impact of the disease on their daily life and their experience with available therapies.³ Key learnings from this initiative included an understanding that patients are technical experts on the burden of disease and the burdens of treatment, and the observation that patients "chief complaints" heard in these meetings often were not factored explicitly into drug development plans, including measures of drug benefits planned in trials. This sort of omission can contribute to later uncertainty about the clinical relevance of chosen endpoints, their meaning to patients, and how trial findings translate to assessed benefit in the regulatory review.

In the course of PFDD meetings in certain disease areas FDA took the opportunity to explore and better understand patients' perspective on participation in clinical

trials, for example, when FDA reviewers and others had noted difficulties in achieving the targeted levels of enrolment in studies. These PFDD meetings gave the patient community an opportunity to voice their desire to be more actively involved in clinical research and participation in trials, and their concerns about unacceptable burdens that often appeared to be required. For example, parents of paediatric patients would describe the impossibly long distances to trial sites, the almost unbearable frequency of painful procedures, side effects of treatment and other features of the studies being conducted. Drug companies and FDA staff listening to these concerns have noted that many of these concerns could be better addressed through more thoughtful upfront planning that enlists the perspectives of patients or their caregivers, to locate and operate the studies and adjust protocols to make them more acceptable, increasing enrolment and supporting sustained participation. Improving study enrolment can yield greater efficiency as well as quality and reducing drop-outs will reduce the level of missing data (and associated uncertainty), enhancing the quality of collected evidence.

Clarifying clinical study objectives upfront

FDA statisticians have recently been engaging with their regulatory and industry counterparts at the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) to advance regulatory guidance and standards related to estimands and sensitivity analysis in clinical trials. Although this topic, pursued by the ICH E9 (R1) Expert Working Group, may sound a bit arcane to the non-statistician, it relates to a key aspect of the quality of evidence collected in trials, and calls for early attention. The importance of this topic was introduced with the observation that randomised trials are expected to be free from baseline confounding, but not from confounding and bias due to events that occur after randomisation, such as discontinuation of treatment, use of rescue medication, treatment switching, and other post-randomisation “intercurrent” events. Although such events complicate the understanding and estimation of relevant treatment effects, they also occur in clinical practice and the expected effects of medicines should be described in a clinically relevant way.

Under current practice these post-randomisation intercurrent events are dealt with implicitly by choices made about data collection and statistical analysis and those choices define the scientific question of interest that will be addressed. Instead, the ICH E9 experts contend, this practice should be reversed, and aspects of trial design, data collection and statistical analysis should be informed by clarity on the key scientific question of interest, and consideration of post-randomisation events is critical. Having clarity in the trial objectives and accounting explicitly for

intercurrent events when describing the treatment effect of interest, can then inform trial design, data collection and statistical analysis.⁴ This approach can lead to better-quality evidence of clinical benefit and reduce uncertainty in assessing how the clinical trial evidence of benefit will translate to benefit for the broader indicated population.

Building consistency and transparency into the regulatory review

Building quality into development programmes can help to ensure that better-quality evidence can be submitted to regulators to inform their benefit-risk assessment of a new drug. FDA has also taken steps to enhance the quality of that regulatory assessment and related decision making. Efforts in this area began with the recognition that FDA makes regulatory decisions based on both scientific evidence and US law and regulations. FDA regulatory decisions may be challenged in court and litigated. It is important that agency decisions not be “arbitrary and capricious”; they must reflect a consistent policy, otherwise they are not fair. FDA regulatory decisions thus form a sort of “case law” and each decision is made either in alignment with established policy or establishes new policy. In making benefit-risk assessments, for example, FDA considers the evidence for the current case and also takes into account any precedents.

In addition, decisions based on benefit-risk assessment are included by established statutory and regulatory standards, societal expectations and reviewers’ personal values and perspectives. Because only limited information is available at the time of a premarket review decision, it is also understood that the evaluation of the drug’s benefits and risks will likely evolve as more is learned over the life cycle of the product. These elements of judgement and uncertainty can also feature differences in clinical and scientific judgements among FDA experts and can lead to differing individual opinions and conclusions regarding the benefit-risk assessment. Reconciling such differences and understanding where trade-offs are made can be challenging. Although often limited to clinical development experience, the sheer quantity of information submitted by the sponsor that must be evaluated and considered by FDA is substantial, making the assessment task complex.

To assist reviewers in consistently organising and thinking through this prodigious volume of information and evidence, including the attendant uncertainties, FDA developed a structured framework to be used to summarise the relevant facts, uncertainties, and key areas of judgement, and clearly explain how these factors influence the agency’s regulatory decision. During the five-year authorisation of

PDUFA beginning in 2012, FDA implemented the use of this benefit-risk assessment framework (Figure 5.2) for all NDA and BLA reviews and has completed an extensive third-party evaluation of the experiences of reviewers and sponsors to assess its value. The analysis of 43 applications, including interviews with 104 FDA staff, 45 applicant representatives, and 154 external stakeholders found that the framework was successfully integrated into the regulatory review documents and was effective in communicating the reasoning behind reviewers' regulatory recommendations or decisions to internal and external stakeholders (including application sponsors). In addition, three-quarters of the FDA interviewees considered the framework useful in organising their thinking about benefits and risks, reminding reviewers to cover key points, training new reviewers and communicating the benefit-risk analysis in a concise standardised fashion.⁵ Based on the success to date, FDA plans the continued use and enhancement of this approach.

Readier access to relevant data and knowledge

Timely access to decision-critical information is important to decision quality; making it easier to find decision-relevant data can help reduce another source of avoidable uncertainty. Regulatory decisions regarding the marketing approval of a new drug or biologic are typically based on very large volumes of submitted data collected during years-long drug development programmes. The size of NDAs and BLAs submitted to FDA often exceed 10GB and without sufficient organisation of the information or standardisation of clinical and other data, can present significant challenges for regulatory reviewers, who must conduct their assessment within tightly constrained review goal timeframes.⁷ To gauge the value of receiving applications for review in a more structured format, FDA conducted an analysis of submission-level data for all 862 original NDAs/BLAs submitted to CDER from FY2003 to FY2009 in the review cycle prior to first FDA action. Using logistic regression to estimate the multivariate correlation, FDA examined factors that affect the timing of the first-cycle action and factors that affect the outcome of the first-cycle action. Improved submission quality, defined as receipt in ICH electronic Common Technical Document (eCTD) format,⁷ was correlated with an increase in the probability of first-cycle approval. Submissions in eCTD format had statistically significant higher likelihood of first-cycle approval. In addition, non-eCTD submissions had not only a lower likelihood of first-cycle approval, but also had statistically significant lower likelihood of meeting FDA review goals. These findings prompted industry support for FDA to be granted authority to require certain regulatory submissions in specified electronic formats through binding guidance.

This authority was provided under the FDA Science and Innovation Act of 2012, which amended the US Food Drug and Cosmetics Act adding a new section

Figure 5.2. The FDA Benefit-Risk Framework supports greater consistency and transparency in approaching and communicating regulatory review decisions.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Sets the context for the weighing of benefits and risks: <ul style="list-style-type: none"> How serious is this indicated condition, and why? How well is the patient population’s medical need being met by currently available therapies? 	
Current Treatment Options		
Benefit	Characterize and assess the evidence of benefit: <ul style="list-style-type: none"> How meaningful is the benefit, and for whom? How compelling is the expected benefit in the post-market setting? 	
Risk	Characterize and assess the safety concerns: <ul style="list-style-type: none"> How serious are the safety signals identified in the submitted data? What potential risks could emerge in the post-market setting? 	
Risk Management	Assess what risk management (e.g., labeling, REMS) may be necessary to address the identified safety concerns	
Benefit-Risk Summary and Assessment		

745A, which addresses electronic submissions. This statutory provision gave FDA the authority to issue binding guidance so that starting 24 months after issuance of final guidance for a specific submission type, sponsors must use the standards defined in the FDA-published data standards catalogue (for submissions for NDAs, ANDAs and BLAs).⁸ The agency has not only put forward requirements for the organisation of submissions, addressed with the ICH eCTD standard, but has also engaged in work through standards development organisations such as the Clinical Data Interchange Standards Consortium (CDISC), to reference standards for the data submitted within various sections of the application, such as clinical study data. The requirement for eCTD submissions has enabled the development of vendor tools for both FDA and sponsors to more easily find information in the application, and for FDA reviewers to see the most current version of the application, correctly reflecting additions made by the sponsor through submission of amendments, which frequently follow the first submission of an application during a review cycle. Standardised data similarly enables use of standard analysis and visualisation tools that enable more rapid reviewer detection, review team discussion and potential sponsor follow-up to any critical review questions. A timely response to such questions can lead to earlier issue resolution and permit marketing approval sooner than would otherwise be possible.

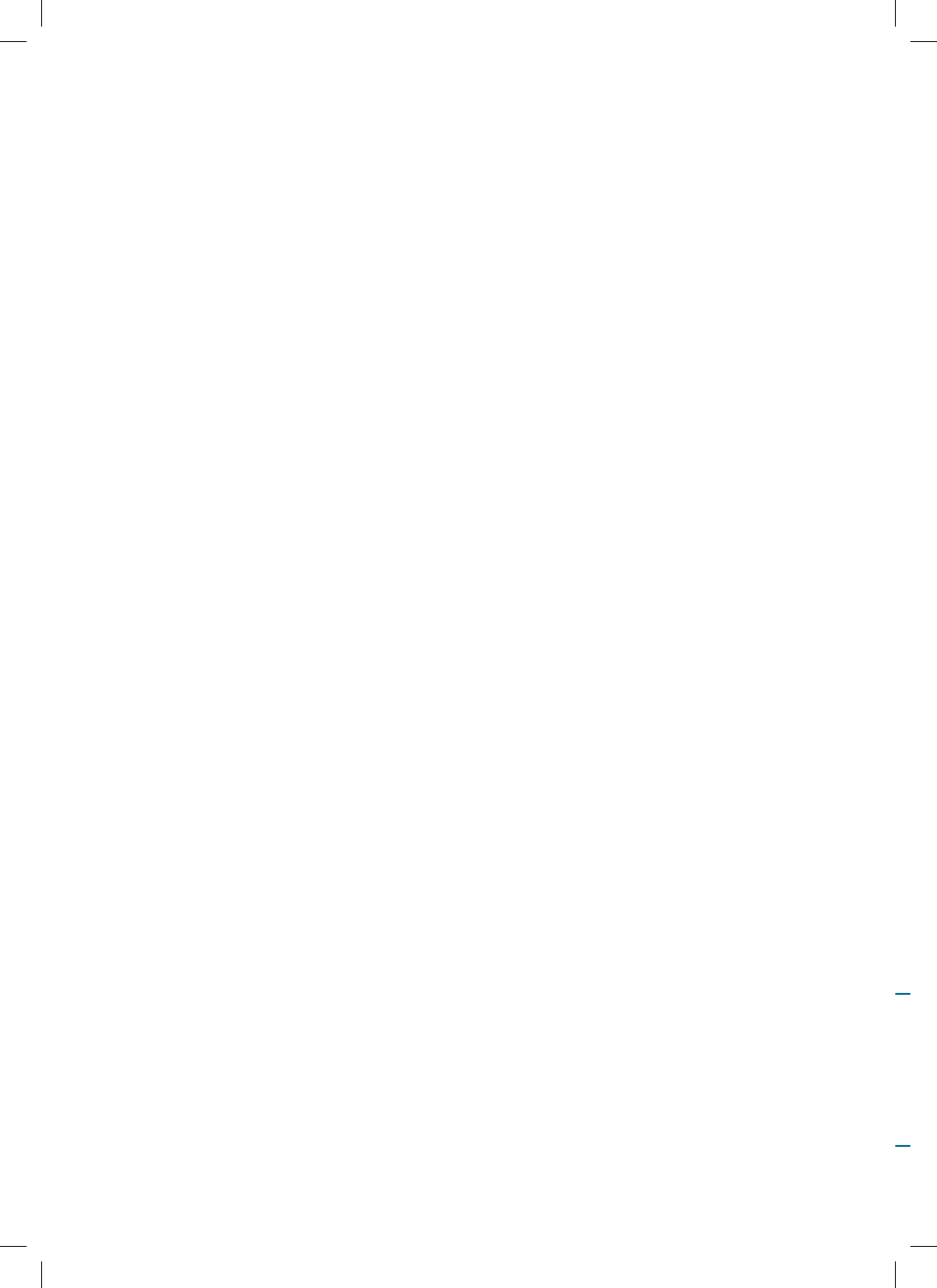
Modernisation of the approach to regulatory data and informatics is likely to play an increasingly important role in supporting and enhancing the drug review process and decision quality. In this area FDA's vision for the desired state includes data being readily accessible, allowing intake and analysis and the ability to display data from multiple sources, for example the review history, relevant precedent decisions, and other documentation, to inform decision making. Use of analysis and visualisation tools applied to these data would support a more collaborative review environment including interdisciplinary team discussions, for example, to comprehensively address important and novel issues. These capabilities and a robust informatics infrastructure additionally enable a knowledge management environment that supports regulatory decision making.

Conclusions

Attention to decision quality includes the need for a regulatory agency to attend to the quality of content as well as process to address critically important decisions in a timely efficient way. FDA's approach to building quality into the decision process has been multifaceted and might be described as one that strives to reduce avoidable uncertainty. Avoidable uncertainty can come from a number of sources, including, but not limited to, imprecision or the potential omission of key stakeholder perspectives that should frame the performance goals for investigational drugs earlier in drug development programmes, related clinical trial objectives and resulting study designs and study planning; lack of structure and consistency in regulators' framing and assessment of benefit-risk considerations and attendant uncertainties; and the inability to gain timely access to potentially available information needed to make the best-informed regulatory decisions should also be included. Addressing such considerations will not only enhance content, but will likely complement and further advance efforts that may be focused on organisational culture and process, which also affect the quality of decision making.

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CHAPTER 6

QUALITY IN DECISION MAKING: AN HTA PERSPECTIVE

“It is time for HTA organisations to shift their traditional view of quality assessment beyond the appraisal of clinical and economic evidence to include a more rigorous approach to assessing the quality of the decisions that HTA bodies make regarding health technologies. More important, perhaps, is a need to put in place the processes that are needed to ensure that there is transparent, rigorous and consistent decision making at the HTA level.”



Dr Trevor Richter

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Introduction

Health Technology Assessment (HTA) organisations are accustomed to viewing 'quality' in terms of the quality of the evidence available regarding the clinical effects and cost-effectiveness of health technologies, such as pharmaceuticals. While the quality of these types of evidence implicitly determines the quality of any decision based upon such evidence, few (if any) HTA organisations have frameworks and processes to explicitly assess the quality of decision making within their organisation.

The work being done by organisations such as the Centre for Innovation in Regulatory Science (CIRS) suggests that it is time for HTA organisations to shift their traditional view of quality assessment beyond the appraisal of clinical and economic evidence to include a more rigorous approach to assessing the quality of the decisions that HTA bodies make regarding health technologies. More important, perhaps, is a need to put in place the processes that are needed to ensure that there is transparent, rigorous and consistent decision making at the HTA level.

The following provides an overview of the extant processes for assessing quality at the HTA level, and expands to suggest how this might evolve in future to improve upon the existing processes for assessments of quality in decision making. The perspective is that of a publicly funded HTA body that carries out health technology assessments of pharmaceuticals for publicly funded drug plans, namely the Canadian Agency for Drugs and Technology in Health (CADTH) Common Drug Review (CDR).

The HTA process in Canada

The CADTH CDR carries out single technology HTA reviews of pharmaceutical products approved for use in Canada by the regulatory authority, Health Canada (HC). After approval of a product by HC, in order to be considered for reimbursement by publicly funded drug plans, manufacturers submit an application to the CADTH CDR for the product to undergo an HTA review. CADTH review teams that comprise a variety of technical experts (clinical reviewers, health economists, clinicians, methods experts, etc.) review available evidence to produce HTA review reports. The clinical HTA report comprises a systematic review and critical appraisal of published clinical evidence and also includes unpublished evidence where relevant (if available). The economic HTA report comprises a critical appraisal of an economic model and report that is provided by the applicant.

HTA reports generated by CADTH review teams are passed to an independent CADTH committee, the Canadian Drug Expert Committee (CDEC), which

considers the evidence in the HTA reports, along with other sources of information, including patient input and input from expert clinicians. Following deliberation of the evidence, CDEC issues a recommendation that specifies whether the product under review should be reimbursed by the Canadian public drug plans that participate in the CDR process, along with criteria or conditions associated with the recommendation. These recommendations are then delivered to individual drug plans, which in turn determine for themselves whether they will fund the product. At the same time, the pan-Canadian Pharmaceutical Alliance (pCPA) determines whether to enter into price negotiations for the product.

Any pharmaceutical products that receive marketing approval (a Notice of Compliance or NOC) from HC could be eligible for a CDR review. More specifically, the types of product that are eligible for review through the CDR process include any pharmaceutical with a new indication(s), therapeutic vaccines, certain blood products, biosimilars, branded generics, and line extensions. Generics are not reviewed by CDR. The CDR process does not generally review drug products that are derived from human blood, drugs that are used primarily in a hospital-setting, prophylactic vaccines, or generic products. Oncology drugs are reviewed through an oncology-specific CADTH programme, the pan-Canadian Oncology Review (pCODR; <https://cadth.ca/pcodr>). In addition, not all jurisdictions within Canada participate in the CDR process: the province of Quebec has its own HTA process, namely the *Institut national d'excellence en santé et en services sociaux* (INESSS; <https://www.inesss.qc.ca/en.html>).

CDR is a reactive process in that CADTH is required to review a submission that meets the eligibility requirements; therefore, most CDR reviews are manufacturer driven. In addition, drug plans that participate in the CDR process can file submissions or resubmissions to CADTH, although these are relatively rare. The focus of the remainder of this Chapter is the CADTH CDR, although the CADTH pCODR process and the HTA processes used by INESSS in Quebec are broadly similar to the CADTH CDR process.

Current HTA processes for quality assessment

The CDR HTA process has within it several processes to ensure that the evidence that is submitted to CADTH for review is of sufficient quality and to allow for an effective HTA assessment. In addition, there are processes in place to allow for assessment of the quality of the CDR assessments.

Submission quality assessment

The first step involves screening a submission to determine whether it meets the requirements for eligibility to the CDR.¹ This includes an assessment of

the quality of the submission based on pre-specified requirements. These requirements specify the type and format of the clinical and economic information that must be included in the submission package. For example, CADTH requires that wherever possible, the default approach used for an economic assessment is a cost-utility analysis (CUA) from the perspective of a public payer. Once the submission meets the eligibility requirements, the CDR review is initiated.

The quality of clinical evidence

The quality of clinical evidence provided by the manufacturer and evidence identified through a systematic literature review is assessed using established HTA critical appraisal methodology. CADTH review teams use a variety of well-established and validated quality assessment tools such as A MeaSurement Tool to Assess systematic Reviews (AMSTAR; <https://amstar.ca>) or Scottish Intercollegiate Guidelines Network 50 (SIGN 50; <http://mtd.dec.gov.ua/images/doc/sign50.pdf>). The quality of the economic model is assessed by health economists against the CADTH economic guidelines² and internationally established standards for economic analyses.^{3,4}

In order to ensure that the quality of submissions to the CADTH CDR meet the highest standards at the outset, CADTH has published guidelines that assist applicants in preparing their submissions to meet appropriate standards of quality.⁵ These include:

- › Submission Guidelines for the CADTH Common Drug Review¹
- › Guidance on Reporting Indirect Comparisons⁶
- › Guidelines for the Economic Evaluation of Health Technologies: Canada⁷
- › Submission Templates⁵

In addition, CADTH staff provide advice to manufacturers prior to their submission⁸, as well as offering an early scientific advice programme to manufacturers⁹.

CDR evaluations of clinical and economic evidence are themselves subjected to quality assessments through rigorous peer review by external clinical experts and internal and external methodology experts. In addition, the quality of summaries of input received from patient groups is assessed by the patient groups themselves.¹⁰

HTA decision points

The key decision points from a Canadian HTA perspective are (1) whether a drug product is eligible for review and (2) whether the product should be recommended for reimbursement by public drug plans. Implicit within the latter decision is whether the evidence available is sufficient to support a recommendation to reimburse the product.

Eligibility

According to the Submission Guidelines for the CADTH Common Drug Review¹, a manufacturer or the drug plans may file a submission for a new drug, a drug with a new indication, a new combination product, or a biosimilar that:

- › has received a NOC or a NOC with conditions (NOC/c) for the indication(s) to be reviewed; or
- › has a pending NOC or NOC/c for the indication(s) to be reviewed.

Submissions are screened for eligibility based on the aforementioned guidance. Screening of submissions includes an assessment of whether there is compliance of the submission with certain quality standards, including whether the required content is provided and whether appropriate analytical and reporting methods have been followed. Should these quality requirements not be met, submissions will not be accepted for review until the deficiencies have been addressed by the applicant.

Decisions regarding eligibility that are not based on quality assessment include determination of eligibility based on the product type. Specifically, submissions that are ineligible for CDR review include certain line extensions of marketed products (e.g., new dosage forms with the same route of administration and new strengths of the same dosage form), generic products, and typically also include certain blood products, hospital products, and prophylactic vaccines. As noted above, oncology products are ineligible for CDR review but are reviewed through the CADTH pCODR program.

Recommendations

Once an eligible product has been accepted for review, and the available evidence has been reviewed by CADTH, evidence reports are passed to the independent CADTH CDEC committee. CDEC assesses the available evidence and then issues a recommendation that specifies whether the product under review should be reimbursed by public drug plans, and under what conditions the product should be reimbursed.

The CDEC deliberation and resulting recommendation is arguably the most important decision point within the HTA process within Canada. Assessment of the quality of the evidence available for a product under review is based on the reports produced by CADTH review teams, which in themselves are quality assessments. To ensure that the decisions made by CDEC are consistent, transparent and equitable, the committee uses a deliberative framework.¹¹ To further enhance the quality of CDEC decision making, the committee develops recommendations that are guided by a publicly available recommendation framework.¹²

CDEC recommendations are non-binding; that is, the individual drug plans that participate in the CADTH CDR process determine whether to reimburse a product, including determining the conditions under which reimbursement could occur, such as the price of the product. CDEC recommendations are effectively a mechanism to enable public drug plans to make a decision regarding whether or not to reimburse a particular product. CDEC can recommend that a product:

- › not be reimbursed
- › be reimbursed with certain criteria and/or conditions
- › be reimbursed without any certain criteria and/or conditions (i.e., in accordance with the indication approved by HC)

The majority of CDEC recommendations are to reimburse with certain clinical criteria and/or conditions. Such recommendations provide guidance to public drug plans to facilitate their funding decision for the product under review, including appropriate populations that should be covered; starting/stopping criteria; and appropriate price points.

Quality assessment of decision making

While the quality of decision making in the HTA context is not assessed explicitly at present, it could be argued that the fact that having in place a clearly defined, equitably applied, rigorous HTA assessment process in itself provides a level of assurance that decisions based upon this process are of high quality, particularly if 'quality' in decision making is defined as decisions that are consistent, fair (equitable), transparent and based on a consistent, inclusive and rigorous assessment process.

In addition to the implicitly high quality of decisions articulated above, there are several procedural mechanisms¹³ in place to further enhance the rigor and quality of decisions made by CDEC, which are explained below.

Draft versions of CDR evidence reviews are reviewed by external clinical experts, patient groups, participating drug plans, and (most importantly) the applicant (most often the manufacturer) of the product under review. Each of these stakeholders provides input directly to the CDR review teams, which are obligated according to CDR procedures to provide a written response to each issue raised by the stakeholders. This provides an opportunity for the evidence reports to be revised to address any issues raised, including erroneous data reporting, misinterpretation or misrepresentation of evidence, and the omission of potentially relevant information. The responses of the review teams to stakeholder feedback, including how the evidence reports have been revised, is provided to the drug plans and the applicant.

Similarly, CDEC recommendations are initially released in confidence to the drug manufacturer and the participating drug plans, prior to being finalised. In addition to providing manufacturers with an opportunity to provide feedback on the factual content of CDEC recommendations, the applicant can determine at this stage whether they wish to have CDEC reconsider their recommendation. A request for reconsideration can be made on one or both of the following grounds¹³

- › CDR and/or CDEC failed to act fairly and in accordance with its procedures in conducting the review, and/or
- › The CDEC recommendation is not supported by the evidence that had been submitted or the evidence identified in the CDR review report(s).

If a request for reconsideration is granted by CADTH, the manufacturer is able to provide material to the committee to articulate their position regarding changes to the recommendation, including a rationale to support issues such as differences in the interpretation of evidence.

In addition to the reconsideration process, any manufacturer is able to resubmit a product to the CADTH CDR to be reviewed again on the basis of new clinical or economic evidence.¹³ The resubmission process results in the development of a new evidence review by CADTH and an updated CDEC recommendation. Individual drug plans that participate in the CADTH CDR process are themselves able to ask that CDEC re-visit specific recommendations for a variety of reasons, such as challenges implementing clinical criteria recommended by CDEC, a process that entails the submission of a 'request for advice'. This triggers a review of the relevant evidence by the CADTH review teams and a re-assessment of the evidence by CDEC, which can result in a new recommendation being issued. As noted above, any new CDEC recommendation is subject to the same process of external review and consultation prior to being finalised.

While the procedural processes have been developed and implemented to ensure that CDR review reports and CDEC recommendations are of a high quality, there are several additional processes in place that further enhance the quality of the CADTH CDR HTA process. Specifically, all CDR review reports and CDEC recommendations are posted publicly on the CADTH website. In addition, prior to making any substantial or potentially contentious changes to existing CDR processes, CADTH invites the input of all public stakeholders via a consultation process, and gathers feedback from a variety of sources, including clinicians and clinical groups, patients and advocacy groups, drug manufacturers and their industry associations, HTA consultants, and government agencies. This feedback is carefully considered prior to making any decisions, and the final decisions are themselves made public. The processes not only exemplify how a rigorously applied HTA process can ensure

quality in decision making, but in addition underscore the value of transparency in ensuring high quality in decision making.

Subsequent to the HTA-based decision regarding whether a product should be recommended for reimbursement, there are several decision points prior to the addition of a new product to a public drug plan formulary, including whether the drug plan is able to afford the product and whether the addition of the product to a formulary is needed (based on local priorities) and can be implemented at a jurisdictional level. These are beyond the scope of this chapter, but the degree to which these downstream decisions rely on high quality decision making during the HTA process emphasises the importance of producing high-quality decisions.

HTA decisions based on evidence quality: Current issues

Despite the quality assurance measures that relate to decision making in the HTA context, there are several challenges that limit the quality of such decision making. First, in the same manner that decisions made subsequent to the HTA process rely on high-quality decision making, decision making during the HTA process itself relies on high-quality decisions being made upstream by the regulator. For instance, if a drug used to treat an extremely rare condition is approved by the regulatory authority on the basis of evidence where the clinical value of the product is uncertain (e.g., small, short-term studies evaluating surrogate endpoints), it can be challenging for an HTA body to accurately assess the clinical and economic value of the product and to consequently make a high-quality decision regarding reimbursement. In a similar manner, any assessments and reimbursement recommendations made by HTA bodies are likely to be perceived as being of suboptimal quality if they are based on poor-quality evidence provided by the applicant, such as a poor-quality indirect treatment comparison. This issue is not a consequence of a lack of quality in decision making at the level of the regulator but rather reflects inherent differences in the evidence requirements of regulators versus HTA agencies. For instance, regulators generally require that pivotal trials be randomised controlled studies without requiring that manufacturers include within such studies the comparators that are relevant from a payer's perspective. In addition, unlike HTA bodies, regulators do not assess value based on cost-effectiveness. Finally, the endpoints used in registration trials are frequently not the most relevant endpoints from an HTA perspective.

Second, the quality of decision made by HTA bodies is directly dependent on the quality of the evidence available to them. More specifically, decisions made by HTA bodies such as CDEC may be viewed as being of low quality if they are unable to provide clear direction regarding a reimbursement recommendation.

A more common example of how the quality of evidence affects the quality of decisions based upon such evidence relates to the economic assessments provided by manufacturers. Due to factors that are inherently uncertain (including the true price of comparators, the size of eligible populations, the effect sizes of relevant treatments and the persistence of therapeutic effects), estimates of cost-effectiveness and potential budget impact are associated with varying degree of uncertainty. Therefore, a decision to recommend a product for reimbursement based on an acceptable estimate of cost-effectiveness might not be the best decision for drug plans that already have private agreements in place that ensure lower access to lower prices of competitor products.

Third, the HTA process within Canada operates within highly prescribed time restrictions. While a prescriptive timeline for delivering HTA reviews is an absolute requirement to ensure that access to new medications remains timely, the trade-off is a potential compromise in the quality of the assessments that must be completed within the requisite time limit. Striking an optimal balance between rigour and timeliness is not a new issue for HTA, nor is an issue that is likely to ever be resolved completely. Nevertheless, the persistence of this issue highlights the need for HTA organisations such as CADTH to strive to continuously improve the rigour of HTA assessments within the limits of prescriptive timelines (in addition to other limits, such as uncertainty and a paucity of evidence, as noted previously). Attendant with the continuous improvement that is necessary to produce highly rigorous assessments within a relatively short amount of time is the need to ensure that quality standards are still met. While there are several internal and external mechanisms to do this at CADTH, which are discussed above, there remains a need to improve quality control procedures themselves.

Finally, perhaps the biggest gap in terms of assessing the quality of decision making at the CADTH CDR is an explicit process to assess the quality of decisions that are made by CDEC (i.e., reimbursement recommendations) and the subsequent decisions made by public payers that are based upon the CDEC recommendations. External organisations have consistently attempted to elucidate how CDEC recommendations (that is, decisions regarding reimbursement made by the HTA body) are translated into decisions made by the public payers that utilise the CDEC recommendations to inform their reimbursement decisions.¹⁴ While this type of analysis has helped to quantify the degree to which public drug plans align their reimbursement decision making with the recommendations made by bodies such as CDEC, a clear process is still not in place to directly assess the quality of decisions made by CDEC. Efforts that could address the issue of assessing the quality of decision making in this context could include mechanisms to explicitly assess

(i) the degree of consistency in decision making within the CDR program, (ii) the degree to which decision making adheres to the existing CDR recommendation framework, and the degree of congruence with other HTA bodies, both within Canada; for example, INESSS and internationally.

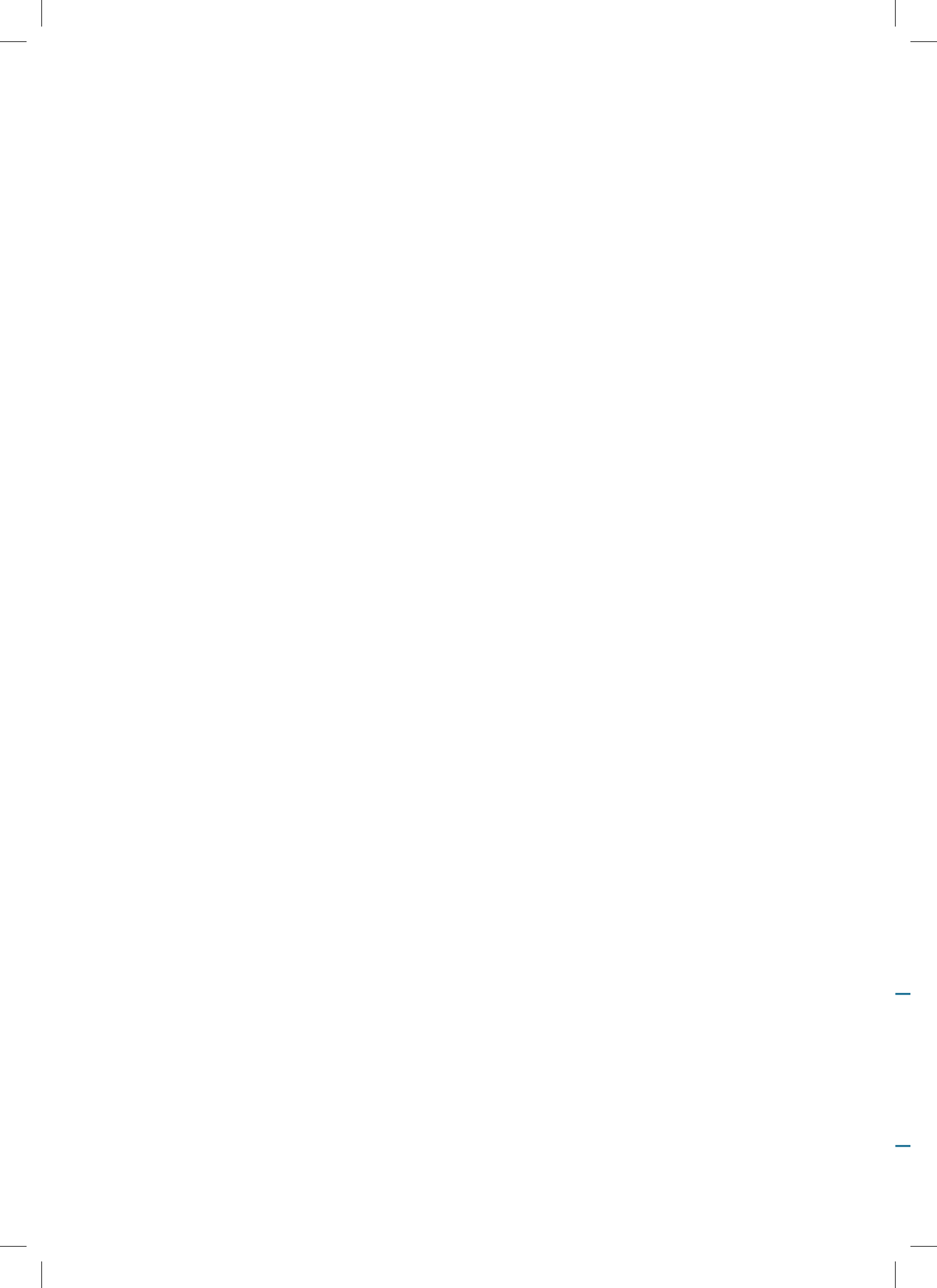
Opportunities for improving decision making in HTA

Each of the issues associated with HTA decision making that is presented above represents an opportunity for improving decision making in HTA. In addition to these current opportunities, there are several developments within the field of HTA that in future could represent additional opportunities for improving decision making. For instance, real-world evidence is becoming increasingly widely available, and such evidence might be integrated into regulatory approval processes and more particularly into HTA and reimbursement processes; this is an active field of research at present. The use of real world data holds much promise in potentially enabling more rapid access to drugs earlier in their life-cycle, but is conflated with an attendant increase in uncertainty. Perhaps building mechanisms to assess the quality of decision making into the current and future processes that look to integrate real-world evidence represents an opportunity to improve the quality of decision making in HTA, particularly in relation to reassessment of value.

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CHAPTER 7

AWARENESS OF THE TYPES OF BIASES THAT AFFECT DECISION MAKING AND POTENTIAL WAYS TO DEBIAS THE PROCESS

“Biases have the potential to impact the quality of our decisions. By learning about them, we can identify which are most relevant, as well as heighten our awareness to avoid them, and minimise their impact.”



Dr Carl Spetzler

Cofounder, Chairman and CEO
Strategic Decisions Group



Introduction

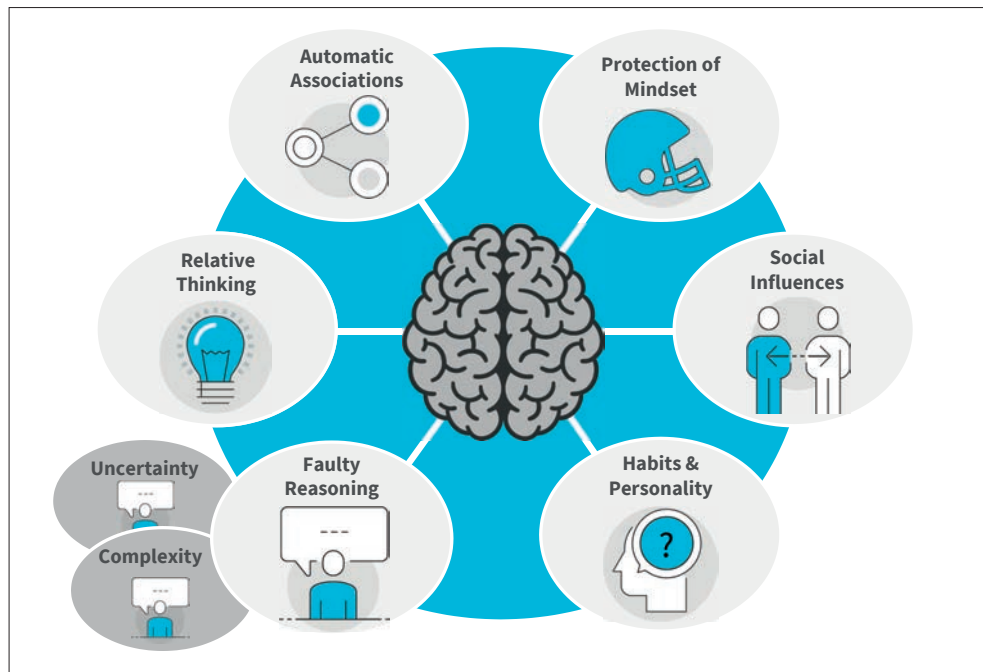
The human mind is simply not wired to achieve decision quality (DQ) in a natural, intuitive way. Because of how our minds work, mental traps and biases frequently get between our best intentions and true decision quality. The following presents an overview of the types of biases that affect our decision making, and offers guidance on how to avoid resulting decision traps.¹

Biases that affect decision making

There are many mental mechanisms that distort our judgement and become decision traps. Over 190 cognitive heuristics have been identified and catalogued by behavioural scientists in academic studies over the last five decades. Every year, a few more are deciphered, illustrating how human nature is wired to deviate with consistent and predictable mental errors from the rational decision model.

When addressing biases, it is important to understand the “mental mechanisms” that both mitigate and cause them. Because biases have the potential to undermine DQ, recognising and avoiding them is fundamental to making high-quality decisions.

Figure 7.1. Biases that directly affect decision making are organised into six categories according to the mental behaviours that cause them.



The six categories used to organise the many heuristics follow:

Protection of Mindset

Mindset is all the stuff in our heads, including our beliefs, lessons learned, preferences and prejudices. We use our mindset to make sense of the world and to make judgements and our first impulse is to reject something that conflicts with it. Rebuilding our mindset is difficult because we are wired to reject evidence that conflicts with our existing beliefs. This is called *Confirmation Bias*. We find having two conflicting ideas quite difficult since it causes cognitive dissonance and we have the urge to discredit or ignore information that does not fit into our current mindset; *Hindsight Bias*, when we look back and rationalise that we knew the right answer all along; *Self-serving Bias*, overestimating positive qualities while writing off failures to situational factors or bad luck; and *Status Quo Bias*, whereby we cling to the current position too strongly and for too long. Overcoming biases in this category requires gaining awareness, creating a learning frame habit to prepare our mind and emotions for change, and for doing things differently. With practice and repetition, we can develop a habit of mind capable of reducing tendency toward this mechanism of the mind.

Personality and Habits

Each of us has a collection of habits and specific personality characteristics that are not in themselves problematic. They become a source of biases when we approach the situation “as we see it” rather than “as it is.” Using the most popular personality indicator, the Myers-Briggs Type Indicator (MBTI), we can recognise *Preference-based Habits* that colour our judgement about what is required to address a decision. Personality preferences leading to specific habits of mind that affect decision making include: *Habitual Frame*, repeating easily accessible facts or interpretations, and *Content Selectivity*, focusing on information that fits our customary way of viewing the world.

Faulty Reasoning

Even if we are in a careful thinking mode, multi-dimensional problems with complexity, interrelated factors, and lots of data causes us to become confused. An example of faulty reasoning is *Selective Attention* to specific variables that seem important while ignoring other variables and causing an inability to combine many clues reliably. Another example is when we use a substitution heuristic to replace a tough question with an easier one, which may not have anything to do with what we really need to answer. *Order Effects* represent a faulty reasoning trap that leads us to remember the first or last idea presented – but not all ideas. Oversimplification is not a bad thing if we simplify only to a point where the framing of a proposed

solution or a problem still captures what is important to the decision situation and not to a point where we are tackling the wrong problem. Of note, when uncertainty enters a difficult decision (and it usually does) the mind is increasingly confounded. Regardless of expertise, people generally do not think well about uncertain events and their outcomes. The first step toward quality in important decisions is recognising we cannot trust our intuition about uncertainty.

Relative Thinking

Biases caused by relative thinking can result in judgements made through connections, comparisons, or associations. Examples are: *Ease of Recall Bias*, where a future event is assumed to be likely because it is easily imagined or remembered; *Availability Bias*, where we believe something heard recently is more likely to happen again than what we heard some time ago; *Vividness Bias*, where the more vivid our memories or impressions about something are, the more likely they will influence our judgments; and *Narrative Fallacy Bias*, where compelling stories that are not true can convince us.

Automatic Associations

Significant distortions in our judgement can result with automatic associations. These distortions are often used by professionals in areas including marketing and politics to influence and manipulate. The *Halo Effect Bias* causes things and situations to be perceived as more powerful than they really are. An example of this effect is when leadership of a company is perceived as having a great strategy, even when the company's market success is only due to market fluctuations. *Anchoring Effect Bias* is the tendency to rely too heavily, or "anchor" on one trait or piece of information when making decisions—and failing to sufficiently adjust from that onto what we have latched. This bias is particularly problematic for experts estimating future outcomes of an uncertain factor. It is most powerful when there is uncertainty as to what the "right number" might be in a situation because anchors act as reference points—even when they are irrelevant. *Framing Effect Bias*, the way a question is presented, directly influences how a matter is framed in our mind, as does *Thrown Frame Bias*, which can imply moving ahead with something is good, although moving ahead with something else might be of higher value.

Social Influences

Each of us is socialised in beliefs and behaviours, and our social nature contributes to stability and collaboration. It is true that conformity, acceptance and peer pressure create unconscious and subtle encouragement of like-minded thinking. It is also true that individuals, through the *Effects of Suggestibility* will accept and act on the suggestion of others, launching a sort of domino or cascading effect

that, in the extreme, can result in lynch mobs. Of note, *Groupthink*, with its general tendency to discourage diverse views, is an influence that can generate dangerous overconfidence in teams exhibiting self-reinforcing cohesiveness, and unanimity of perspective. Contradictory evidence is not welcome, thus a strong hazard on the path to DQ.

7

Brain systems 1-3

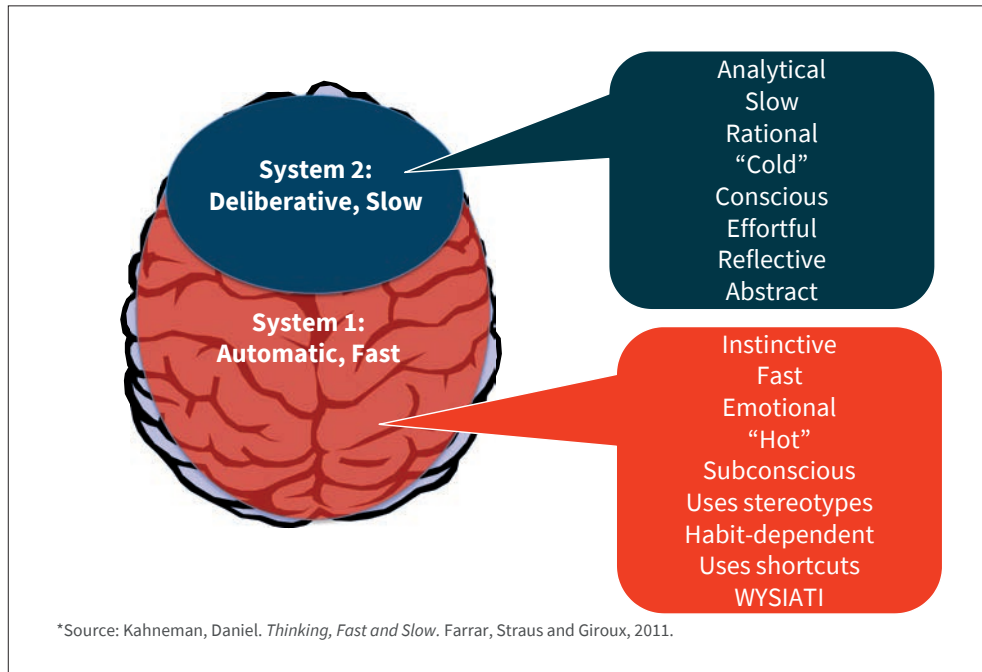
In the book “Thinking fast and slow,” Daniel Kahneman says humans use two distinct mental processes to make judgements and decisions (Figure 7.2).²

System 1 is amazingly fast and emotional, and takes numerous shortcuts. It works according to the “What You See Is All There Is” principle (WYSIASTI), believing what matters is whatever is accessible. Because of its speed, System 1 allows us to do repetitive sophisticated tasks, however it cannot be trained to reason correctly for deliberate decision making. Without intervention, it leads us into biases and traps. This fast brain is very important because that is where all of our decision habits reside. For example, if we have grown up driving in warm weather country, we probably do not know how to drive on ice and snow. Those of us that live in ice and snow in the winter know that if we have not learned to steer into the slide we will have an accident. This is counterintuitive, and it is not in our automatic brain at first. We can learn it, but the only way we get to learn it is to repeat, repeat and repeat, until it is on automatic.

System 2 is the deliberative brain. This is where our analytical capabilities reside. This brain is slow in comparison to the fast brain. This part of the brain is rational, conscious, effortful and reflective and it is where we can deal with abstractions that we cannot do very easily in System 1. System 2 requires effort and attention. System 2 is both social-emotional and rational, it is considered cool instead of hot, and has a very powerful ability that can be trained to do decision tasks by installing the knowledge and procedures that minds use to achieve tasks, also referred to as “mindware.” System 2 is not unbiased. We cannot solve complex decision problems in our heads especially when the problem features uncertainty and interactions among many factors.

While Kahneman talked about two systems, we want to introduce a third system. **System 3** is equally important in decision making in that it is where we augment our mental processes with support sources: tools, processes, experts, and data. System 3 reaches outside our brain in allowing us to overcome and work out problems. Less research and focus has been placed on System 3, but we know it is a critical addition when making complex decisions with interrelated factors, because we need to use external resources. Without using System 3, we fall victim to unpredictable

Figure 7.2. In the book "Thinking fast and slow," Daniel Kahneman says humans use two distinct mental processes to make judgments and decisions.



biases from faulty reasoning. Also, many of the repairs and preventions to avoid the distortions from biases come from enhancing System 3.

Taken one at a time, biases have the potential to impact the quality of our decisions. By learning about them, we can identify which are most relevant, as well as heighten our awareness to avoid them, and minimise their impact (Figure 7.4). Repairs come in developing new habits, particularly decision habits.

It is necessary to both avoid biases and know our destination. Make decision quality a habit by saying: "Here is where we are trying to go" and asking: "What are we trying to avoid?" Once we install DQ mindware, we have what we need in our heads to be able to think about the situation clearly as well as the ability to judge the quality of each element.

Consider how System 2 and System 3 can be used to avoid mindset biases by seeking out information that challenges initial beliefs and by appointing a respected team member to challenge assumptions and encourage others to step outside their current frame and drop some unmerited overconfidence. A focus on System

Figure 7.3. The augmentation of mental processes happens through System 3 when humans reach out for tools, data and input from others.

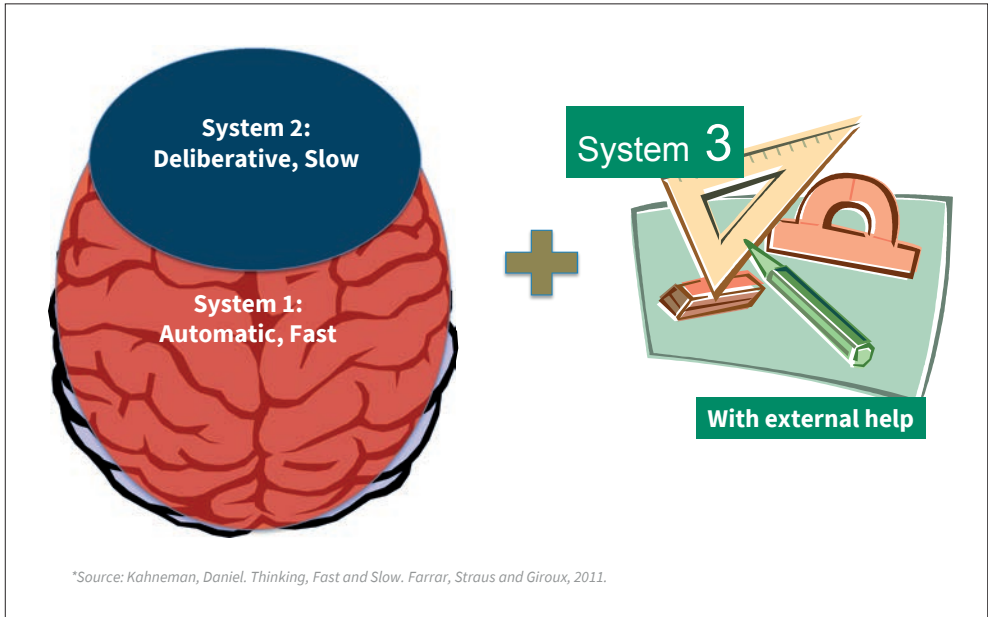


Figure 7.4. Reduce our biases by using deliberate strategies to prevent or override our automatic responses.

1	2	3
Develop New Habits	Improve Awareness and Mindware	Reach for Tools, Data, and Expert Sources

2 thinking helps us create new habits to override our automatic responses and understand the change or changes we want to make. We can use proactive leadership and System 2 thinking to counteract the negative effects of groupthink, conformity and other social pressures.

Followed by repetition, a new automatic response is developed in our System 1 brain where we can discipline ourselves to do what is needed even if doing so will take us outside of our preferred approach. We can use System 2 with System 3 tools to decipher what really matters in complex situations and what is the true nature of a problem. We can imbed new mental habits of questions and assertions, and then discard them when they are not good reference points.

Megabiases

Some clusters of biases create large effects – megabiases. These megabiases are frequently encountered in organisations and cause dysfunctional decision making. Megabiases often are a greater threat to good organisational decision making than individual biases. Measures to avoid megabiases draw upon the thinking of Systems 1, our fast parallel-processing brain that makes judgements on automatic pilot; System 2, our deliberative conscious thought processes that help us to reason through problems mentally; and System 3, the reaching out for tools, experts, data and systematic procedures that help us deal with complex decisions. A synthesis follows of actions to avoid five specific megabiases: Narrow Framing, Illusion of DQ, the Agreement Trap, Comfort Zone, and the Advocacy/Approval Myth.

Narrow Framing

For people to solve a problem, we frequently make the problem smaller. A smaller problem gets us to an answer faster but it often leads to framing the problem in a way that when we look back we see that this missed the most important parts that were just outside the boundaries that we set. Because the human mind is not good at coping with complexity, we use mental frames to simplify and make sense of the world. The complex reality may be approachable but thinking may be limited by the frame of the problem and staying inside it. The tendency to frame decisions too narrowly with unsupported assumptions that are treated as fact is problematic and one of the most common causes of low decision quality in many organisations. Of note, the need for reframing decisions often becomes apparent only after people have run into trouble and wasted a great deal of time. The bias for action tempts us to plunge in, resulting in choosing (consciously or not) a frame that is too limited. We view the situation through lenses coloured by what we are most comfortable doing and what we can quickly accomplish. Participants align around a frame that seems “good enough” but are set up to solve the wrong problem.

We can avoid narrow framing by making a personal and organisational habit of consciously and deliberately defining the frame for important decisions. System 1 instinct should ask: “What is the most important decision frame for the situation?” Proper framing can be developed through System 2 training and repetition activity. A powerful System 3 behaviour to avoid narrow framing is conscious attention to framing tools and processes for DQ, including a well-structured framing workshop to generate several different frames, debate the merits of each, select the most appropriate, ward off groupthink behaviours and generate more out-of-the-box thinking.

Illusion of Decision Quality

Built-in hindsight bias makes us feel good about our decisions, but when we list the six requirements of decision quality, go through each element of our decision and remember that a decision is no better than the weakest link, then we see a big gap. Many executives think they already do make good decisions; that they would not have reached the position they are in if they did not have natural decision-making capabilities (Figure 7.5). Once they fully understand the six requirements of the decision quality journey, and see that reaching DQ frequently doubles a decision’s potential value, compared with what would have been achieved without it, they never want to make decisions any other way again (Figure 7.6).

An enlightened decision maker, one whose destination is DQ, is no longer someone who says: “I make ‘good-enough’ decisions and believe they are the best decisions.” Good-enough decision makers can make themselves feel good about their choices by finding confirming evidence, applying hindsight, and using other self-serving biases (Figure 7.7). Avoiding this illusion requires recognition of this possible shortcoming, then installing DQ mindware; the six requirements for DQ and the definition of 100% into our System 2. We can then build our System 1 habit of checking for DQ before we make significant or strategic decisions. We can use System 3 to reach out for tools like the DQ Slider Scale, the DQ Appraisal Cycle (for significant decisions), and the Dialogue Decision Process (for significant decisions). When the illusion of DQ has been overcome, we will find ourselves reaching for these tools and processes whenever an important choice must be made (Figure 7.8).

The Agreement Trap

In the right situation, groups form better judgements than individuals. The judgement of groups is not always good, however, because the dynamic of group behaviour can lead us into conformity, groupthink and the exaggeration of the DQ illusion. We tend to confuse agreement with a good decision. Agreement has little to do with the requirements for DQ. Sizeable gaps are often discovered in the agreed choices when groups evaluate the quality of the decision in terms of DQ.

Figure 7.5. The illusion of decision quality affects nearly every decision maker.



Figure 7.6. Typically, executives rate their decision making as “good”, but after assessing DQ, often find that this is an illusion.

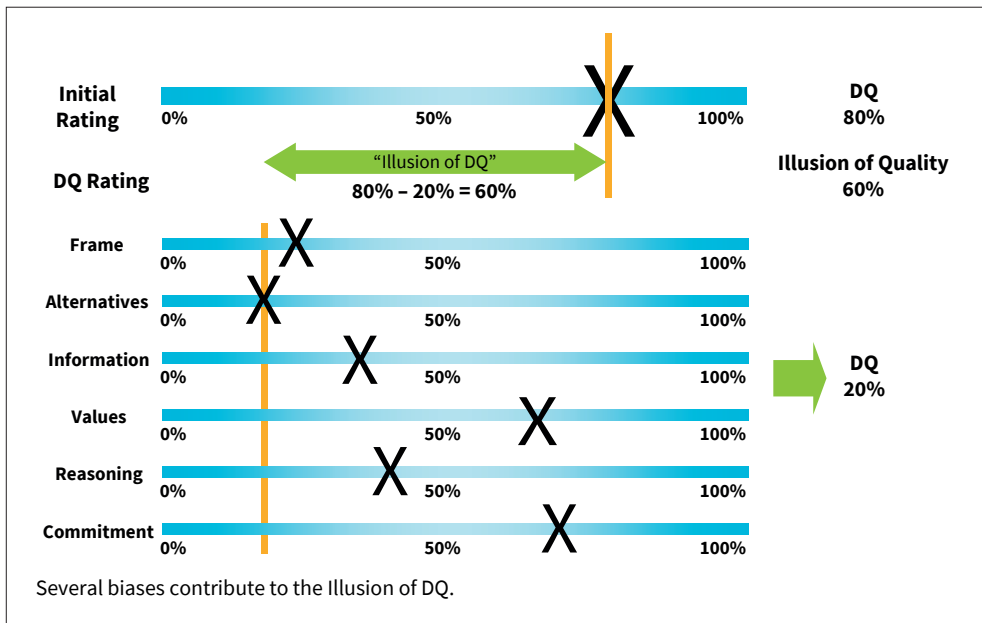


Figure 7.7. The illusion of DG results from a multitude of biases.

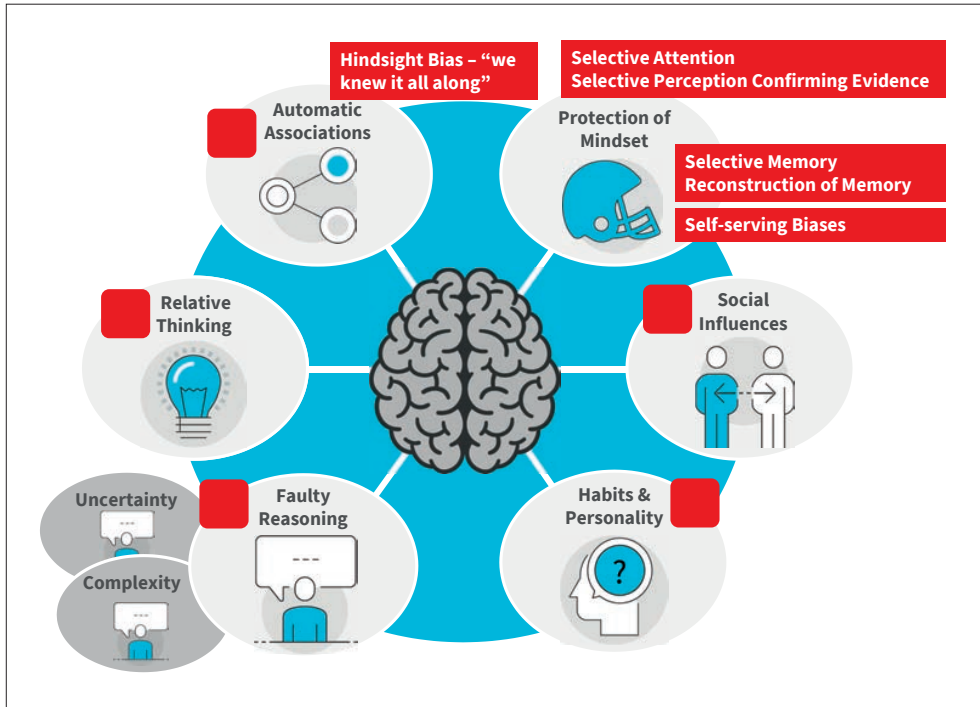
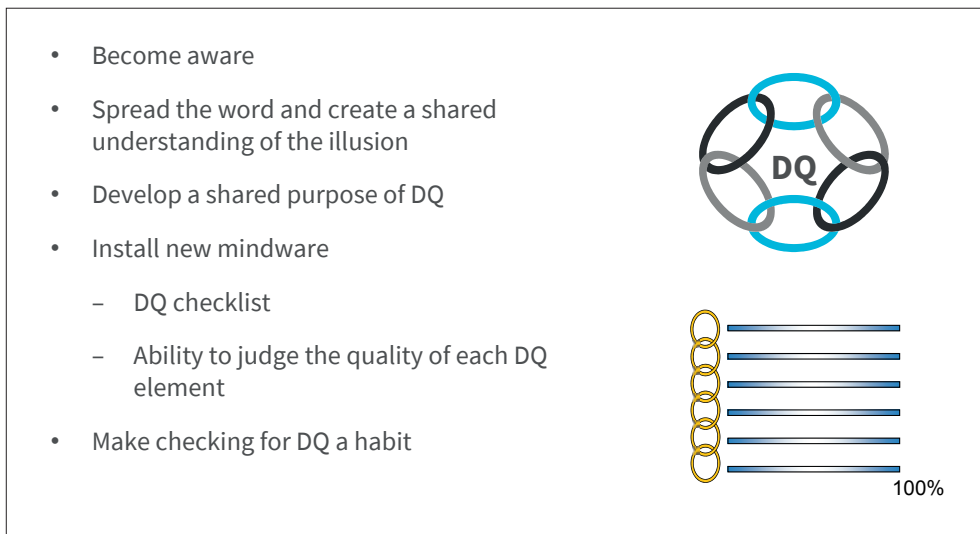


Figure 7.8. Reducing the illusion of DQ in organisations.



Agreement around the table is frequently equated with decision quality. However, agreement is not DQ and this confusion leads decision quality to not be pursued in many organisations. Most people have a strong bias for action; they want to get something done. Given this bias, we want to get to agreement around something we can act on quickly.

The first line of defence against this megabias is recognition that agreement does not equal DQ. Installing the requirements of DQ as System 2 mindware and using them consciously before deciding can counteract the social psychology that confuses agreement with DQ. Avoiding premature agreement is designed into the DQ-based decision processes (the DQ Appraisal Cycle and the Dialogue Decision Process), which foster dialogue and testing before reaching a final agreement.

Comfort Zone Bias

Preference-based habits can create the “What You See Is All There Is” (WYSIATI) view; meaning what we have is all we need to address a situation. When combined with other biases, the resulting comfort zone bias essentially solves a problem that does not need to be solved. This bias combines several individual biases and results in doing what we know how to do, rather than what the decision requires.

The key to avoiding this bias is to use our System 2 and System 3 to understand the true nature of the problem in terms of magnitude, organisational complexity, analytical complexity, content challenge and likely decision traps. The best approach to finding the most value follows from diagnosis. Developing a frame that is truly appropriate for the decision is the next step, as well as seeking outside help if our tools and skills fall outside our comfort zone. We can guard against this megabias by asking ourselves: “How would this situation be thought of with very different skill sets or with a different experience base?” This is a powerful Systems 2 practice of seeking disconfirming evidence and breaking away from what we are used to doing. Savvy decision makers use iteration, starting with a simple decision model and back-of-the-envelope analysis. They follow this with testing the sensitivity of different assumptions, improve where it matters and iterate again.

Advocacy/Approval Myth

Most organisations use an advocacy/approval decision process in that a decision problem is assigned to an individual or team who is then responsible to find the best solution and advocate for its acceptance by an approval body of decision makers who will either accept or reject the recommendation. Two problems happen with this process, however, advocacy myth and approval myth. Advocacy

myth is where effective advocacy is misinterpreted as evidence of quality of the recommended decision. Advocates do their best to defend or “sell” their proposals and are highly biased toward selecting data, alternatives, and evaluation results that bolster their case. They are not likely to offer significantly different, creative and compelling alternatives. The approval myth assumes that any proposed solution that is approved after intense interrogation by the approval body must be high quality. However, decision makers who can only accept or reject a single recommendation give up their right and responsibility to assure decision quality. The advocacy/approval myth has the mistaken belief that decision quality can be reached this way by relying on advocacy and questioning. The advocacy/approval myth suppresses the development of alternatives and encourages advocates to use whatever information will turn the contest or sale of their proposal in their favour. It fosters the manipulative use of anchors, narrative fallacies and misleading framing effects. In addition, it encourages oversimplification and distortion of uncertainty to make the most compelling case. Avoiding this megabias requires shifting from inherent competition between advocate and approver to a competition among alternatives. It is the alternatives, not the people that should compete. This shift changes the process by fostering debate and a thorough understanding of the inherent uncertainty and the value drivers of each alternative. The shift is at the heart of the Dialogue Decision Process.

To get to a quality decision, we must understand biases and come up with repairs for them, know how to avoid them, and how to minimise them so that we do not distort the input to making decisions (Figure 7.9).

While behavioural psychologists have documented how individuals behave, others have been studying the behaviour of organisations. When they give prescriptive advice, telling us how we should act, rather than how we naturally act, they mainly describe how to recognise and avoid decision traps resulting from human biases. This is valuable but it is not enough to get to DQ. We need to understand the destination we are trying to reach. In decision making, that destination is DQ.

It should be remembered that megabiases destroy DQ. Pay attention to them with a first line of defence of awareness and recognition of their damaging potential. What to do next depends on which megabias we are trying to avoid and the decision’s context. Once the conscious decision is made to prevent megabiases on our journey to reach DQ, System 1, 2, and 3 can be engaged to change habits of mind, install new mindware, and reach out for experts, data, tools and processes but particularly decision processes (Figure 7.10).

Figure 7.9. Summary of biases and modes of judgement.

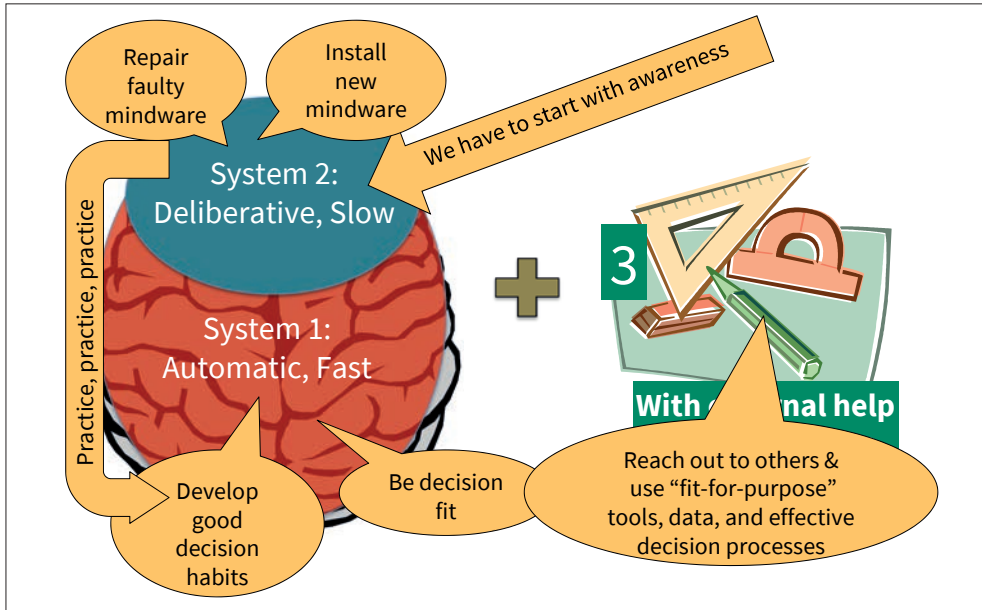
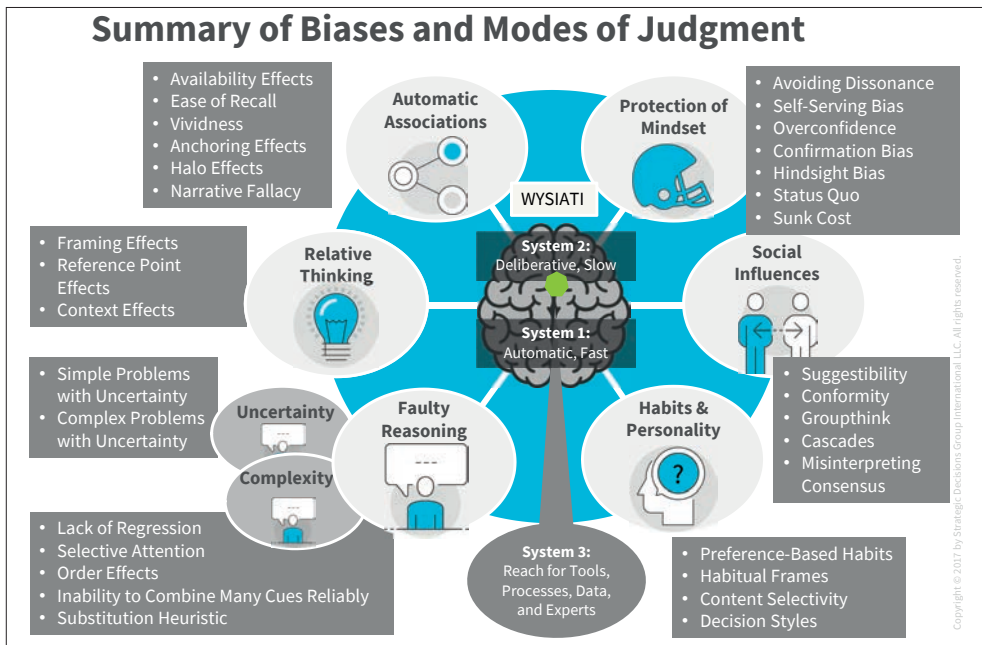


Figure 7.10. Summary of overcoming biases and megabiases.

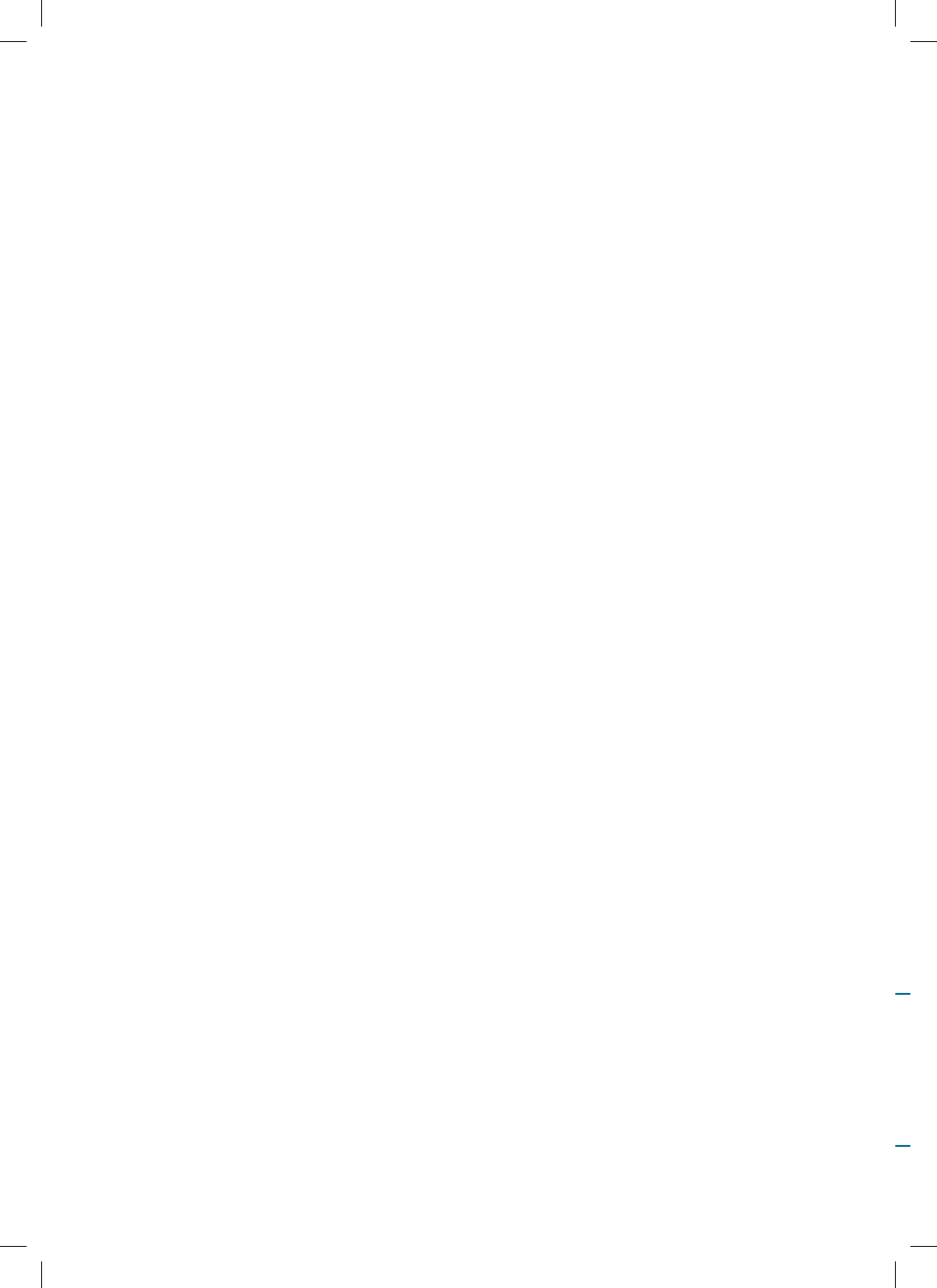


Notes

1. The structure for biases in decision making was developed in collaboration with Dr. Barbara Mellers, I. George Heyman University Professor at the University of Pennsylvania, jointly appointed as Professor of Marketing in the Wharton School, and Professor of Psychology in the School of Arts and Sciences. The three-person team, Dr Mellers, Carl Spetzler and Jennifer Meyer created the structure for the course “Biases in Decision-Making.”
2. Other resources the reader may enjoy related to biases and decision making include: Dan Ariely, *Predictably Irrational: The Hidden Forces that Shape Our Decisions* (HarperCollins Publishers, 2008); Robert A. Burton, *On Being Certain: Believing You Are Right Even When You are Not* (New York: St. Martin’s Press, 2008); Michael J. Mauboussin, *Think Twice: Harnessing the Power of Counterintuition* (Harvard Business Press, 2009); Richard H. Thaler and Cass R. Sunstein, *Nudge: Improving Decisions about Health, Wealth, and Happiness*, rev. and exp. ed. (Penguin Books, 2009); Phil Rosenzweig, *The Halo Effect: ... and the Eight Other Business Delusions That Deceive Managers* (New York: Free Pres, 2007); and Paul Nutt, *Why Decisions Fail: Avoiding the Blunders and Traps that Lead to Debacles* (San Francisco: Berrett-Koehler Publishers, Inc., 2002).
3. DQ tools mentioned in this chapter are available from the SDG Decision Education Center. Visit: <https://www.sdgdecisioneducation.com/>

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2. Kahneman D. *Thinking, Fast and Slow*. New York: Farrar, Straus and Giroux, 2011.



CHAPTER 8

KEY QUALITY DECISION-MAKING PRACTICES FOR THE DEVELOPMENT AND REVIEW OF MEDICINES: THE PRACTICALITY AND APPLICABILITY OF (QoDoS) AN INSTRUMENT FOR EVALUATING DECISION MAKING

“This work increases awareness as to the quality decision-making practices that need to be considered when making decisions and identifies the strengths and areas of improvement for an organisation, It reduces uncertainty around decision making and decreases the burden of recycling bad decision making or continuing with failing projects.”



Prof Stuart Walker

Professor of Pharmaceutical Medicine, Cardiff University and Founder
Centre for Innovation in Regulatory Science, UK



Introduction

Many decisions are made every day; some are strategic and important while others are trivial and of little consequence. Some years ago, the Centre for Innovation in Regulatory Science (CIRS) developed an eight-step framework for the benefit-risk assessment of medicines together with a documentation system and a user manual, which has since been assessed and found to be useful by many international regulatory agencies. Against that background, this particular topic is of critical importance, which is why CIRS developed ten Quality Decision-Making Practices (QDMPS) as well as a tool to assess these practices and to examine their practicality and applicability in the development, regulation and reimbursement of medicines.

The importance of decision-making practices

In his book, *Thinking fast and slow*, which is recognised as the primer in the area of decision making, Nobel Prize winner Daniel Kahneman memorably said “An organization that seeks to improve its decisions should also routinely measure the quality of its decision making.”¹ However, despite the justifiable acclaim accorded to Dr Kahneman’s work, much remains to be accomplished. Participants at the 2011 CIRS Workshop pointed out that “the methods for enhancing and measuring the quality of decision making had yet to be defined” and it was further stated at the CIRS Workshop the following year that “CIRS should encourage the use of a framework and toolbox for decision-making methodologies.”

It is crucial to measure the quality of decision processes and not just the quality of the outcomes. In fact, Workshop participants recommended that “CIRS should explicitly explore quality in decision making separately from the quality of the submission and the quality of the review.” The importance of that separation was also cited by Howard Raffia and colleagues who stated that: “Under conditions of uncertainty, good decision-making does not necessarily lead to good consequences. On balance, however, the long-running use of quality systems for making decisions should increase the probability of more favourable results.”²

Quality Decision-Making Practices and the Quality of Decision-Making Orientation Scheme

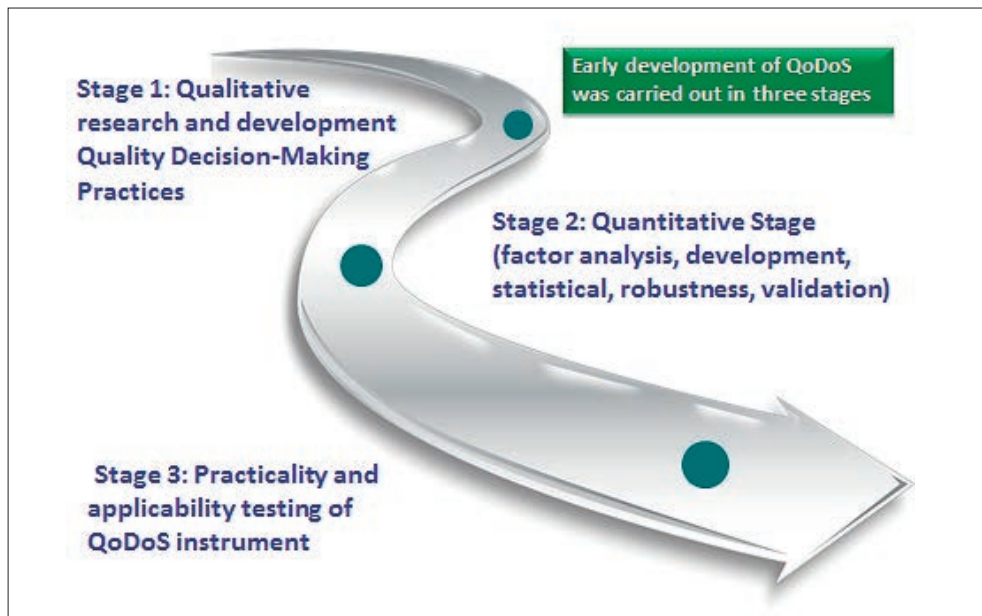
In 2010, CIRS and Dr Ronan Donelan in collaboration with Professor Sam Salek and Cardiff University initiated a study using a standardised approach and qualitative and quantitative techniques to develop and validate an instrument, the Quality of Decision-Making Orientation Scheme (QoDoS), for assessing the quality of decision making in medicines’ development and the regulatory review. This initiative is currently being continued through an association with the University of Hertfordshire and the work of a doctoral candidate Magda Bujar (see Chapter 4).

In the qualitative approach used in stage 1 of the research, in-depth structured interviews were conducted with 29 key opinion leaders from the European Medicines Agency (EMA), the European Union (EU) National Regulatory Agencies, EU and US pharmaceutical companies and US Contract Research Organisations regarding their subjective understanding of the approaches, influences and other factors in individual and organisational decision making in pharmaceutical development and regulation (Figure 8.1).

Analysis of the output from these interviews using NVivo 8[®] software resulted in the identification of 32 major and 97 sub-themes, which were consolidated into 19 overarching themes. One important result of this investigation was the development of the Ten Quality Decision-Making Practices (Figure 8. 2).³ It was determined that the QDMPs can be structured into four areas: *Structure and Approach*, *Evaluation*, *Impact* and *Transparency and Communication*. (Figure 8.3)

In addition to the development of these themes, subthemes, and QDMPs, valuable insights surrounding individual and organisational decision making were gleaned from individual participants, including quotes from three regulators on the subject of individual versus group decision making, transparency and impact analysis (Box 8.1).

Figure 8.1. The development of QoDoS.



Box 8.1. Regulator participant commentary from QoDoS interviews

“There is a difference between the organisation’s decision-making process and that of the individual. We have a good understanding of how a committee makes a decision, but we do not necessarily understand how the individuals on that committee have made their own decision.”

“Transparency, the justification for decisions, and understanding why a decision has been made needs to be documented, it is good practice.”

“We should all take time to perform impact analyses and try to learn from the good and the bad decisions.”

In the quantitative approach used in stage 2 of the research, content validation and psychometric evaluation testing of the 96 items from phase 1 resulted in a reduced list of 76 items. Factor analysis, reliability testing and construct validation, then produced the final 47-item QoDoS instrument.⁴ All 47 items on the final questionnaire could also be mapped to the ten QDMPs.

Whilst it is true that individuals make up organisations, there is often quite a disparity between what the individual thinks about their own competency and that of their organisation. Therefore, this instrument was divided into four sections containing questions regarding the individual’s assessment of their organisation’s decision-making approach, and their organisation’s decision-making culture as well as their own decision-making competence and their own decision-making style (Figure 8.4).

These questions allow respondents to consider whether their organisation uses a structured approach to decision making for important strategic questions, whether they provide training in decision making or clear unambiguous instructions and whether their organisation’s decision making is ever influenced by the vested interests of individuals. Participants using the QoDoS tool can also assess whether their own decision making is transparent and knowledge based and determine what role emotion plays in their assessments; for example, those who need to make a business decision about a breast cancer drug may understandably be influenced by emotion if a family member or close friend has been diagnosed with breast cancer.

Figure 8.2. Ten Quality Decision Making Practices (QDMPs).

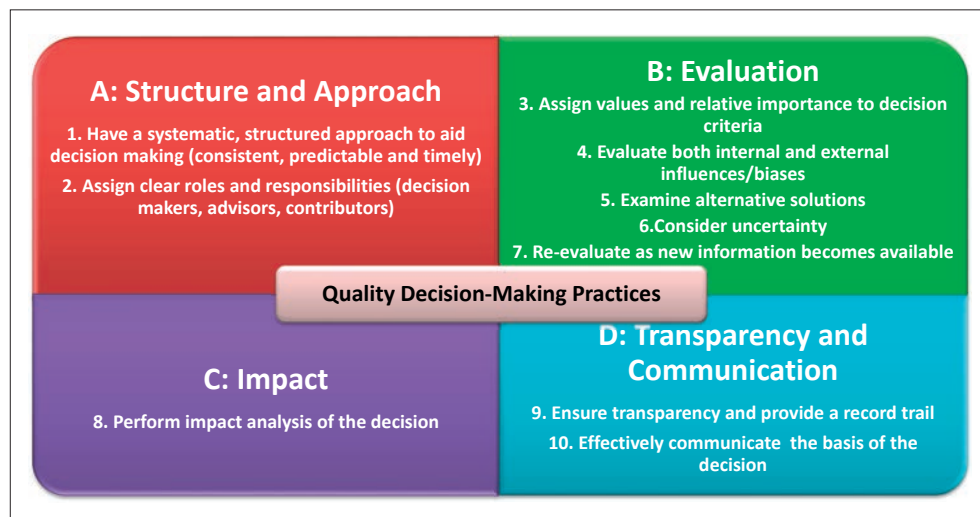


<p>QDMP 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely)</p> <ul style="list-style-type: none"> • Establish the decision context, objectives and assumptions made. • Employ frameworks, guidelines and tools for structuring the decision-making process. • Such an approach should ensure that the process is systematic, which in turn would enable better consistency compared with similar past decisions, as well as predictability and timeliness.
<p>QDMP 2. Assign clear roles and responsibilities (decision makers, advisors, information providers)</p> <ul style="list-style-type: none"> • The roles and responsibilities should be clearly defined in terms of individuals who provide information (including external input), compared with those who advise on the decision or make the final decision. • The roles and responsibilities of each stakeholder (regulatory authorities, HTA agencies and companies) should be transparent and well communicated, which should help manage expectations.
<p>QDMP 3. Assign values and relative importance to decision criteria</p> <ul style="list-style-type: none"> • The relevant criteria for the decision must be determined to ensure that these are in line with the decision context and overall objective. The criteria should be weighted, for example, by ranking or rating their relative importance.
<p>QDMP 4. Evaluate both internal and external influences/biases</p> <ul style="list-style-type: none"> • Stakeholders need to be aware of personal considerations, subjective influences and biases, acknowledge them and minimise where possible. Potential biases that need to be considered¹: <ul style="list-style-type: none"> ○ Action-oriented bias: excessive optimism, overconfidence in own judgement and gut-feeling ○ Interest-oriented bias: inappropriate attachments and misaligned incentives ○ Pattern recognition: generalising based on recent events and seeking out information that supports a favoured decision, which could lead to perpetuating previous mistakes ○ Stability bias: preference for status quo and tendency for inertia in the presence of uncertainty
<p>QDMP 5. Examine alternative solutions</p> <ul style="list-style-type: none"> • Decision makers should actively explore possible options during the decision-making process. • The alternatives need to be assessed, for example using a SWOT analysis, against the relevant decision criteria in order to determine the best outcome.
<p>QDMP 6. Consider uncertainty</p> <ul style="list-style-type: none"> • The extent and limitations of available information need to be judged for each decision criterion in relation to the alternative options. • Stakeholders must be explicit regarding acceptability of benefits and harms and how this affects their approach.
<p>QDMP 7. Re-evaluate as new information becomes available</p> <ul style="list-style-type: none"> • This should be actively carried out at all stages during the lifecycle of medicines' development. • This may be a safeguard against plunging in or procrastination and/or perpetuating previous mistakes as well as identifying cultural/organisational/hierarchical influences (e.g. individual vs. organisational, group successes and group failures).
<p>QDMP 8. Perform impact analysis of the decision</p> <ul style="list-style-type: none"> • The impact of the decision needs to be considered on both internal and external stakeholders. • The analysis must relate to present situation, but also to the future and should take into account elements of quality/validity of data, political/financial/competitor influences and procedures for similar decisions.
<p>QDMP 9. Ensure transparency and provide a record trail</p> <ul style="list-style-type: none"> • It must be clear how the decision was made and details must be consistently documented in a manner that can be easily followed or audited by appropriate stakeholders.
<p>QDMP 10. Effectively communicate the basis of the decision</p> <ul style="list-style-type: none"> • The basis of the decision needs to be appropriately communicated to the relevant stakeholders, both internally and externally.

The practicality and applicability of QoDoS in the regulatory environment

To further understand the utility of QoDoS in real-world decision making, CIRIS performed a pilot study of its use among 76 participants; 50% from 23

Figure 8.3. Quality Decision-Making Practices can be organised into four areas.



pharmaceutical companies and 50% from 12 regulatory agencies.⁵ The results of this pilot study revealed that 39% of participants said that their organisation never or only sometimes used a structured approach to decision making and that 70% indicated that they have never or only sometimes received training in decision making.

Examining responses to the QoDoS pilot against several of the ten QDMPs can demonstrate the appropriateness and effectiveness of current decision-making practices. For example, QDMP 1 is to *have a systematic structured approach to aid decision making*. This approach would include establishing the decision context, objectives and assumptions made and employing frameworks, guidelines and tools for structuring the decision-making process. A *decision-making framework* can be defined as “a set of principles, guidelines and tools that provide a structured systematic approach to guide decision makers in selecting, organising, understanding and summarising subjective values and judgements that form the basis of a decision, as well as communicating the evidence relevant to the decision.” Such an approach should ensure that the decision-making process is systematic, which in turn would enable consistency, predictability and timeliness. By examining the responses to the QoDoS pilot study mapped to Quality Decision Making Practices it was observed that many respondents rated their individual decision-making practices, such as consistent decision making and applying a structured approach, as more favourable than those of their organisation (Figure 8.5).

Figure 8.4. The final QoDoS tool is divided into questions regarding organisational and individual decision making.

Part I: Organisational-level influences	Part II: Individual-level influences	Never	Sometimes	Frequently	Often	Always	Not applicable	
A. Decision-Making Approach 1. My organisation evaluates the impact of the decisions it makes 2. My organisation's decision making is transparent 3. My organisation's decision making is consistent 4. My organisation uses a structured approach in its decision making 5. My organisation's decision making is influenced by external stakeholder's demand 6. My organisation assigns qualitative values to its decision-making criteria 7. My organisation assigns quantitative values to its decision-making criteria 8. My organisation is open to using better alternatives in its decision making 9. My organisation encourages innovative decision making 10. My organisation considers uncertainties in relation to its decision making 11. My organisation provides training in the science of decision making 12. My organisation re-examines its decision making as new information becomes available B. Decision-making culture 13. My organisation has suffered a negative outcome due to slow decision making 14. My organisation's culture has resulted in its inability to make a decision 15. My organisation's decision making is influenced by organisational politics 16. My organisation's decision making results in making the same mistake as in the past 17. My organisation's decision making is influenced by the vested interest of individual (conflict of interest) 18. My organisation underestimates problems which adversely impact its own decision 19. My organisation continues with projects/products which should be terminated at an early stage 20. My organisation's decision making is influenced by similar organisations or competitors 21. My organisation's decision making is influenced by incentives or penalty payments 22. My organisation effectively communicates the decisions it makes 23. My organisation provides clear and unambiguous instructions for decision making		A. Decision-making competence 24. My decision making is knowledge based 25. My decision making is consistent 26. I consider uncertainty and unknowns in my decision-making approach 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making 28. I present contingencies or achievable options as part of my decision making 29. My decision making is transparent 30. I understand the context of the decision I am being asked to make 31. I understand the importance of the decisions I make 32. I use a structured approach in my decision making 33. I assign qualitative values to its decision making criteria 34. I assign quantitative values to its decision making criteria 35. I receive training in the science of decision making 36. I use intuition or "gut-feeling" in my decision making 37. My professional experience is important when having to make challenging decisions B. Decision-making style 38. Emotion is part of my decision making 39. I have experienced "paralysis by analysis" caused by my slow decision making 40. I have experienced a negative outcome by a decision not being made 41. In my decision making, I make the same mistakes as in the past 42. Recent or dramatic events greatly impact my decision making 43. My procrastination has resulted in a negative outcome 44. My decision making could be improved by assigning relative importance to decision criteria 45. I underestimate problems which adversely impact my decision making 46. I continue with projects/products which should be terminated at an early stage 47. I feel that I could make better quality decisions						

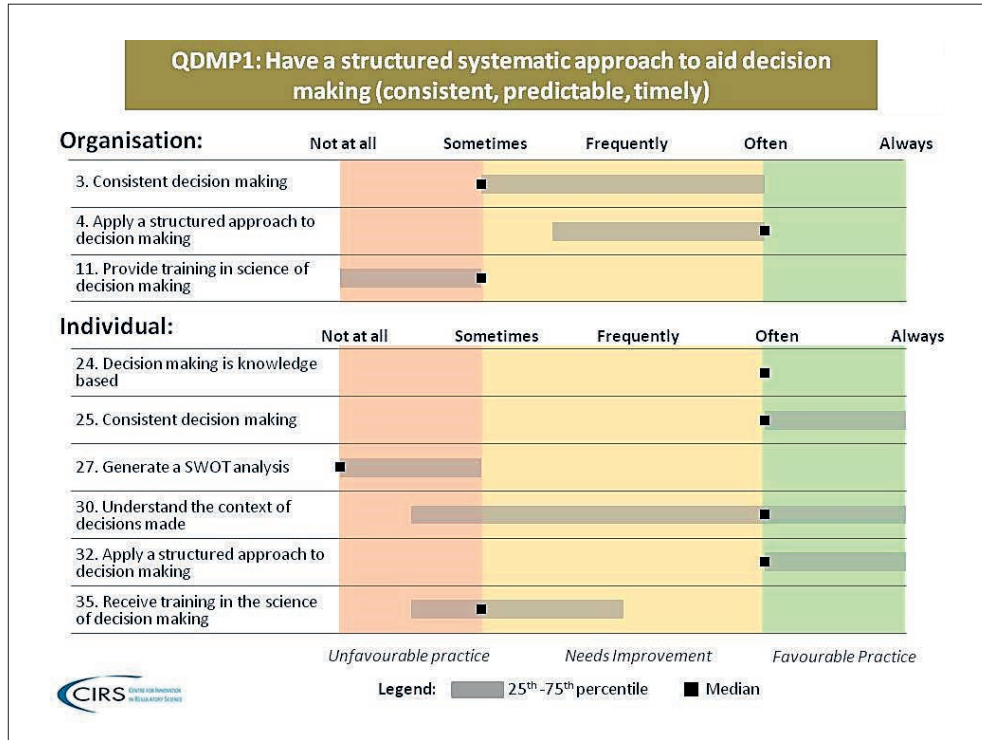


QDMPs AND QoDoS

QDMP 2 is to *assign clear roles and responsibilities*; that is, to ensure that before starting the process, all stakeholders are 'labelled' to distinguish individuals who provide information compared with those who advise on the decision as well identify who makes the final decision. This identification serves to ensure that the decision context and the objectives of the decision are aligned across all individuals and to provide clear and unambiguous instructions for the decision-making process. Again, responses indicated that while participants *often* or *always* recognised the importance of experience in decision making, they thought that their organisations *never* or only *sometimes* provided clear unambiguous instructions for decision making. However, the majority of participants did show that the decision making within their organisations was *never* or only *sometimes* influenced by company politics.

QDMP 8 is to *perform an impact analysis of the decision*. The impact of the decision needs to be considered on both internal and external stakeholders. The analysis must relate to the present situation, but also to the future and should take into account elements of quality/validity of data, political/financial/competitor influences and procedures for similar decisions. Although some respondents indicated that their organisations *always* performed an impact analysis of the decision, the majority said that it was only *sometimes* or *frequently* performed. While individuals responded that they *frequently, often* or *always* understood the importance of

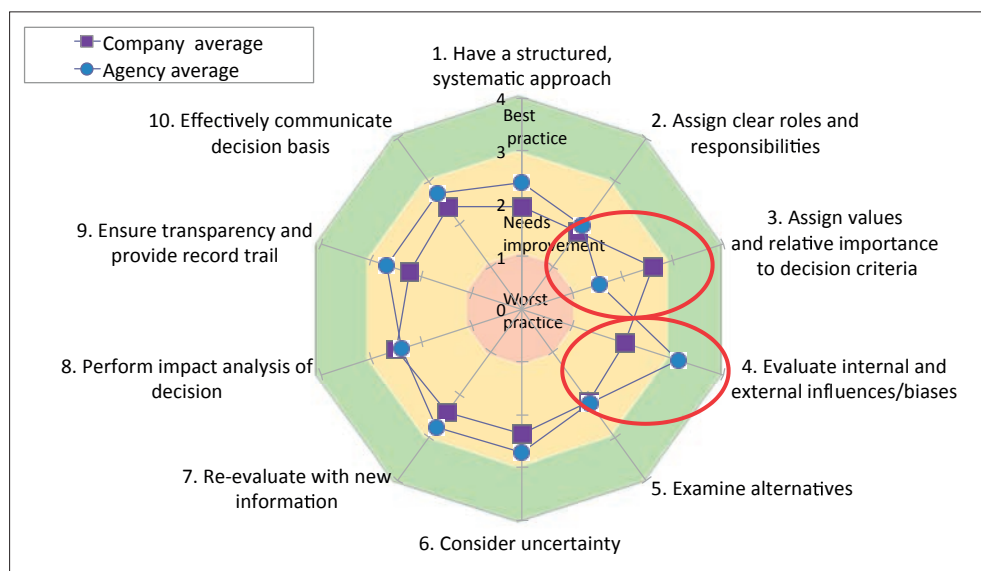
Figure 8.5. QoDoS pilot responses plotted against the ten Quality Decision-Making Practices.



the decision, responses also indicated that they *sometimes*, *often* or even *always* felt that they could have made a better-quality decision.

QDMP 9 is to *ensure transparency and provide a record trail*. It must be clear how decisions are made and details must be consistently documented. This documentation should be easily followed or audited by appropriate internal and external stakeholders who participate in the decision-making process or who rely on the outcome for their own processes. Responses were fairly evenly split among those who said their organisations *sometimes*, *frequently*, *often* or *always* engaged in transparent decision making, but more uniformly were positive about individual transparency, most frequently rating this quality as occurring *often* or *always*. When plotting QoDoS responses against all ten QDMPs for agency and company practices, differences could be observed, particularly for items 3 (assign values and relative importance decision criteria) and 4 (evaluate internal and external influences and biases), but there is room for improvement for both groups of stakeholders (Figure 8.6)

Figure 8.6. Agency and company QoDoS organisational responses mapped to the ten Quality Decision-Making Practices.



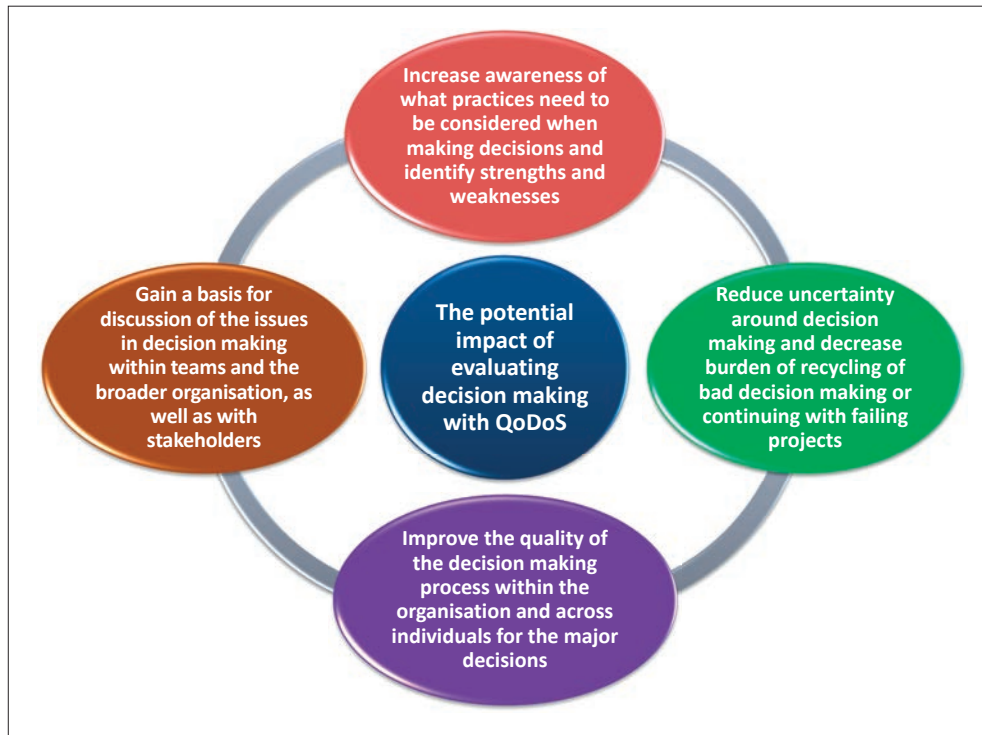
Conclusions

Feedback from companies and other organisations suggests four major benefits to evaluating decision making with tools like QoDoS. This work increases awareness as to the practices that need to be considered when making decisions and identifies the strengths and weaknesses of an organisation. It can also reduce uncertainty around decision making and decrease the burden of recycling bad decision making or continuing with failing projects. It can improve the quality of the decision-making process within an organisation and across individuals for major decisions. Finally, it can provide a basis for discussion of the issues in decision making within teams and the broader organisation, as well as with other stakeholders. (Figure 8.7)

Lovallo and Sibony suggest four steps to improving the quality of decision-making practices. First of all, decide which decisions warrant the effort. Second, identify the practices that are lacking and the biases that are most likely to affect the critical decision. Third, select the frameworks and the tools that might help you to improve quality and counter the most relevant biases. Finally, incorporate the practices into formal processes and thus ensure consistent application.⁶

A systematic literature review undertaken by CIRS has identified a relative paucity of research in quality decision making in the area of medicines development, regulatory review and reimbursement.⁷ A few techniques have been developed

Figure 8.7. The benefits of assessing decision making with an instrument such as QoDoS.

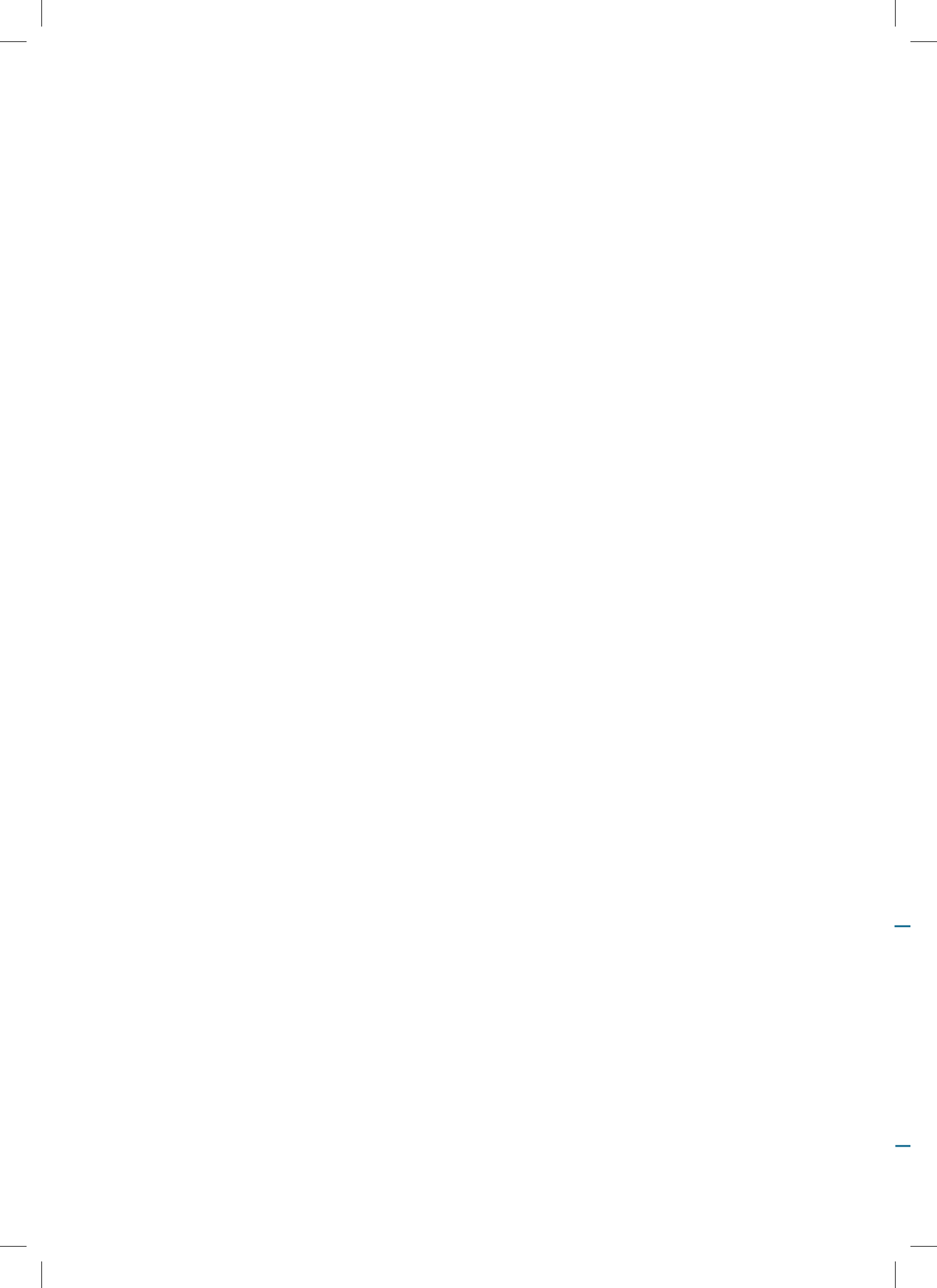


for evaluating quality decision making, but there is a general lack of systematic application as well as no apparent consensus around a gold standard. It would appear that QoDoS is a promising technique for assessing decision making in the lifecycle of medicines and the next steps in our research would be to further test its validity, sensitivity and reliability.

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CHAPTER 9

EXPERIENCE WITH EVALUATING QUALITY DECISION MAKING UTILISING QoDoS: FUTURE TRENDS FOR THE PHARMACEUTICAL INDUSTRY

“The QDMP framework and QoDoS questionnaire provided a platform not just to evaluate decision making, but also to ignite a debate on both the strengths and areas for improvement. The tool also helped to initiate the discussion on where there may be inherent biases in our decision-making processes.”



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Senior Vice President

Global Regulatory Affairs, Pharma & Consumer Health, Bayer

and

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Introduction

A countless number of decisions are made on a daily basis and these decisions range in terms of complexity. While some of these decisions appear to be made completely unconsciously and almost instinctively, a myriad others require the input of significant mental effort. Decisions can also be further categorised by the nature of their outcome (positive or negative) but almost disappointingly, the complexity and effort put into a decision do not always directly reflect the overall impact or direction of the outcome.

For the pharmaceutical industry, after the outcome of a decision becomes known, it is considerably straightforward to assess the quality of the results; for example, a drug approval is better than a rejection and a quality label describing the unique properties of the product is better than a class label. However, an assessment of the quality of the decision-making process is not as easy and comes with a certain amount of ambiguity. This uncertainty raises a very important question with relevance not just for personal decision making, but also with respect to decision making within an organisation: regardless of whether the end result is known (or is positive or negative), is there an objective method implemented, or even available, for measuring the quality of the decision-making process?

In most cases, the answer to this question will likely be “no”. The difficulty with implementing such a method lies partly in the challenge of assessing a topic thought to be mostly subjective. There may also be a somewhat muted level of receptivity to the idea of examining the quality of the decision process, especially if the resulting outcome was good. Nevertheless a well-validated tool could prove valuable to enhance decision-making quality and create aligned processes across teams within an organisation.

The Quality of Decision-Making Orientation Scheme (QoDoS) instrument represents such a tool for examining and improving the quality of the decision-making process within an organisation and across individuals. At Bayer, the Regulatory Affairs (Pharma and Consumer Health) Leadership Team (RA LT) had the opportunity to utilise this tool. The following is a review of Bayer’s experience with QoDoS, an overview of the results obtained and the resultant learnings with a commentary on next steps that can be taken to improve the quality of decision-making processes.

Rationale for utilising the QoDoS tool

Peter Drucker, the great business thinker who is often described as the founder of modern management, is thought to have popularised the saying that “what gets measured gets managed.” However, making quality decisions, or having good

“judgement” is a topic that is scarcely mentioned or described in literature. How can something so important be so understudied? CIRS attempted to tackle this issue through the development of the QoDoS instrument – a tool that can be used by pharmaceutical companies, regulatory authorities and health technology assessment agencies, throughout the life cycle of medicines, to examine the quality of decision making.

Bayer is a Life Science company with more than 150-year history and core competencies in the areas of healthcare and agriculture. Operations are managed in three divisions – Pharmaceuticals, Consumer Health and Crop Science. In all divisions, as a new product moves through the pipeline, the product development process may have some variability, but in general, the end goal is an extensive use of the product, which is achieved through rapid regulatory approval and a unique innovative product profile. This journey has a well-defined start and end point, but along the way, critical strategic and operational decisions need to be made. This type of process is termed a “decision-centric workflow” along a value chain in which decisions to progress a compound from milestone to milestone are driven by inherent product properties, scientific evidence, regulatory and customer requirements and a variety of other factors.¹

The approach to decision making for Regulatory Affairs (Pharma & Consumer Health) at Bayer has typically been results driven and linked to the objective of being “best in class”. How do you know that you are best in class? In 2004, the Regulatory Affairs organisation chose the key performance indicator (KPI) of first-cycle approvals. This measure captures speed of the approval process; any complete response letter delays the approval by often lengthy deliberations and is a reflection of decisions taken during the development of the compound. This KPI represents a relatively straightforward assessment – either approval came in the first cycle, or did not. Bayer makes an effort to determine the likelihood of a positive outcome by setting a “regulatory probability of technical success (rPTS)” during the development process. The rPTS is related to the probability of obtaining approval in accordance with a pre-defined target product profile (TPP) and its determination is a decision process in itself. As such, Bayer measures the overall outcome and the inherent quality of the outcome. For Bayer, the KPI for first-cycle approvals has been well above industry standards since 2008/2009.

As described above, Bayer measures the quality of its decision making by evaluating the quality of the outcome. However, the quality of the decision-making process itself is rarely, if ever, formally assessed. When considering QoDoS, the RA LT considered that understanding decision-making quality contributes to insights into

the decision process and enhanced overall productivity. This increased productivity might result from:

- › Improved ability to set benchmarks and KPIs for decision effectiveness.
- › Increased awareness around the obvious and not-so-obvious biases in our decision-making processes
- › Identification of strengths and weaknesses in the decision-making processes, which could be related to disproportionate optimism, inadequate evaluation of uncertainty, internal misalignment, or excessive time pressure
- › Establishment of a foundation for discussing the problematic areas in decision making within the organisation, especially as they relate to decisions involving other internal stakeholders

In spite of the recognition of these benefits, there was still a healthy level of scepticism when the QoDoS was introduced to the team. The RA LT is composed of 12 individuals (5, 42% male; 7, 58% female) with an average of 20 years of work experience (range, 9-30 years), with positions at the Director, Regional Head, Vice President, and Senior Vice President level. The uncertainty in using the tool was founded in perspectives that are likely to be common across all types of organisations:

1. if we already do a good job of making decisions, we are unlikely to learn something new;
2. the subjectivity of decision making renders the process impenetrable to an objective tool; or
3. that outputs from the survey will be too difficult to put into action.

However, with an open mind, and following an information session with Professor Stuart Walker from CIRS, the team was convinced that there was much to be learned from experimenting with this novel tool. In October 2016, the RA LT responded to the 47 items which make up the QoDoS by rating them on a five-point Likert scale. The survey was used to analyse one key decision point for a pharmaceutical division: the decision-making process to submit a new drug application (NDA) to a regulatory agency. Bayer currently has a framework for this particular decision-making process along the product development value chain. The framework was developed internally and has been formally defined and codified. A pre-assessment of the process revealed that it incorporates each of the 10 Quality Decision Making Practices (QDMPs) developed by CIRS, with the potential exception of QDMP 2 (Assign clear roles and responsibilities). The QDMPs are behaviours or approaches that underpin a quality process and that have been found to be relevant for both pharmaceutical companies and regulatory agencies. After the Bayer RA LT utilised the QoDoS, the resulting data were analysed using descriptive statistics and the 47 QoDoS items were mapped against 10 QDMPs.

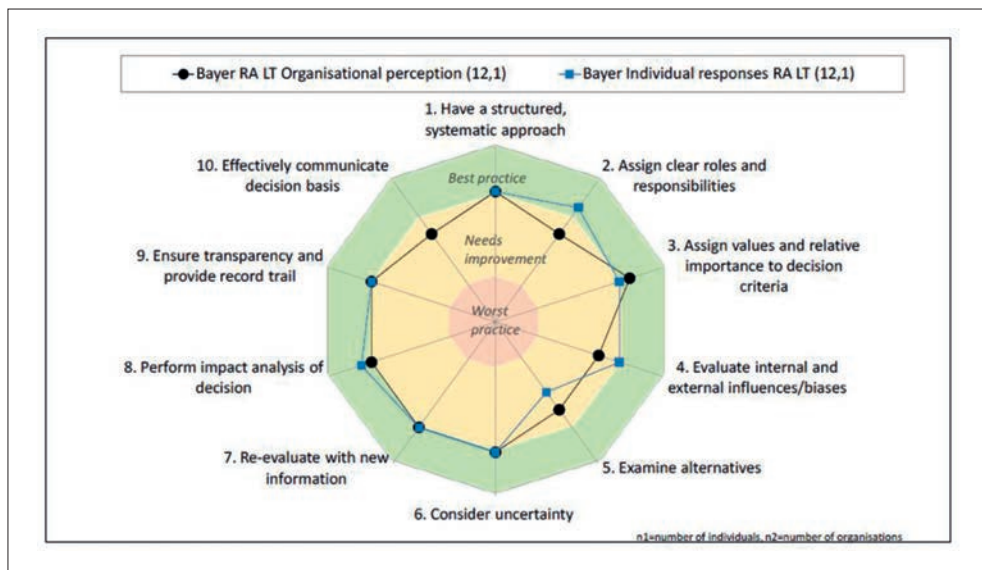
Results from the QoDoS

As a disclaimer, the results discussed below are averages of the individual responses of each of the RA LT members. These members have different perspectives on the processes from their roles in the RA organisation. Therefore, it is not considered unusual to see some spread in the results as depicted in Figures 3 and 4. The reader should keep this in mind while reviewing the discussion of the results.

An important outcome of the QoDoS was an examination of the relationship between the participants' perception of the organisation's decision-making approach and their own personal decision-making style (Figure 9.1).

In general, the Bayer RA LT scored very highly towards best practice for most QDMPs for both the individual's perception of the organisational and their own individual decision making. This output indicated that best practices were QDMPs 1 (have a systematic, structured approach to aid decision making), 3 (assign values and relative importance to decision criteria), 6 (consider uncertainty), 7 (re-evaluate as new information becomes available), 8 (perform impact analysis of the decision) and 9 (ensure transparency and provide a record trail). On the other hand, lower scoring practices that may need improvement and monitoring were QDMPs 2 (assign clear roles and responsibilities), 4 (evaluate both internal and external influences), 5 (examine alternatives) and 10 (effectively communicate decision basis).

Figure 9.1. Average aggregated QoDoS items relating to the participants' perception of their organisational (RA LT) and individual decision making, mapped to the 10 Quality Decision-Making Practices.



influences/biases), 5 (examine alternative solutions) and 10 (effectively communicate the basis of the decision). That QDMP 2 came out as an area needing work is a validation of the QoDoS accuracy – Bayer pre-identified this area as a potential weakness in the current decision-making process.

Overall, there was general alignment between how individuals perceive themselves and the RA LT group. However, some differences were noted for QDMP 2 and 4; for both, individuals were, in general, more critical of the organisation than themselves. The opposite was true for QDMP 5 – the individual score was lower compared to the organisation. While this might be an indicator for the presence of bias, it is possible that areas of disparity between individuals and organisations may point towards deficient practices. Feedback from CIRS suggests that if these deficiencies could be improved at the individual level, they could be translated into better overall organisational practices.

The QoDoS instrument could also be used to generate a sense of how the RA LT's decision-making process compares with that of other competitors in the pharmaceutical industry. An analysis of this nature is extremely valuable in setting benchmarks versus industry and gaining a better understanding of why some companies may outperform others with respect to decision making. It also has the potential to direct the organisation's attention to key areas where changes might yield the most considerable improvement.

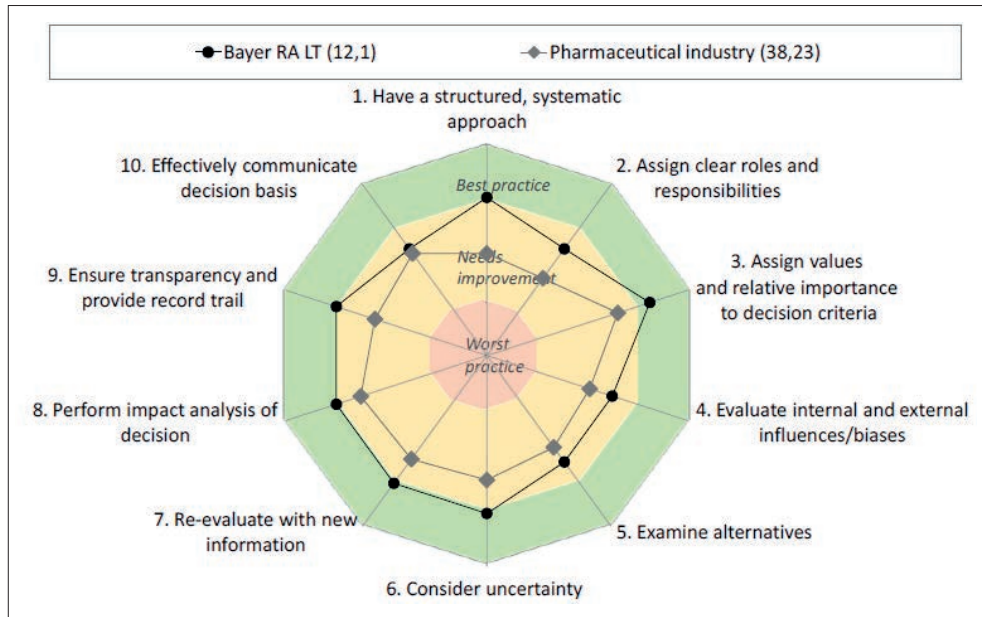
Figure 9.2 shows results from Bayer RA LT vs a sample of industry. However, it should be noted that pharmaceutical industry results are from a range of different companies and departments without a pre-specified decision point and consequently are only for illustrative purposes. Still, an examination of this chart suggests that overall Bayer utilises best practices as they relate to the QDMPs. In nearly all cases, Bayer averages somewhat higher than the industry average. However, the results point out that effectively communicating decision bias is an area where some improvement might be required.

Next steps

Perhaps the most important question about the QoDoS relates to how the results can be used to promote tangible change and improvement to an organisation's decision-making process. An answer to this question can be found by taking a closer look at the QDMPs which were identified as needing improvement.

As previously mentioned, QDMP 5 and QDMP 10 were two of the areas highlighted as needing additional attention in order to maximise the decision-making process

Figure 9.2. Average aggregated QoDoS items relating to the RA LT's perception of their decision making vs the pharmaceutical industry, mapped to the 10 Quality Decision-Making Practices.



of the Bayer RA LT (Figures 9.3, 9.4). An examination of alternative solutions (QDMP5) is already considered to be integrated into the current decision making process within the Bayer RA LT. Nevertheless, as suggested by the large variance in the responses to questions 8, 9 and 28, the QoDoS revealed that this practice was perceived to not be consistently applied by the team. The space for improvement here is fairly obvious – innovative decision making might be encouraged at the organisational level, but may not necessarily be consistently operationalised. As a next step toward fostering improvement, Bayer may critically examine or monitor how decision makers explore and assess alternatives. In addition, further improvement in this area could be achieved by proactively starting discussions at all levels of the organisation about how to encourage productive debate among colleagues. Most importantly, promoting this kind of change within the organisation might require a cultural shift. Employees should be encouraged to leverage their past experience, but in a way that challenges the status quo. To make this change it is critical to embrace cognitive flexibility and avoid the mentality of “it cannot be done because it comes with too much risk.”

Closer examination of QDMP 10 (effectively communicate decision basis) tells something of a different story. While it is perceived that effective communication

Figure 9.3. QDMP5: Examine alternative solutions.

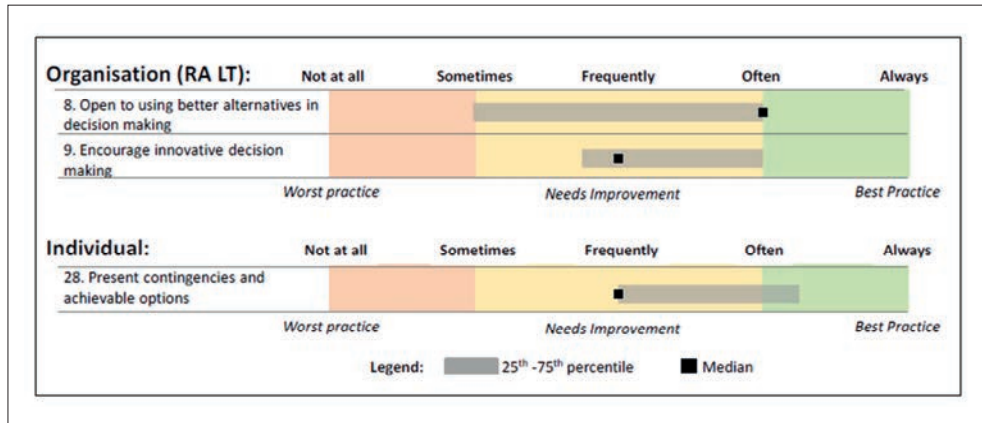
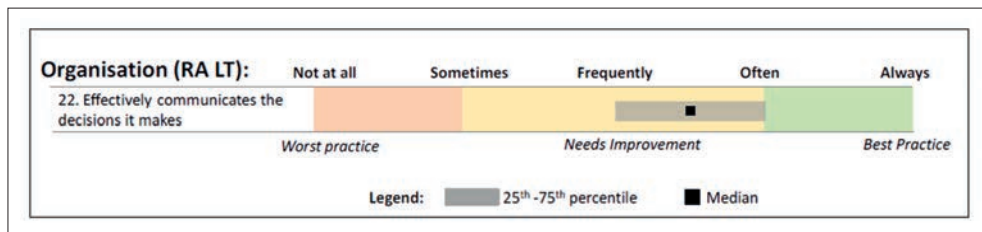


Figure 9.4. QDMP 10: Effectively communicate decision basis.



about a decision is currently performed on a frequently/often basis (Figure 9.4) within the RA LT, there still appears to be room for improvement in order to bring this behaviour up to the level of a best practice. Taking this step may require further monitoring and exploration to ensure that a decision is being appropriately communicated both internal and external to the RA organisation. From an inward looking perspective, imperfect communication might be contributed to by a less collaborative company environment or lack of trust between colleagues. On the other hand, ineffective external communication may result from weak networks between functions or a deficit in the understanding of the information needs of external partners. What is clear, however, is that much in the same way that solution exploration requires a cultural shift, optimising communication culture requires a mindset adjustment. There is a fine line between what should be shared and what should not, but a communication philosophy must be in place that recognises and supports the notion that, in general, information opens more doors for new solutions than it closes. A lack of transparency is likely to contribute only to the making of poor-quality decisions.

Future trends in decision making for pharmaceutical organisations

Earlier in this chapter, the drug development journey was discussed – not always a straight road, the process requires several decisions to be made that are not always of the go/no-go variety. Given the unpredictable and dynamic market and regulatory landscape, more so now than ever, making these decisions with speed and efficiency is paramount for effective and timely product launch to market.

9

EXPERIENCE WITH QoDoS

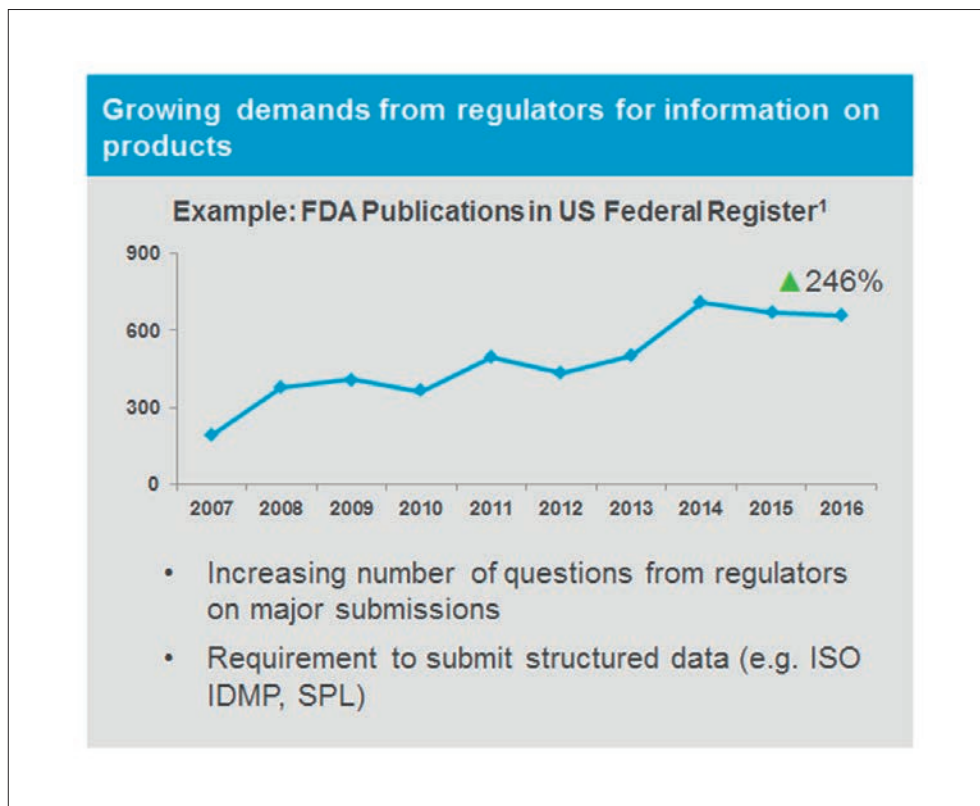
How can this speed and efficiency be enhanced further? Today we are experiencing an unprecedented wave of technological advancements that is magnified by the 'Internet of Things', big data and artificial intelligence (AI). As the volume of structured and unstructured data available to organisations continues to grow at seemingly incomprehensible rates, the need for tools to support decision making is becoming more apparent. Decisions on three levels – operational, tactical and strategic – will have to change to consider vast amounts of data in a fraction of the time through self-learning algorithms that are being created today. This evolution will lead to the establishment of machine / human interaction also referred to as the "centaur" concept. The centaur is considered stronger in decision-making ability than a human or machine on its own.

This is not a trend to which pharmaceutical companies, health authorities or health technology agencies will be immune. Over the last several years, the number of demands from regulators for information has steadily increased² and increasing volumes of data are being generated in order to meet regulatory requirements (Figure 9.5). With this trend in mind, in order to make quality decisions both more rapidly and with more accuracy, it will be critical to leverage innovative technologies to analyse larger and larger volumes of internal and external data.

As AI starts to play a larger role in the workplace, regulatory professionals will need to find ways to take advantage of the advancements and to consider that AI will raise the value of human judgement – the ability to determine benefits and costs of a different decision in different contexts.³ A recent publication in the *Harvard Business Review* by Kolbjornsrud and colleagues, suggests that successful managers (but in reality, employees at all levels) must embody "judgment-oriented skills of creative thinking and experimentation, data analysis and interpretation, and strategy development" in order to succeed in a technological future.⁴

At the moment, the perceived value of AI will be a reduction in the cost of predictive analysis – the ability to use data that is already available to create data that does not exist but has actionable business value because it helps to improve

Figure 9.5. The number of FDA publications in the US Federal Register has increased by nearly 250% over the last decade. ISO IDMP = International Organization for Standardization Identification of Medicinal Products; SPL = Structured product labelling.



decision-making quality.⁴ But, at least for the moment, only humans can understand an organisation’s objectives and can decide how to take machine-generated predictions and turn them into action. Therefore, while machines may take over the role of prediction in decision making and learn to do this better over time, this will be only a supplement to human judgement in making a quality decision.³

Conclusion

Quality decision making is a key success factor throughout the life cycle of medicines for pharmaceutical companies, regulatory authorities and health technology assessment agencies. However, it is not so straightforward to objectively assess the quality of a decision regardless of the nature of the end result.

The QoDoS instrument represents a unique tool for examining and improving the quality of the decision-making process within an organisation and across

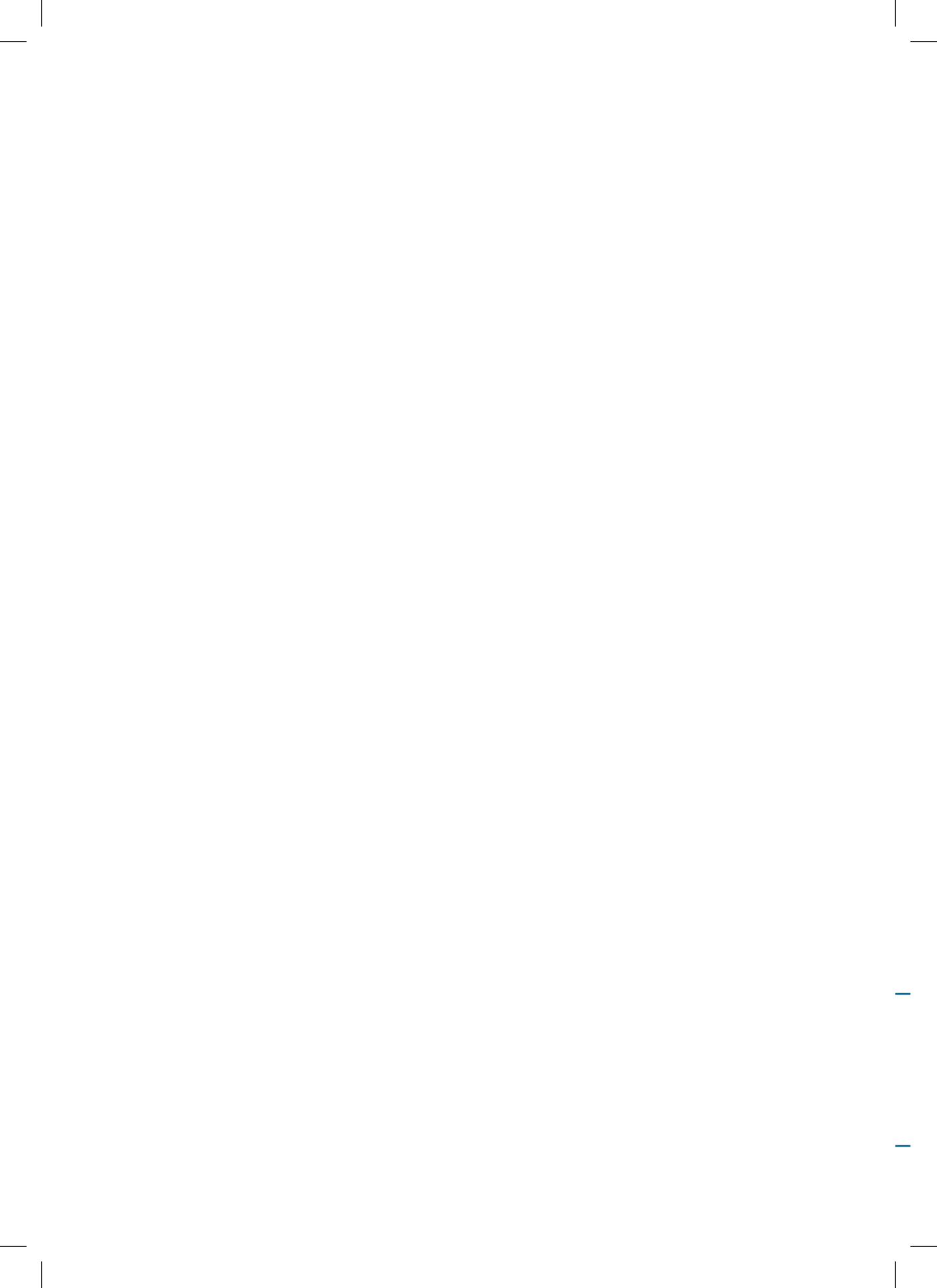
individuals. The RA LT at Bayer recently experimented with the QoDoS with the objective of improving the quality of its decision making. Overall, the experience with the tool was very positive. The QDMP framework and QoDoS questionnaire provided a platform, not just to evaluate decision making, but also to ignite a debate on both the strengths and areas for improvement. The tool also helped to initiate the discussion on where there may be inherent biases in our decision-making processes.

9

Understanding the quality of decision making is imperative in a world where the trend is towards technological and data-intensive analytics. Advances in technology ranging from predictive analytics to artificial intelligence to machine learning will enhance decision making in the future. However, in order to truly understand the impact of these advancements and to take strides in the future, it is important that we have a firm grasp on where we are today – measuring the quality of our decision making is a first and critical step towards that understanding.

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CHAPTER 10

BUILDING ORGANISATIONAL DECISION QUALITY INTO DRUG DEVELOPMENT AT LILLY RESEARCH LABORATORIES

“The journey to organisational decision quality has led to a number of key changes and areas of focus. The approach attempts to mitigate biases, enable external and multiple perspectives as inputs and strives to enable clarity and commitment to action. This has resulted in a culture that supports organisational decision quality and leads to more efficient and more effective decisions.”



Charles Persinger

Research Advisor – Decision Sciences
Eli Lilly and Company



Introduction

Eli Lilly and Company has been on a 25+ year journey of enabling “decision quality” in drug development decisions within the research company and in 2016, was awarded the Raiffa-Howard Award for “Organizational Decision Quality” by the Society of Decision Professionals. The concepts of decision quality and organisational decision quality will be introduced and then insights provided into how the company has built organisational decision quality.

Decision quality and organisational decision quality

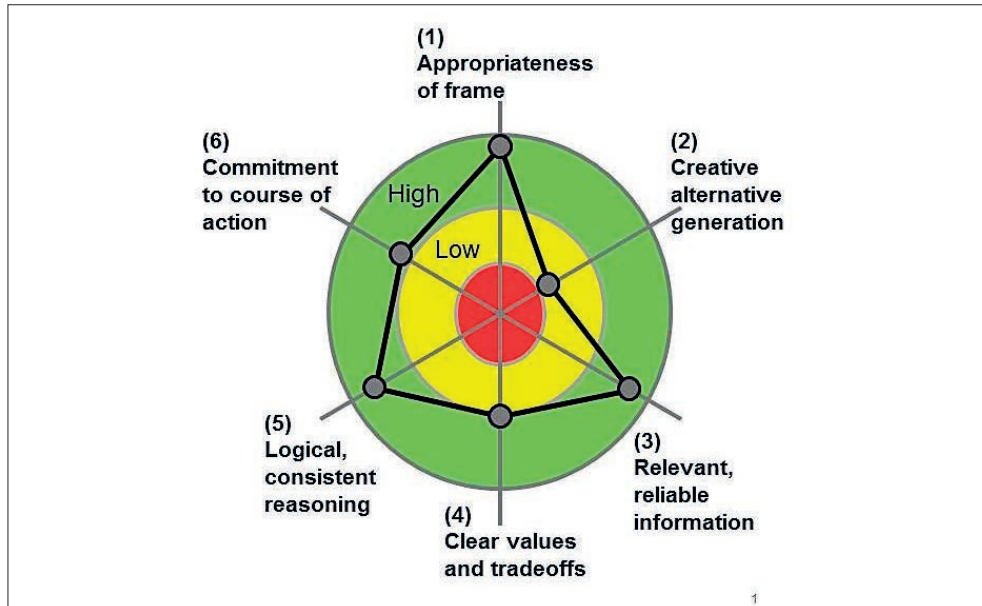
Lilly’s journey started in the late 1980s after a senior leader in Lilly Research Laboratories was exposed to the field of decision analysis. The principles, concepts and tools he saw seemed a natural fit for gaining clarity of action and helping enable better decisions in the complex, uncertain, challenging situations he faced in pharmaceutical drug development. He understood that an organisation enables (or destroys) value through the decisions it makes and thus, making “better” (and often more efficient) decisions would lead to providing more value to patients, shareholders and other stakeholders.

The foundational decision analysis concept of “decision quality” provides the framework the company uses for judging the quality of any individual decision and provides guidance into the actions required to enable a “high-quality” decision. Decision analysis defines the “quality” of a decision with the following elements (where a decision is only as good as the weakest link in the chain; Figure 10.1).

The six elements of decision quality are

- › **Appropriate frame:** Working on the right problem / opportunity and having clear goals and objectives
- › **Creative alternatives:** Creating good, creative and do-able alternatives from which to choose
- › **Relevant, reliable information:** Informing the decision with relevant and reliable information
- › **Clear values and trade-offs:** Ensuring the decision maker(s) understand the implications of the possible choices on the value criteria they need to consider
- › **Logical, consistent reasoning:** The approach to the decision is logical and minimises/mitigates potential biases
- › **Clarity and commitment to course of action:** The decision maker gets to clarity of their possible choices and implications of those choices and the approach to the decision enables commitment to the chosen course of action.

Figure 10.1. The six elements of decision quality.



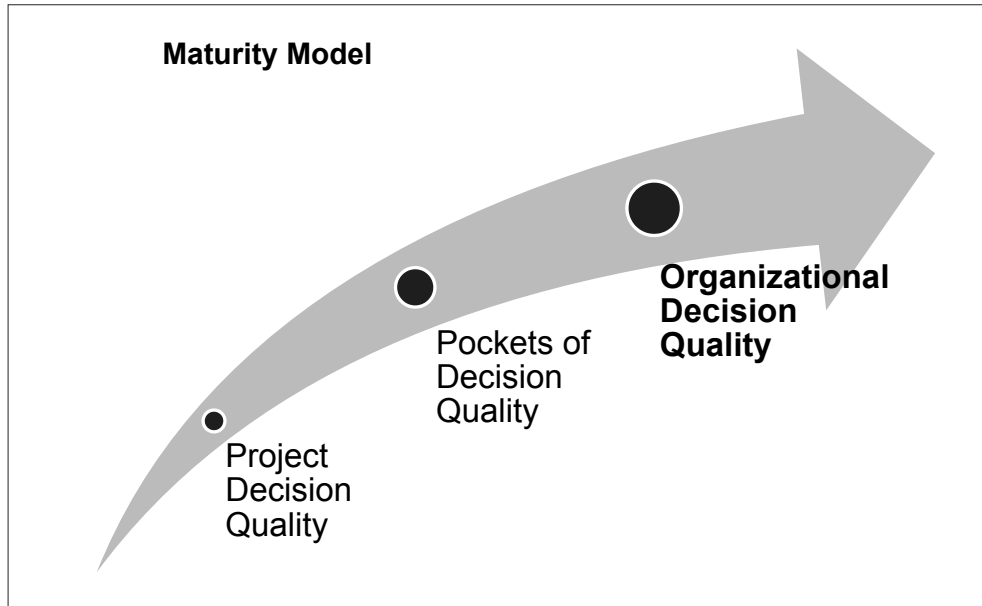
These elements of “decision quality” and the tools, processes and approaches to enabling these elements form the foundational mindset that helps enable decision quality on individual project decisions within the research company.

Lilly has also strived to reach organisation decision quality. Organisational decision quality (ODQ) is the concept of moving beyond enabling decision quality on a few individual project decisions to consistently enabling decision quality on decisions across the organisation (Figure 10.2).

As part of the Raiffa-Howard Award criteria, the Society of Decision Professionals identifies the aspects that help enable organisational decision quality as:

- › **Culture:** Is it supportive of decision quality?
- › **Decision makers:** Do they knowledgeably utilise decision quality on a routine basis?
- › **Decision staff:** Is the analytical staff competent and trusted by the decision makers?
- › **Process:** Are the processes institutionalised, sustainable, effective and efficient?
- › **Tools and analysis:** Are they technically correct, complete and used on a fit-for-purpose basis?
- › **Results:** Is the organisation clearly achieving its objectives through the use of ODQ?

Figure 10.2. Moving from decision quality to organisational decision quality.



The journey to organisational decision quality

After the initial senior leader's exposure to decision analysis in 1989, he took a number of steps that allowed the concepts of decision analysis and decision quality to take hold in the organisation:

- › He worked to expose others in the organisation to decision analysis
- › He leveraged external consultants to use decision analysis to support a few key decisions within his organisation (providing early, tangible examples of the benefits)
- › He established a small group (Decision Sciences) within the research company to provide expertise and help embed and enable decision quality in decision throughout the organisation

Thus began the 25+ year journey to build and then strengthen, sustain and enhance organisational decision quality. The key elements of that journey have been:

1. People (experts, owners, expectations)
2. Education (exposure, mindset, tools)
3. Embed (processes and culture)

People

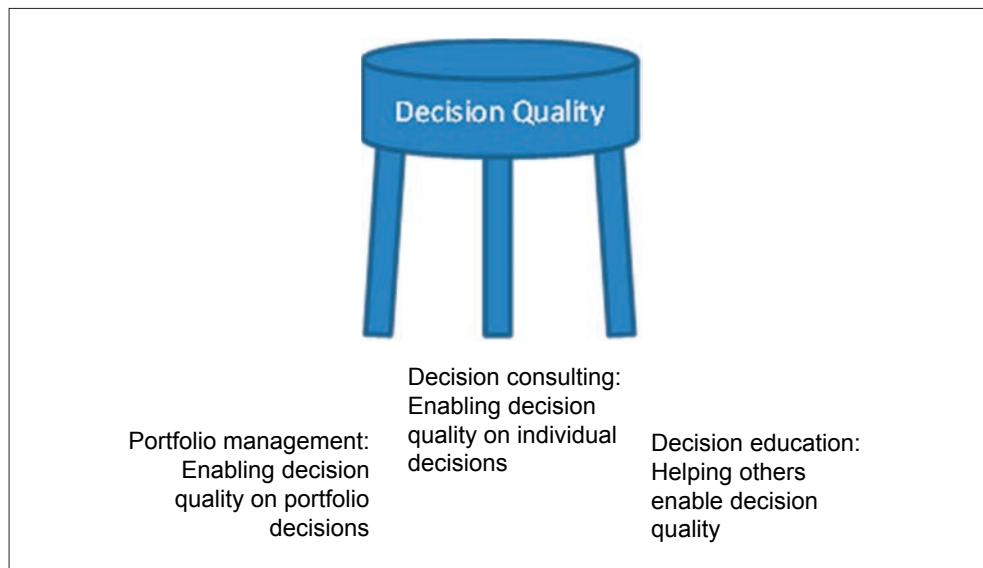
After gaining some traction for decision analysis and the concepts of decision quality within Lilly, the senior leader established a small group of dedicated experts

to help enable and embed decision quality. While formed under the sponsorship of this initial “champion”, this group still exists 25 years later because the organisation quickly saw and supported the value that this small group brought. This small group of experts (Decision Sciences) leverages a “3-legged stool” strategy to enable decision quality and organisational decision quality (Figure 10.3)

There are two main types of decisions that deliver value to the company (and thus benefit from decision quality) – portfolio decisions and project decisions. Portfolio decisions are the recurring decisions leaders have to make about how to prioritise and manage its portfolio of projects. Decision Sciences supports these portfolio decisions by creating and owning the systems of data and analyses that enable real-time information to support these decisions and by being the trusted advisor to leadership when they make these decisions. Examples include providing semi-annual portfolio reviews to senior leadership, enabling real-time prioritisation decisions and supporting ad-hoc decisions involving portfolio considerations.

Project decisions are the individual decisions made on an individual project within the portfolio. These vary greatly from the mundane and routine to the highly complex and complicated decisions that may involve investment of hundreds of millions of dollars under significant uncertainty and/or potentially affect patients. Decision Sciences supports these individual project decisions (typically the more

Figure 10.3. The three-legged stool strategy to enable decision quality and organisational decision quality.



complex, high-value decisions) through its decision consulting efforts. In decision consulting, a decision maker or team leverages Decision Sciences' expertise to help a team frame the problem, develop and analyse alternatives and provide decision makers with the insights they need to gain clarity and commitment to action. Examples of these decisions include decisions to submit (or not) for regulatory review based on outcome of a phase 3 programme, decisions to invest in expensive phase 3 programmes (and how), and decisions on how best to proceed in earlier phases of drug development. These decisions can be complex based on analytical complexity (e.g., uncertainties, unknowns, multiple value criteria) and organisation complexity (e.g., multiple stakeholders). Decision Sciences brings decision analysis tools and processes to enable decision quality in an efficient and effective manner in these complex situations.

While the small Decision Sciences group is the most visible aspect and is engaged on many high-value decisions, it only touches a small fraction of the decisions made within the research company. Enabling organisational decision quality requires leveraging many more people. On the front lines of organisational decision quality within drug development are the drug development teams, led by Project Managers. The teams make many day-to-day decisions and are responsible for making recommendations to senior leadership on most other meaningful project decisions. The Decision Sciences group provides training to Project Managers (and other key team members) to help ensure that they are able to enable decision quality. Their management and senior leadership (the decision makers) also hold the teams (especially the Project Managers) accountable for enabling decision quality. At times, this can be a challenging situation for Project Managers. Their main task is moving a team forward, often through the difficulties and challenges that their team encounters while trying to develop a medicine. This task requires them to be a cheerleader, champion and advocate. However, to ensure decision quality, they also have to be objective, dispassionate and sometimes think beyond their team to broader portfolio objectives when providing alternatives, information and recommendations to senior leadership. This can create challenges, but over time, the expectation of senior leadership that teams help enable clarity of action through robust discussion and evaluation of good, creative alternatives has led to a culture where the teams and Project Managers support this effort.

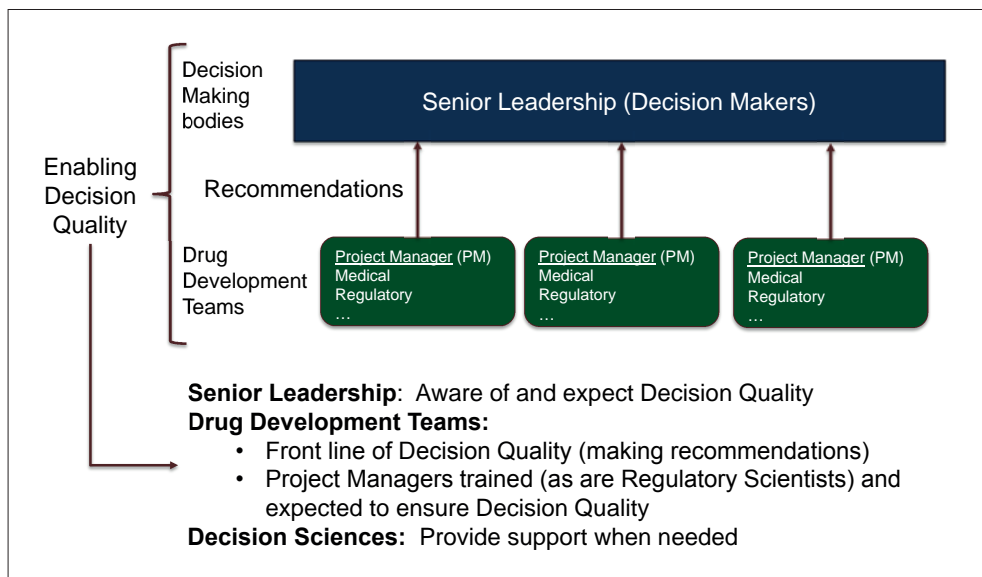
This collection of people (awareness and pull from leadership combined with educated drug development teams (especially Project Managers) on the front-line of decision quality and occasional support directly from Decision Sciences) is the key component to enabling organisational decision quality (Figure 10.4).

Education

For many years, Decision Sciences has provided education and training in the mindset, concepts and tools of decision analysis as a way to enable others to achieve decision quality across the organization. This has certainly helped enable organisational decision quality as even general awareness of the concepts can be helpful and those that are aware often reach out to the Decision Sciences group for consulting on complex decisions. The approach to education became even more focused and effective in the mid-2000s when, in conjunction with asking Project Managers to take a clear role in enabling decision quality, Decision Sciences developed a focused training course to help provide the tools necessary for the Project Managers. This internal course, called "Quality Decision Making" is a 2-day course required for all Project Managers. The course starts with a day and a half of lecture and group activities to present and discuss the concepts and tools of Decision Analysis. While the course mainly uses drug development examples to provide context, often the conversation turns to discussions of personal, life and other business decisions. The course is a readily engaging topic to all participants because everyone in the room has experience with the topic of decision making every day in work and in life.

The course concludes with a half-day case study. This case study is a drug development case that allows the participants to work in a team to develop and

Figure 10.4. People enable decision quality at Lilly.



evaluate alternatives and then make a recommendation to a mock decision board. The intent is to provide a similar experience to what they would face if they were the Project Manager on a drug development team. The mock decision board includes senior leaders/decision makers who are on the real decision-making bodies within the organisation. This allows the teams to gain an authentic experience in their interaction with the decision board. The mock decision board evaluates the teams' work using the elements of decision quality (Figure 10.5). This reinforces the concepts to the teams and provides another touchpoint to educate the senior leaders on the mock decision board in the principles of decision quality.

A culture focused on decision quality has developed at Lilly, in part, through this combination of formal education of Project Managers (and others throughout the organisation) and less formal exposure of team members and leadership through decision consulting projects, informal presentations on decision-making concepts and branding of discussions of these topics around "decision quality" and "quality decision making".

Figure 10.5. As part of the Decision Science training course, a mock decision board evaluates team case study decisions.

Team Score Sheet

The bubbles along the spokes moving outward from the center of the decision quality wheel denote: "poor", "fair", "good," "excellent." Check the score that best applies for the team. Some guidance for scoring is provided below:

Poor

The decision quality element was not addressed, or was addressed but was poorly aligned or poorly dealt with relative to needs of the case. (e.g., alternatives generated were outside scope of the frame, key uncertainties we not considered, etc.)

Fair

The decision quality element was addressed, aligned and properly dealt with relative to needs of the case, but to a limited extent. (e.g., uncertainty branches in the decision tree were correctly modeled, but the probability values assigned were poorly thought out.)

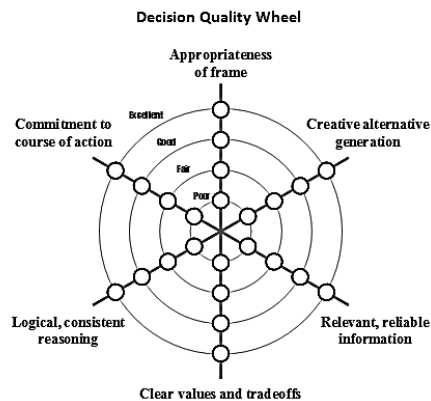
Good

The decision quality element was addressed, aligned and properly dealt with relative to needs of the case, to the extent that additional analysis would provide little additional benefit. (e.g., uncertainty branches in the decision tree were correctly modeled and the probability values assigned were well considered and appropriate.)

Excellent

The decision quality element was addressed, aligned and properly dealt with relative to needs of the case, to the extent that additional information would provide trivial additional benefit. The analysis can be readily extended to accommodate new information and provide additional insight beyond the current scope. (e.g., the treatment of the decision quality element is sound, complete and robust.)

Team: _____



Notes:

Embed

The final approach to achieving organisational decision quality has been to embed processes and approaches that help enable decision quality in everyday operations and decision making. Ultimately through these processes, education and expectations, decision quality became part of the culture.

The most direct embedding of approaches to enable decision quality is the formalisation of the approach to the decision to move a project into phase 3, the last phase of drug development intended to confirm the benefit-risk profile to enable regulatory approval of the potential drug. This is the most significant project investment, often in the hundreds of millions of dollars and has significant portfolio implications as funds spent on one phase 3 project may prevent other projects from receiving funding. Given the significant implications of these decisions, senior leadership requested a robust and required process to make these decisions. Leadership engaged Decision Sciences to help create the process, which includes a robust understanding of the project, potential alternatives and an evaluation of the alternatives:

- › Opportunity (unmet need, treatment paradigm, competitive landscape)
- › Rationale (scientific/medical, clinical data, etc)
- › Alternatives (strategies, development plans)
- › Evaluation (costs, timelines, valuation, etc)

Beyond these project-specific aspects, the approach also includes a view of the portfolio implications (e.g., how this opportunity compares to other potential investments) to ensure senior leadership are able to make this project decision within a portfolio context. To help mitigate potential biases, the approach also includes external inputs, a contrarian view and other measures. Overall, the intent is to ensure that the decision maker (often the CEO) has a well-informed view of the alternatives, understands the implications of the choices and is able to achieve clarity and commitment to action.

In addition to approaches to these major decisions, the formal approaches to evaluate alternatives and inform more routine project and portfolio decisions have embedded approaches to enable decision quality. These focus on ensuring the decision quality elements of “relevant and reliable information” and “logical and consistent reasoning”. These include the approaches used to consider uncertainty in timelines and revenue forecasts but the most visible approach is the approach to assessing the probability of technical success, $p(\text{TS})$. $p(\text{TS})$ is the assessment of the probability that the drug will be “successful”, where success is defined as

the drug meeting requirements for both regulatory approval and commercial/ clinical significance.

This is a key input into project and portfolio decisions. These assessments are challenging and can be subject to conscious and subconscious biases. Some companies decide to use historical averages for all projects, but Lilly believes that we know enough about individual projects to be able to provide individual project assessments that are more accurate, appropriate and informative than just historical averages. The approach starts with inputs and an assessment from the drug development team. A formalised p(TS) assessment group (made up of senior drug development experts) reviews the information from the team and then provides the official assessment. The approach includes best practices from the field of decision analysis and the group regularly measures and validates the performance of these assessments.

Embedding processes and approaches (either formal decision processes or processes to aid decision making) has allowed many of the concepts enabling decision quality to become part of the way we do business. This has helped expand decision quality from something achieved on a few project decisions to the way the organisation makes decisions in general (and thus organisational decision quality).

Conclusions

Lilly has been on a journey to enable decision quality on individual decisions and to strive for organisational decision quality. It has become a part of the culture of drug development. The approach that has been effective has been to:

- › Use the elements of decision quality as the guide
- › Use approaches, tools and best practices from the field of decision analysis
- › Enable people (experts, project leaders, decision makers) to help ensure decision quality
- › Embed and infuse the necessary knowledge, tools and processes throughout the organisation instead of purely a top-down executive mandate
- › Embed the mindset and expectations that become part of the culture (instead of a "check-box" exercise)

The journey to organisational decision quality has led to a number of key changes and areas of focus. It has leveraged a consistent decision-making approach, consistent decision-making forums and consistent value considerations for decisions. It shifted the organisation from a "sales pitch" approach to a decision-

quality approach that includes an identification of possible alternatives and an open, objective, transparent evaluation of the implications of the alternatives. The approach attempts to mitigate biases and enable external and multiple perspectives as inputs and strives to enable clarity and commitment to action. This has resulted in a culture that supports organisational decision quality and leads to more efficient and effective decisions.

10

ORGANISATIONAL DECISION QUALITY





CHAPTER 11

COMMUNICATING DECISION MAKING TO INTERNAL AND EXTERNAL AUDIENCES: AN EMA PERSPECTIVE

“The European Public Assessment Reports (EPARs) and the European Medicines Agency (EMA) Effects Table are two concrete examples of how the EMA has attempted to improve the communication of its decision making with both internal and external audiences and how the success of those efforts has been measured.”



Prof Hans-Georg Eichler
Senior Medical Officer
European Medicines Agency



Introduction

The European Public Assessment Reports (EPARs) and the European Medicines Agency (EMA) Effects Table are two concrete examples of how the EMA has attempted to improve the communication of its decision making with both internal and external audiences and how the success of those efforts has been measured.

European Public Assessment Reports

In a 2004 regulation, the European Parliament mandated that the EMA develop and make publicly available an assessment report for every centrally authorised medicine.¹ Accordingly, the European Public Assessment Report (EPAR), a multi-component source of information about medicinal products that have been granted or denied marketing authorisation, is published on the EMA website and could be considered to be the most important product delivered by the agency (Figure 11.1).

EPARs contain the authorisation's details, product information and assessment history for a new medicine as well as a summary developed for the general public,

Figure 11.1. European Public Assessment Reports are readily available on the EMA website.

The screenshot shows the EMA website interface. At the top left is the EMA logo with the text 'EUROPEAN MEDICINES AGENCY' and 'SCIENCE MEDICINES HEALTH'. To the right is a search bar with 'Site-wide search' and a 'GO' button, and a link to 'Advanced document search'. Below the logo is a navigation menu with 'Home', 'Find medicine', 'Human regulatory', 'Veterinary regulatory', 'Committees', 'News & events', 'Partners & networks', and 'About us'. The 'Find medicine' menu is expanded to show 'Human medicines', 'European public assessment reports', 'Patient safety', 'Pending EC decisions', 'Withdrawn applications', 'Paediatrics', 'Rare disease designations', 'Medicines under evaluation', 'Medicines for use outside the EU', 'Referrals', and 'Periodic safety update report single assessments'. The main content area is titled 'European public assessment reports' and includes a breadcrumb trail: 'Home > Find medicine > Human medicines'. The page content states: 'This page allows you to find the European public assessment reports (EPAR) for human medicines published by the European Medicines Agency (EMA). The EMA publishes an EPAR for every medicine granted a central marketing authorisation by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). EPARs are full scientific assessment reports of medicines authorised at a European Union level. Use this search to find information including a public-friendly summary in question-and-answer format and the package leaflet. You can also find information on medicines that have been refused a marketing authorisation or that have been suspended or withdrawn after being approved. As of October 2016, EMA publishes the clinical data submitted² by pharmaceutical companies to support their marketing applications for human medicines under the centralised procedure, allowing the public to better understand the Agency's decision-making. For more information see clinical data publication. The Agency does not evaluate all medicines currently in use in Europe. If you cannot find the medicine you need through this search, please visit the website of your national health authority. More information is available on the Central authorisation procedure and in EPARs: background and context.'

which is structured as a series of questions and answers. Although EPARs are readily available to all healthcare stakeholders including patients and healthcare providers, in reality they are likely most often used by the pharmaceutical industry and health technology assessors and payers. Because EPARs are a reflection of regulatory deliberation and conclusions of the EMA Committee for Medicinal Products for Human Use (CHMP) and include information from the CHMP assessment on the quality and importance of the design and results of clinical research for a new medicine as well on the balance between the benefits and harms that may be associated with its use, they are considered particularly useful as a source for a relative effectiveness assessment conducted by health technology assessors or payers.

The content and format of the EPAR has developed over time and it is expected that it will continue to evolve. Part of that evolution was initiated in 2008 through the input of several groups. The Medicine Evaluation Committee (MEDEV) includes 22 national authorities from 18 member states and Switzerland, who are responsible for the assessment, pricing and reimbursement of medicines in Europe. In 2008, MEDEV, which facilitates informed dialogue on EU pharmaceutical policy, sent critical comments on the format and content of the information and discussions in EPARs. Among these comments, MEDEV called for EPARs improvements including “better justification of positive benefit-risk” and the inclusion of “more facts than prose.”

Around the same time the Pharmaceutical Forum, a high-level ministerial platform for dialogue among stakeholders that include the EU pharmaceutical industry, healthcare professionals, patients, and insurers, recommended a political mandate for collaboration between EMA and the European Network for Health Technology Assessment (EUnetHTA) to improve the availability and best use of data relevant to health technology assessment and relative effectiveness assessment, specifically, data within the EPARs. EUnetHTA was developed as a network of organisations to facilitate efficient use of resources available for HTA, to create a sustainable system of HTA knowledge sharing, and to promote good practice in HTA methods and processes in Europe.

Initiated in 2010, the 2-year EUnetHTA-EMA EPARs collaboration began with EUnetHTA input on the utility of the EPARs documents. Based on this input, EMA developed revised EPAR templates and guidance documents, which were subsequently implemented by CHMP assessors.

In the second phase of the collaboration, EMA and EUnetHTA teams reviewed EPARs for the first ten products evaluated after the implementation of the revised

templates for compliance with the revisions and to determine if those revisions resulted in the inclusion of information in EPARs that was appropriate for purposes of health technology assessment. Using a 36-item questionnaire, EUnetHTA and EMA reviewers could choose from three possible compliance rates observed in components of the ten assessments; that is, more than 80% compliant, 50% to 80% compliant and less than 50% compliant (Figure 11.2).

In general, EUnetHTA reviewers rated the compliance of the assessments more highly than did EMA reviewers (Figure 11.3). Although overall reviews indicated that there was still room for improvement in the design and use of EPARs, the largely positive ratings were regarded as an encouraging indicator of a successful effort to improve communication and raise levels of trust between regulators and an important external audience.

The EMA Effects Table

With the goal of improving the transparency of the benefit-risk decision-making process and the internal and external communication of the process and rationale underpinning decision making for new medicines at the EMA, the agency initiated the Benefit-Risk Methodology Project in 2008.

One of the recommendations to arise from the five work packages of that project was the use of an Effects Table to succinctly summarise the important benefits, risks and uncertainties in the CHMP assessment report for a marketing authorisation application, thus providing a condensed display of the known factors and uncertainties that influenced the EMA decision. Until the development of the Effects Table, the EMA had not systematically and explicitly documented uncertainties surrounding regulatory decision making.

Effects Table Pilots

Two pilots in the use of the Effects Table were conducted by the EMA. In the first pilot in 2013, the rapporteurs in the review of nine new active substances prepared an Effects Table as part of either their Day 120 or Day 180 Assessment Report (Figure 11.4).

In the second pilot, Effects Tables were developed during the EMA review of 12 new active substances. As part of both pilot studies, a short feedback questionnaire was sent to review participants after the review completion (Figure 11.5).

Figure 11.2. EUnetHTA and EMA perspectives on the compliance with revised EPARs templates. Reprinted with permission from Berntgen et al. *Value Health*. 2014;17:634-641.

Overall compliance (%) accounted to EUnetHTA review			Review item	Overall compliance (%) accounted to the EMA review		
<50	50-80	>80		<50	50-80	>80
Format and scientific content						
		X	Table of contents [‡]			X
	X		List of abbreviations [‡]		X	
X			Clear referencing of data from publications [‡]	X		
		X	Structural formula for chemical substances [‡]			X
	X		Structural characteristics for biologicals [‡]			X
	X		Description of standard treatments in the EU [‡]			X
	X		Discussion of compliance with legal requirements [‡]	X		
		X	Discussion of compliance with scientific guidelines (EMA/CHMP) [‡]		X	
	X		Discussion of compliance with scientific advice [‡]			X
X			Discussion of outcome of any GCP inspection and its impact on data reliability [‡]	X		
	X		Discussion of key elements of the study design: Patient population [‡]	X		
X			Discussion of key elements of the study design: Comparators [‡]	X		
X			Discussion of key elements of the study design: Duration of the study [‡]	X		
	X		Discussion of key elements of the study design: End points and/or composite end point [‡]	X		
		X	Display of participant flow (graphically or tabular) [‡]			X
		X	Summary of the main efficacy data in the template table [‡]			X
X			Explanation for reasoning for additional analyses, if requested [‡]			X
	X		Explanation if a subgroup data were considered of particular relevance for the overall assessment of efficacy [‡]			X
	X		Justification for waiver of study or replacement by literature data [‡]	X		
X			Highlighting of shortcomings of the efficacy data including impact on the assessment [‡]		X	
	X		Reflection of additional input from external experts (SAG, ad-hoc expert group, PDCO), if requested [‡]			X
	X		Rationale for deciding that the risk-benefit balance is positive is adequately discussed [‡]			X
Support for summary of product characteristics (SmPC)[‡]						
	X		SmPC section 4.1: Reflection of approved therapeutic indication including selection of patient population and age range, as applicable [‡]		X	
	X		SmPC section 4.2: Substantiation of dose recommendations [‡]		X	
X			SmPC section 4.3: Substantiation of contraindications [‡]		X	
	X		SmPC section 4.4: Substantiation of warning/precautions for use [‡]		X	
	X		SmPC section 4.5: Substantiation of interaction statements [‡]		X	
	X		SmPC section 4.6: Substantiation of use during pregnancy and lactation [‡]		X	
X			SmPC section 4.7: Substantiation of effects on ability to drive and use machines [‡]		X	
	X		SmPC section 4.8: Substantiation of adverse drug reaction profile [‡]		X	
	X		SmPC section 4.8: Definition of ADRs consistent between SmPC and Assessment Report [‡]			X
X			SmPC section 4.9: Substantiation of information on overdose [‡]		X	
	X		SmPC section 5.1: Information on approved therapeutic indication(s) in line with information in the Assessment Report [‡]		X	
X			SmPC section 5.1: Available data in the pediatric population [‡]			X
	X		SmPC section 5.2: Substantiation of pharmacokinetic properties [‡]			X

ADR, adverse drug reaction; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; GCP, good clinical practice; HTA, health technology assessment; EPAR, European Public Assessment Report; EU, European Union; EUnetHTA, European network for Health Technology Assessment; PDCO, Paediatric Committee; SAG, Scientific Advisory Group.

‡ Because a separate reference listing is required only for EPARs with referencing to numerous publications and none of the EPARs subject to the review did fulfill this criterion, the review item "separate reference listing" (planned to be reviewed using a binary question) was not applicable and is therefore not reported in terms of compliance.

† Item reviewed using a binary question; i.e., the aspect is included "yes/no."

‡ Item reviewed using a graded question; i.e., the aspect is included "excellent/good/could be improved/no."

§ Item added by HTA organizations at the time of EUnetHTA review.

| Only aspects of sections 4.1, 4.2, and 5.1 (Information on approved therapeutic indication) were topics specifically addressed through revisions of template/guidance.

Figure 11.3. EUnetHTA reviewers tended to rate EMA compliance with revised EPARs templates more highly than did EMA reviewers. Reprinted with permission from Berntgen et al. *Value Health*. 2014;17:634-641.

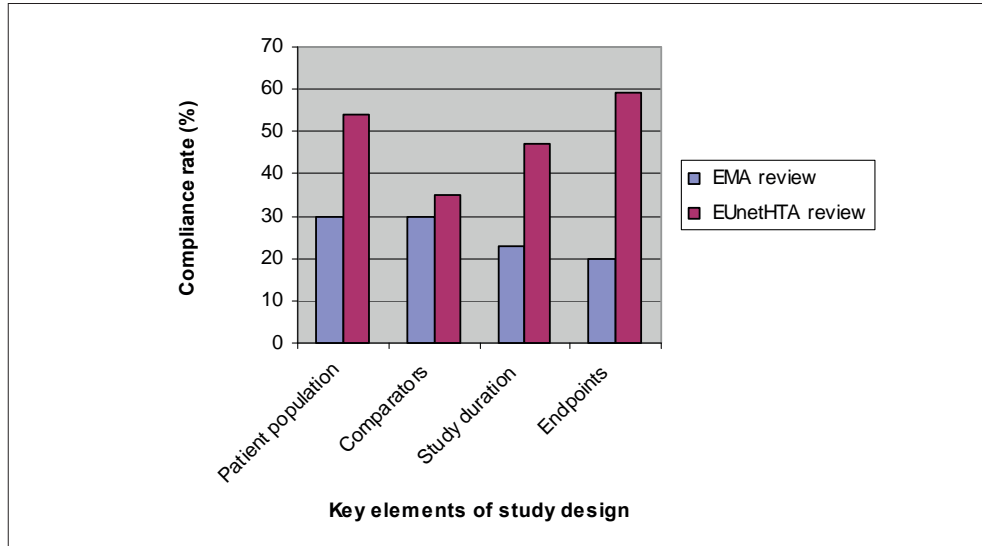


Figure 11.4. EMA Effects Table for Cymruza (ramucirumab).

	Effect	Short Description	Unit	Placebo	Cymruza	Uncertainties/ Strength of evidence	
Favourable	OS (HR)	From randomization to death	N/A	1	0.776	Inconsistency across regions, gender and histological subtype; no info on effect VEGFR2 expression	
	OS (median)		Months	3.8 (2.8-4.7)	5.2 (4.4-5.7)	Small, but significant effect	
	PFS (HR)	From randomization to progression or death (RECIST 1.0)	N/A	1	0.483	Inconsistency across gender (no effect in women); no info on effect VEGFR2 expression	
	PFS (median)		Mo	1.3 (1.3-1.4)	2.1 (1.5-2.7)		Small, but significant effect.
		ORR	Proportion of complete or partial responders	%	2.6%	3.4%	P=0.7556
		Quality of life	Change from baseline in global health status score (EORTC-QLQ-C30) At cycle 4	-	-3.2	-3.1	P=0.4371 47.9% of Cymruza arm and 24.8% of placebo arm provided data.
				-	5.6	-0.8	
Unfavourable	Hypertension	All grades	%	7.8	16.8		
		≥grade 3	%	2.6	7.6		
	≥1 TEAE	All grades	%	88	95		
		≥grade 3	%	58	57		

Figure 11.5. Effects Table pilot participants were asked to complete a short survey about their experience.

	Agree	Slightly agree	Neither agree nor disagree	Slightly disagree	Disagree
The ET improves clarity					
The ET is comprehensive					
The ET is helpful					
The ET is easy to read					
The ET is concise					
The ET does not oversimplify					

Effects Table questionnaire responses

Although the questionnaire response rate was low, especially from the Pharmacovigilance Risk Assessment Committee, the resulting feedback on the utility of the Effects Table in communicating decision making was positive overall in 15 of 17 responses. Certain concerns, however, were noted in individual comments from the questionnaires. Among these issues, the risks of focusing on the table and missing the totality of evidence and of oversimplification to external audiences were cited. Some participants noted that the Effects table was not helpful for assessors or the assessment process; that it increased the workload for assessors and that it does not reflect how the data are interpreted by CHMP. A lack of Effect Table standardisation was also cited, as which endpoints, adverse events and trials to include are at the discretion of the reviewer. The relevance and need for the Effects Table was also questioned in the light of the fact that the pivotal studies were already summarised in the clinical assessment report as well as in the overview. Finally, it was observed that without some sort of weighting of the outcomes, all effects, including major and less critical safety concerns seem to have the same importance. A qualitative approach, as part of the evaluation, is essential to conclude on the benefit-risk assessment of a given product – something that cannot be done if the table contains only descriptive (quantitative) information.

Moving forward

Despite these concerns and in response to a largely favourable review, the EMA adopted the use of the Effects Table as part of the EPARs as standard practice in 2015, producing guidance and training assessors in its use. Implementation, which

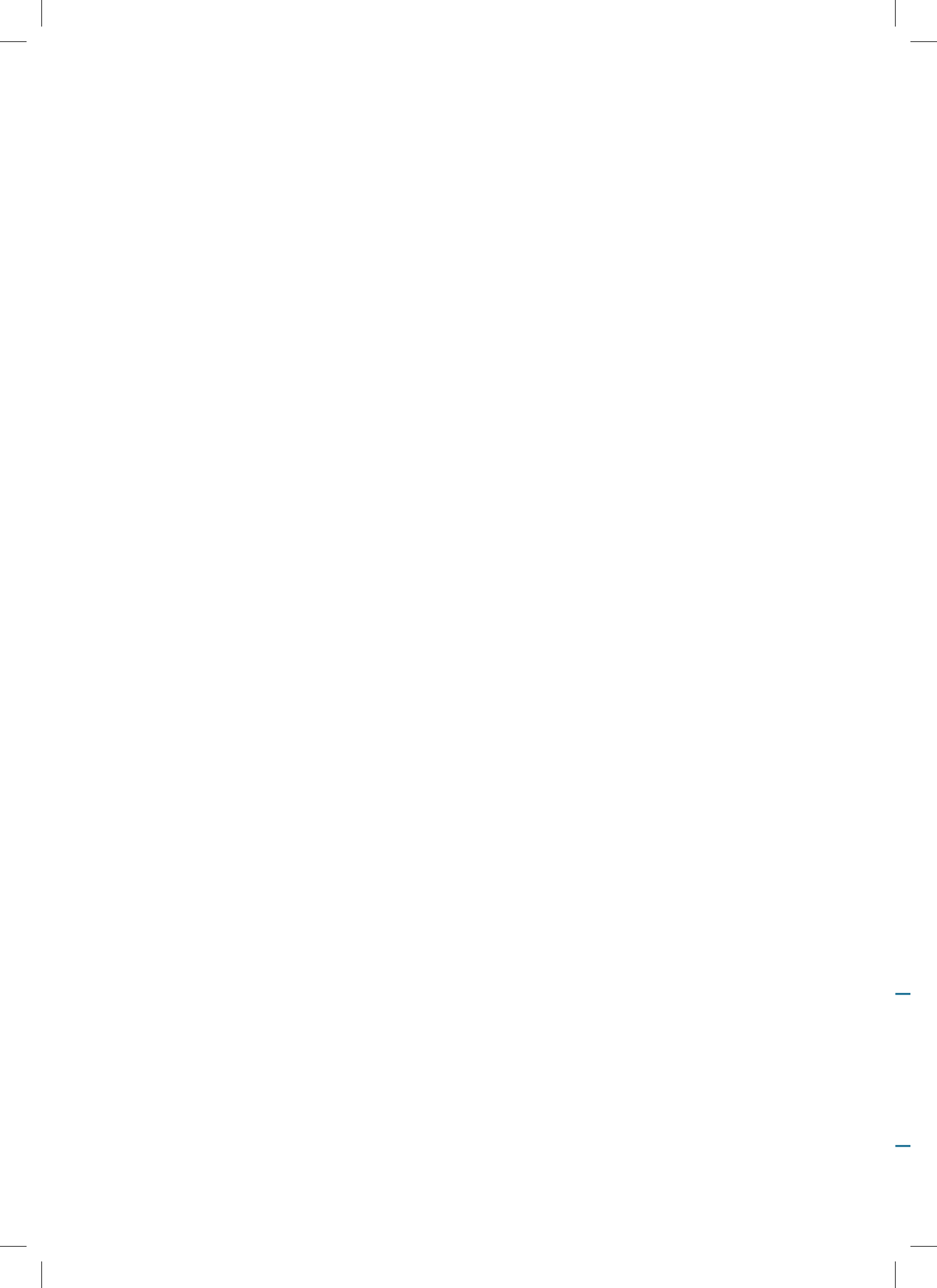
was monitored for the first year in now considered to be complete. Addressing the trade-off between necessary complexity and brevity of the tables remains the biggest challenge to their use.

Overall, the use of the EPAR and Effects Table has likely been beneficial in regulatory communications to internal and external audiences. However, although these tools have been refined and revised with the input of some users, they have yet to be challenged or changed by patient involvement. As the EMA framework for patient inclusion continues to evolve, patient preferences may begin to more fully inform regulatory decisions. Those preferences may contribute to the eventual explicit weighting of benefits and risks. In fact, I would venture to speculate that the current Effects Table is likely to be an intermediate step on the way to an ultimately quantitative benefit-risk model.

References

1. Regulation (EC) No 726/2004 of the European Parliament and of the Council. *Offic J EU*. 2004; 30.4.2004 Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF>
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CHAPTER 12

IMPLEMENTING STRUCTURED BENEFIT-RISK ASSESSMENT ACROSS THE DRUG DEVELOPMENT LIFECYCLE

"It is evident that regulators endorse structured benefit-risk assessment frameworks as valuable tools for introducing greater transparency, consistency and rigour into the medicinal product benefit-risk assessment decision-making process."



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Introduction

Over the past few years, regulatory authorities have begun adopting structured benefit-risk assessment frameworks to guide their assessment of the benefits and risks of medicinal products.^{1,2} Two leaders in this regard have been the United States Food and Drug Administration (US FDA), and the European Medicines Agency (EMA). Since 2015, both agencies have successfully incorporated structured benefit-risk assessment (SBRA) methods into their marketing authorisation review processes.^{1,2} Although the frameworks used differ somewhat, both share certain core elements in common. These elements include a description of: the decision context (i.e., specification of the target molecule, dosage and administration and the intended indication); the unmet medical need being addressed; the key benefits and risks (or “favourable” and “unfavourable” effects); the strengths, limitations and uncertainties associated with the available evidence; the proposed risk management activities; and an integrated summary and conclusion regarding the product’s benefit-risk profile.¹

In 2017, a formal evaluation of FDA’s SBRA implementation efforts showed that the majority of internal review staff viewed the adoption of SBRA methods to have been helpful and to have improved the quality of their marketing authorisation application reviews.³ The response from the sponsors’ perspective was equally positive. Industry representatives noted that it had enabled them to:

1. Better determine the alignment between their and FDA’s experiences with product review;
2. Articulate a concise summary of the product review to internal company management as well as business partners; and,
3. Achieve greater insight regarding ways to improve future development efforts, application materials, and post-marketing activities.³

Despite this enthusiastic endorsement, however, it is not clear to what extent marketing authorisation applicants have begun to consistently apply structured benefit-risk assessment methods themselves. Over the past decade, numerous pharmaceutical companies have experimented with using different structured frameworks and accompanying data analytic and visualisation methods to evaluate the benefit-risk profile of their products.⁴⁻⁹ These activities have been undertaken at both the individual company level as well as via cross-industry collaborations including, for example, the Pharmaceutical Research and Manufacturers of America (PhRMA)-sponsored Benefit-Risk Assessment Team (BRAT), and the Innovative Medicines Initiative (IMI) PROTECT.¹⁰⁻¹¹ However, these initiatives have focused primarily on methodological issues, including comparisons of the relative merits of alternative frameworks, various data visualisation tools, and different decision-

analytic techniques.^{4,10-13} The handful of companies that have employed SBRA methods appear to have done so in only a limited manner, such as to support a specific marketing authorisation application or for use in post-authorisation safety update reports.^{5-8,13}

Companies now face a host of compelling business reasons for changing their internal approach to assessing and managing the benefit-risk profile of their drugs. The adoption of structured benefit-risk assessment frameworks by regulatory authorities is one such reason. A second rationale is that the systematic application of structured benefit-risk assessment methods throughout the medicinal product lifecycle has been advocated as a best practice.¹⁴ A third reason is that the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for Section 2.5.6 (Integrated Benefit-Risk Assessment) of the Clinical Overview have been recently revised. These M4E(R2) revisions require sponsors to employ a structured approach, similar to that specified in existing benefit-risk frameworks, when assessing the product's benefit-risk balance.¹⁵

Additional reasons to incorporate a structured approach to benefit-risk assessment across the drug lifecycle include its potential to: enhance both the rigour and consistency with which product benefit-risk profiles are assessed (both across and within products over time); improve the quality of internal and external communications regarding the product benefit-risk profile; and gain greater insight into the degree to which the regulatory authority's benefit-risk assessment aligns with that of the sponsor's. Not least, there is the potential for achieving a more efficient, and favourable marketing authorisation review.¹⁶

Embedding structured benefit-risk assessment within the drug lifecycle management process: implementation, challenges and solutions

Once a company has made the decision to implement a structured approach to benefit-risk assessment, there are, typically, numerous challenges to address. In Table 12.1 we summarise several of the most common and critical of these and propose solutions for addressing them.

The first challenge is to obtain senior leadership endorsement for implementing the proposed change. Without such support, it is seldom feasible to move forward. Leadership must be convinced that the competitive advantages of implementing a new approach clearly outweigh any attendant resource requirements and potential disruption to the current drug development process. Tactics for successfully

articulating this business case include educating senior leaders on the evolving regulatory landscape in this area, and highlighting competitors' successful use of structured benefit-risk assessment methods in marketing authorisation applications, in advisory committee meetings and in peer-reviewed publications.

A second challenge involves defining the process for integrating structured benefit-risk assessment within the drug lifecycle management continuum. This challenge

Table 12.1. Implementing a lifecycle approach to structured benefit-risk assessment: organisational challenges and tactics to deploy in addressing them.

Key Challenges	Tactics
1. Obtaining senior management endorsement	<ul style="list-style-type: none"> › Articulate a compelling business case › Educate regarding the changing regulatory landscape › Conduct competitive benchmarking › Provide examples where other companies have used structured benefit-risk assessment methods to support a marketing authorisation application filing or at an Advisory Committee meeting
2. Defining the process: scope, triggers, timing and team membership	<ul style="list-style-type: none"> › Establish a cross-functional working group to map out a proposed process, including triggers and timing for initiating and/or updating an SBRA › Identify the business process owner › Identify cross-functional team membership
3. Selecting a SBRA framework and methods	<ul style="list-style-type: none"> › Conduct a comprehensive review of the peer-reviewed literature on SBRA frameworks and methods › Evaluate the different SBRA methods and frameworks endorsed/implemented by regulatory authorities › Select/develop a SBRA framework and accompanying methods and visualisations
4. Gaining cross-functional alignment	<ul style="list-style-type: none"> › Enlist senior management support in championing the new approach › Identify functional area "change agents" › Distribute targeted communications regarding the new process › Provide function-specific training
5. Ensuring consistency across teams, and continuous quality improvement	<ul style="list-style-type: none"> › Develop a SBRA template › Share "lessons learned" across teams › Provide teams with ongoing support from an internal subject matter expert (e.g., Benefit-Risk Management Scientist) › Showcase high-quality examples internally

can be further exacerbated by the fact that some internal company stakeholders may view investing in a new process as being non-essential or too risky to undertake at this point. One solution to addressing this challenge is to designate a business process owner (BPO). Due to the cross-functional nature of benefit-risk assessment, a business process owner could, arguably, be selected from any one of the main contributor groups (e.g., Clinical Development, Patient Safety, Regulatory Affairs). What is important is not so much from which department the BPO is ultimately chosen, but that a clear decision is made early on, that this decision is communicated throughout the organisation and that the BPO is provided sufficient resources to get the job done. Once designated, an important immediate task for the BPO is to assemble a cross-functional working group to map out the SBRA process across the product lifecycle, and to initiate the development of a standard operating procedure.

A third challenge lies in selecting a specific SBRA framework and accompanying methods to use. To date, no consensus exists regarding which of the various benefit-risk frameworks is optimum.¹² As a result, companies may consider conducting a comprehensive review of existing SBRA methods and case studies in order to evaluate the comparative strengths and weaknesses of different frameworks, and to determine which one (or which combination of elements) might best suit their internal needs.

Yet another challenge lies in gaining cross-functional alignment to implement the new process. Benefit-risk assessment is not only a complex undertaking, but a highly cross-functional one. Often, however, cross-functional alignment can be lacking due to differing incentives and divergent priorities across the different departments involved. Key tactics to employ in addressing this challenge include offering function-specific training on the new process, enlisting the support of senior management to champion this new approach, and identifying functional area “change agents”.

A fifth challenge concerns the lack of internal processes to support standard, consistent implementation of the new process.¹⁶ Developing a standard SBRA template is one tool for promoting standardisation across teams and products. Another tactic is to identify an internal subject matter expert (e.g., a Benefit-Risk Management Scientist) to guide teams in developing their SBRAs, and to share new methods and “lessons learned” across teams. Finally, hosting regular internal forums to showcase examples of best practices in benefit-risk assessment can also be effective in supporting continuous quality improvement efforts in this area.

One company's experience

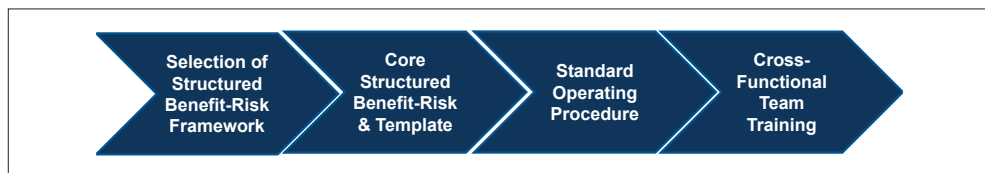
One example of a company that has successfully integrated structured benefit-risk assessment into its drug lifecycle management process is that of Amgen. Over the course of a two-year period (January 2015-December 2016), the company designed and launched an end-to-end, lifecycle approach to conducting structured benefit-risk assessment for all products in its portfolio.¹⁸

This process, which was spear-headed by the Patient Safety department, featured two components: 1) a design phase, which involved developing process maps, a standard operating procedure, and a company SBRA template; and cross-functional team training; and 2) an implementation phase in which each of the product Global Safety teams prepared SBRA for its product's main indications.

Amgen's approach rested upon four main elements: the selection of a specific benefit-risk assessment framework and data visualisations, the design of an SBRA template to support consistency in SBRA documents across products, the development of a standard operating procedure and the execution of extensive cross-functional training (Figure 12.1).

Several features of Amgen's approach are worth particular mention. First, the company coined the concept of a "core" SBRA (cSBRA). The cSBRA was viewed as being analogous to other 'core' documents (e.g., core company data sheet; core Risk Management Plan) in that it was intended to represent the company's position regarding a product's benefit-risk profile and to serve as the "parent" source for various external documents (e.g., Section 2.5.6 of the Clinical Overview; Section 18.0 in the Developmental and Periodic Safety Update Reports) requiring an integrated benefit-risk assessment. The cSBRA was designed to be dynamic: initially created at the end of Phase 2 following the development of the core Risk Management Plan (cRMP), it was to be updated whenever significant new data were received regarding product benefits, The Safety Specification in the cRMP was designated as one of the key reference documents for guiding teams in identifying

Figure 12.1. Key elements supporting organisational implementation of a lifecycle approach to structured benefit-risk assessment.



the key unfavourable effects in the cSBRA, thereby ensuring alignment between the two documents.

Second, upon reviewing the existing benefit-risk assessment frameworks, the Amgen design team ultimately opted to develop a hybrid benefit-risk framework, one that combined the main elements of the FDA's benefit-risk assessment grid along with two accompanying graphical representations: a Value Tree and an Effects Table. The latter two elements were included because they were powerful yet easily accessible visualisations that efficiently summarised the benefit-risk assessment.¹¹ These two graphics were required as a minimum; however, teams could opt to include additional visualisation methods as well (e.g., Forest or Tornado plots).

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STRUCTURED BENEFIT-RISK: AMGEN

A third unique feature of Amgen's approach was the creation of a new type of pharmaceutical professional: the Benefit-Risk Management Scientist. This individual was intended to serve as an internal consultant on benefit-risk assessment methods, including risk minimisation programme design and evaluation and was tasked with supporting Global Safety teams in creating and updating cSBRA for each distinct product indication, sharing learnings across teams, and introducing best practices and new benefit-risk assessment methods as appropriate. The Benefit-Risk Management Scientist role proved to be instrumental in facilitating adoption of the cSBRA framework, socialising newly introduced benefit-risk assessment concepts and approaches, and guiding teams in applying the SBRA template and developing the requisite graphics.

The process yielded several key learnings. Foremost of these was the recognition that developing a structured benefit-risk assessment was an exercise in critical thinking that demanded close, cross-functional teamwork. To do so successfully required that the cross-functional Global Safety teams engage together to discuss and identify the main drivers of the product's benefit-risk profile, select the relevant data sources, and evaluate the strengths, limitations and associated uncertainties in the available evidence. Aside from initial training, other tools that proved instrumental in helping teams collaborate in this way included: 1) a standard slide deck that described the SBRA framework, the steps in its development and the associated timeline, and expectations regarding team member engagement and contributions; 2) the cSBRA template which contained annotated examples; and 3) the sharing of best practices across therapeutic areas via the Benefit-Risk Management Scientists.

Another learning that emerged was how challenging it was for teams to succinctly summarise a product's benefit-risk profile. The cSBRA was designed to be a concise document. Despite this, teams initially struggled to keep within the suggested

length of 5-6 pages specified in the cSBRA template. Part of their struggle stemmed from discomfort in being asked to select a defined set of “key drivers” for the benefit-risk profile, particularly in regard to the product’s safety profile. Relatedly, some teams were concerned that defining key drivers might be construed by regulators as a form of “cherry picking.”¹⁶

Finally, teams also initially questioned the value of creating the Value Tree and Effects Table as standard visualisation tools accompanying the written text of the structured benefit-risk assessment document. Over time, however, this view changed as they became accustomed to developing these graphics and to using them for internal communication purposes. Distributing examples of Effects Tables published by the EMA helped to further convince teams of their relevance for communicating with regulators as well.

Conclusions

Robust methodologies to inform structured benefit-risk assessments of medicinal products continue to be refined and tested. In addition, efforts are underway currently to advance the science of pharmaceutical benefit-risk communication, and to identify rigorous methodologies for incorporating patients’ perspectives regarding product benefits and risks.^{1,17-20} Against this evolving landscape, it is evident that regulators endorse structured benefit-risk assessment frameworks as valuable tools for introducing greater transparency, consistency and rigour into the medicinal product benefit-risk assessment decision-making process, and increasingly agree that patient perspectives on the benefit-risk profile of a product are important to obtain as well.¹ As such, sponsors themselves will face growing incentives to employ SBRA frameworks across the drug lifecycle, and to elicit patient input in these assessments. Doubtless, no single ‘right’ model for doing so exists due to variability in such factors as the size of research and development budgets, pipeline attributes and the number and patent status of established products in the portfolio. Individual companies, instead, may need to define and experiment with operational approaches that could work within their own organisational structures and resource constraints, and be prepared to address a range of challenges in doing so. Importantly, as they undergo this process, they should consider sharing their experiences, successes and failures alike, so as to facilitate the emergence of best practices.

Disclaimer

The views presented herein are those of the author and do not necessarily represent the views or practices of the author’s employer or any other party.

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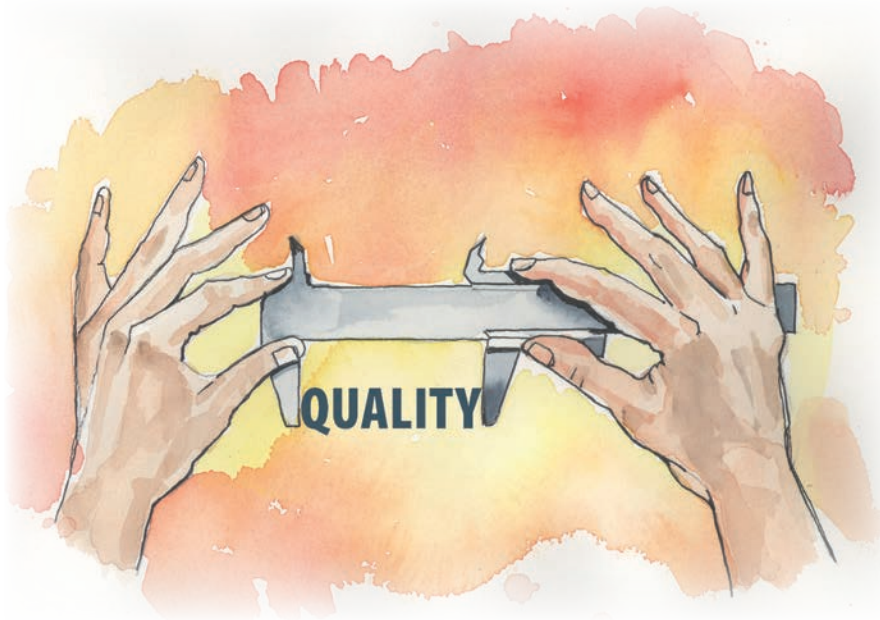
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CHAPTER 13

BUILDING QUALITY INTO DECISION MAKING THROUGH A STRUCTURED APPROACH TO THE BENEFIT-RISK ASSESSMENT OF MEDICINES WITHIN A DEVELOPING AGENCY: ISRAEL MINISTRY OF HEALTH PERSPECTIVE

"The Framework for the Universal Methodology for Benefit-Risk Assessment (UMBRA) was incorporated into the evaluation process for new medicinal products. Such a framework has enabled the Israel Ministry of Health to benchmark what is happening in other regulatory authorities."



Prof Eyal Schwartzberg

Head of Pharmaceutical Division
Ministry of Health, Israel



Introduction

Israel is a small country located at the juncture of three continents (Africa, Asia, and Europe). With a population of just over 8 million in 2015 and an area of just over 22,000 km², Israel's population density is 373/km².¹ The state is a democracy with a parliamentary, multiparty system, with the largest population groups being Jews (75%) and Arabs (21%).² Israel's fertility rate (3.1 children/woman) is the highest among the Organization for Economic Co-operation and Development (OECD) member states³ and in 2016, the population's estimated median age was 29.7 years.⁴ With an estimated life expectancy at birth of 82.4 years, Israel is ranked 11th in the world in terms of life expectancy.⁵

Israel has a modern market-based economy with a substantial high-technology sector and an advanced, modern and effective healthcare system. The main pillar and cornerstone of this system is the equity of universal coverage and health services to all citizens provided through the national health insurance (NHI) system.

Every citizen or permanent resident of Israel is free to choose from among the four competing, non-profit health plans. The health plans must provide their members with access to a benefit package that is specified in the NHI law. The system is financed primarily via progressive taxation and the government distributes the NHI funds among the health plans according to a capitation formula that takes into account the number of members in the plan as well as their age mix, gender and place of residence. The NHI provides access to a broad benefit package ("health basket"), which includes but is not limited to physician visits, hospitalisations, medications, diagnostic procedures, in-vitro fertilisation treatments, dental care for children and mental health care.

Reimbursement for these services, including medications, is determined by a public committee composed of healthcare professionals, economists, ethicists and members of the clergy, as well as representatives from the public and is based on input and/or requests from healthcare organisations and from the public. It should be noted that only registered pharmaceuticals are subject to reimbursement in Israel and a robust process of evaluation throughout registration is required to ensure that only safe, effective and high-quality medications are included in the "health basket".

Regulation of pharmaceuticals, pharmacists and pharmacies falls under the Israeli Pharmacists Ordinance¹⁰ and specific regulations and guidelines. The Pharmaceutical Division of the Ministry of Health which recently changed its name to the Center for Evaluation of Pharmaceuticals and Enforcement, is the body responsible for ensuring that all laws and regulations are followed. The Division's main task is to

ensure that all of the pharmaceuticals on the market meet the standards of safety, efficacy, and quality. The Division oversees the entire life cycle of medicinal products from clinical trials, through approval, distribution and marketing. This is achieved via a robust evaluation and registration process, pharmacovigilance and post-marketing surveillance, as well as rigorous monitoring of the medicine supply chain. The division also set the standards to the pharmacy profession.

Registration process of a new pharmaceutical in Israel

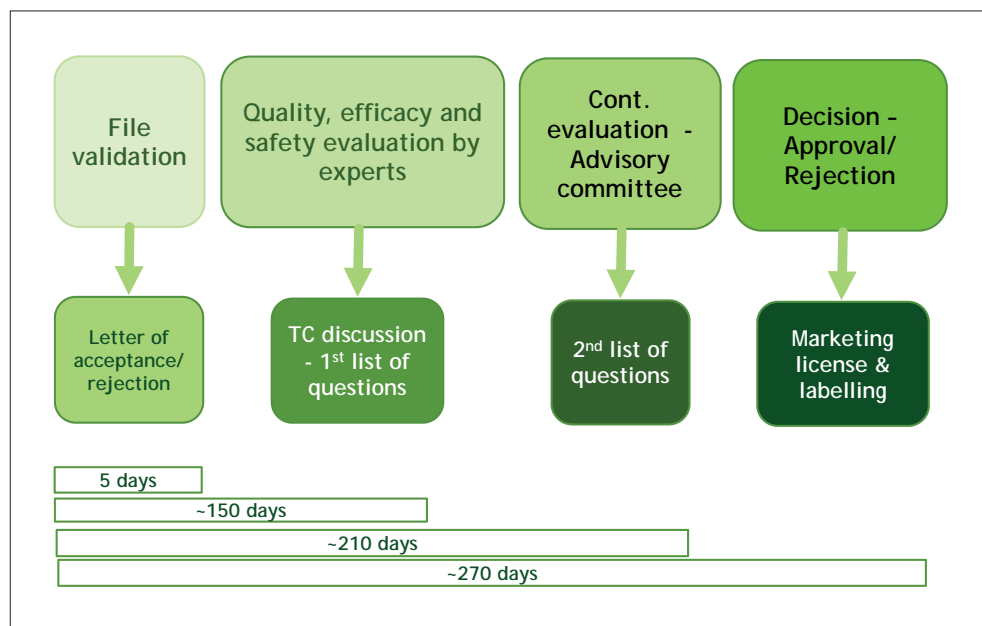
The Pharmaceutical Division consists of several departments (Clinical Trials, Import, Registration and Pharmacovigilance) and an Institute for Standardization of Pharmaceuticals, which are responsible and oversee the registration process. The process of evaluation and registration has recently celebrated its 50th anniversary and about 4000 medicinal products are currently on the Israeli registry. As the division is small in size (200 employees) and has limited resources as well as capacity, it utilises a benefit-risk strategy whereby it accepts medicinal products for evaluation that have been registered in one of the seven “recognised countries”. These countries/authorities are US FDA, Health Canada, EMA, Japan, Switzerland, Australia and New Zealand. These jurisdictions appear in the Israeli legislation and are part of the pharmacy ordinance because Israel has acknowledged their quality systems and processes for medicinal products as robust and meticulous. Thus, a potential marketing authorisation holder (MAH) who wishes to submit a medicine for registration that was previously registered in one of these recognised countries may do so. A built-in risk-sharing mechanism is thereby used for such products, which have been evaluated and registered by a recognised authority. Such registration may also be referred to as dependent or secondary registration.

The Division also has the ability to evaluate and register medicinal products independently that have not been evaluated before or evaluated in parallel with other countries, including generics and innovative drugs. The timeline for the acceptance of the application, review and registration of a medicinal product is set in legislation at 270 days. Exceptions to these timelines are made for products submitted with a full dossier including the questions and answers issued in response to deficiency letters by the relevant regulatory agency (FDA or EMA) with a timeline of 180 days. For well-established medicinal products (also known grandfathered drugs) the timeline is 180 days, for generic drugs that have been registered by the FDA or EMA, the timeline is 70 days, with prioritisation being given to medicines that have been included in the “health basket” and that are registered within 45 days after their inclusion in the national list of services. Medicines that are important in terms on national unmet medical need or the first two generics that save 10 million shekels annually (approximately 3 million US dollars) are prioritised

to the top of the evaluation list and registered within 270 days. This process is extremely robust and sustainable and follows strict international and national guidelines and procedures.

Each new drug application is submitted according to the local requirements, which are based on the Common Technical Document, with regional documentation specifications as part of module 1. The drug application undergoes a parallel quality review and efficacy and safety assessment. The quality review is carried out by the Institute for Standardization and Control of Pharmaceutics. The Drug Registration department is responsible for the efficacy and safety review. Each product is also sent for an independent clinical review, which is carried out by experts who form an external advisory committee. The committee takes quality efficacy and safety information into consideration as well as pharmacovigilance data and makes its recommendation to the Head of the Pharmaceutical Division as to whether to register or reject the product. As of July 2015, in order to further explore the benefit-risk balance of new drugs and indications, MAHs are required to submit a risk management plan (RMP) as approved by other competent authorities or a company RMP, which is examined for possible local implementation (Figure 13.1).

Figure 13.1. Timelines and the procedure for registration of a new drug in Israel, (independent evaluation).



Challenges in the registration process

The Israeli MoH deals with various local and global challenges. Globally, similarly to other countries, the division is subjected to the increasing pressure of industry, public and political expectations. Pharmaceutical companies spend more than ten years and approximately a billion dollars for the development and preparation of a drug application for regulatory approval and wish to see their products registered and marketed as soon as possible. Additional pressure is due to consumers' expectations for rapid registration as well as to that from various non-government organisations and healthcare providers, including HMOs.

Also similarly to the rest of the world, the Pharmaceutical Division deals with new types of health products including advanced tissue therapies, gene therapies and faecal microbiota transplantation (FMT). These new products and their applications require the constant development of new expertise and devising and implementing new regulations, which is time and resource consuming. Drug applications submitted to the Israeli MOH in parallel with submission to FDA or EMA, require independent evaluation under the constraints of limited resources, especially limited manpower

Although different agencies have adopted similar legislation, there are still local requirements and differences in process in the approval of drugs. The ministry occasionally receives drug applications that were denied approval by FDA or by EMA but that were successfully registered by a competent authority. Moreover, even when the same drug is registered by EMA and FDA, variations in the approved indications, posology and other parameters may be found, without knowledge as to the reason behind these differences. In such cases, public assessment reports and communication with EMA or FDA or both are of value in decision making by the Pharmaceutical Division.

Even though there are a growing number of drug applications submitted annually, as a government agency, the Pharmaceutical Division copes with increasing budgetary constraints and limited human and other resources. Despite these limitations, the Pharmaceutical Division carries out its own independent review for drugs already registered by EMA and FDA and other recognised authorities. In many cases, the dossier submitted to the Pharmaceutical Division is different and the quality of the drug varies according to its intended regional destination. Moreover, there have been various cases of medicines approved by major or mature regulatory agencies being withdrawn from the market because of safety concerns. Thus, the Pharmaceutical Division needs to raise the appropriate questions making to ensure confidence in the positive benefit-risk profile of the approved medicine.

Israel is not part of a global consortium and to overcome potential “regulatory isolation,” the Pharmaceutical Division constantly seeks partnerships that will enable exchange of important regulatory information and new knowledge sharing. To this end, in addition to a current excellent collaboration with EMA and SwissMedic, the Pharmaceutical Division would like to develop additional memoranda of understanding with other countries.

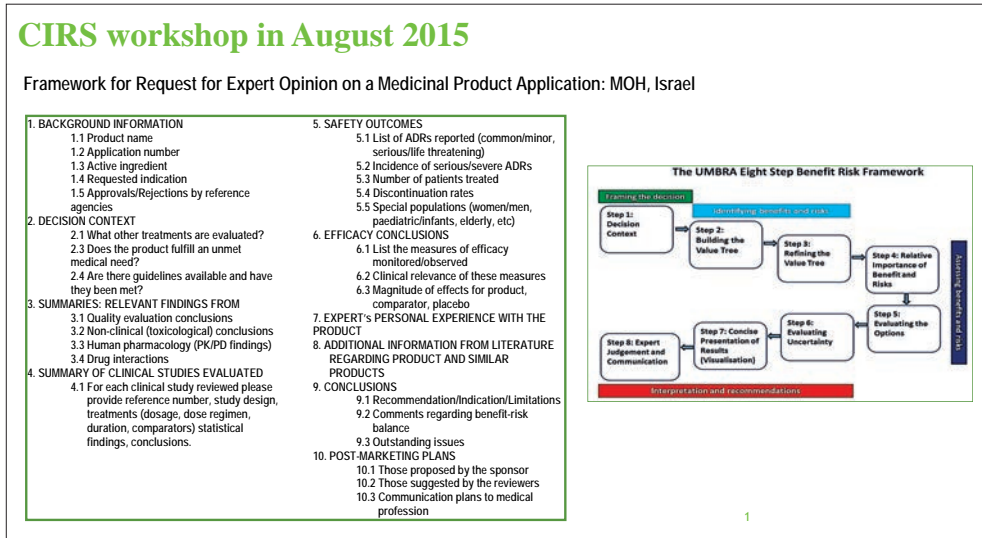
The simultaneous fear of over- and under-regulation creates a dilemma that can be described as the regulatory pendulum. On one hand, the agency is facing industry and public expectations requiring short registration, while evolving regulations that adapt to the challenges of new technologies and innovation. There is a huge expectation for a medicine to be registered promptly and swiftly by the local regulatory agency, especially if it has already been approved by a mature agency. In this case, an agency is expected to act as a relevant, responsive regulator, enabling and facilitating the approval of new therapies with a potential for improving public health. On the other hand, the regulatory agency’s role is also to protect the public health and ensure the registration of safe and effective drugs while performing a careful and comprehensive evaluation of a new medicine and to make sure that a robust and sustainable benefit-risk evaluation is carried out.

Thus, as part of overcoming the “regulatory pendulum” as well as to implement an internal quality improvement process, the Pharmaceutical Division decided to improve its benefit-risk assessment evaluation procedures. Consequently, in 2015, CIRS was invited to convene a workshop in Israel on this issue. At this workshop, CIRS shared the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework, which was subsequently incorporated into the evaluation process for new medicinal products. Such a framework has allowed the division to adopt and benchmark what was happening in other agencies and not to “reinvent the wheel” (Figure 13.2).

The incorporation of quality in the assessment of medicines against the benefit-risk pyramid is presented in Figure 13.3. The four upper parts of the pyramid represent the process framework for product evaluation, whereas the lower parts represent relative, real-world evidence used in the process. All of these parts are of equal importance and their position in the pyramid does not indicate their magnitude, as they are all integrated and contribute equally to the stability and completeness of the benefit-risk assessment process and the stability of the pyramid.

Within the upper part of the pyramid, robustness, uniformity, reproducibility and bias have been identified as core elements of the process framework. It is important

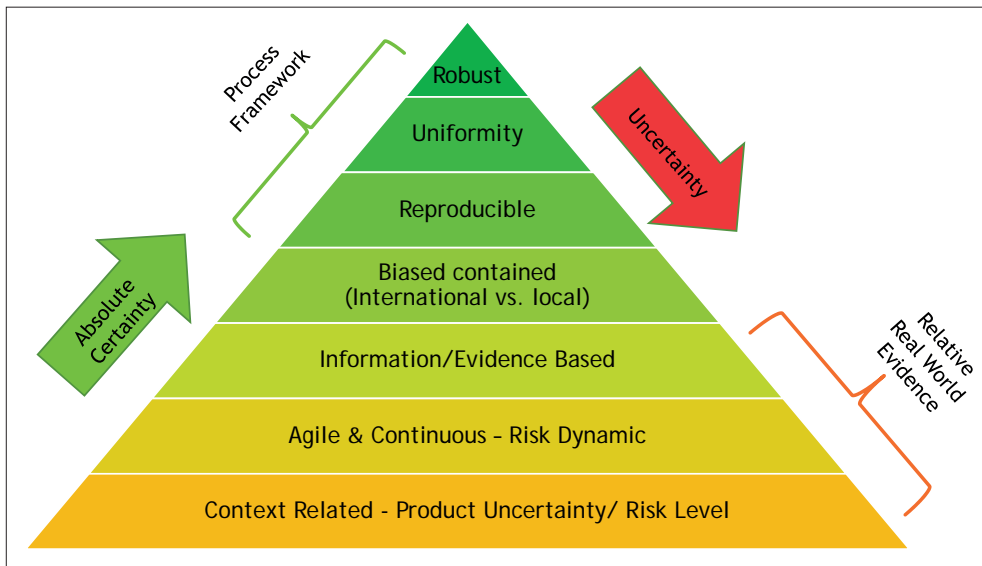
Figure 13.2. CIRS conducted a benefit-risk workshop for the Israel Ministry of Health in 2015.



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STRUCTURED BENEFIT-RISK: ISRAEL MOH

Figure 13.3. Incorporating quality into regulatory process – benefit-risk pyramid.



to use robust methodology for the evaluation process, with distinct timelines and stages. The benefit-risk evaluation process needs to be transparent and the same nomenclature should be used by the regulator and industry. Using a pre-defined and clear framework such as UMBRA assists in creating an agreed regulatory language,

which in turn streamlines the process. In addition, the use of uniform criteria and framework will result in a sustained and reproducible process and contribute towards decreasing the uncertainty involved in benefit-risk assessment. Uniformity of the framework can be achieved by providing consistent training for agency and industry personnel as well as advisory committees involved in the benefit-risk evaluation and retaining consistent agency personnel. External advisors, who may not be experienced in regulatory processes may particularly benefit from regulatory education and training.

Finally, one should consider how to mitigate bias that might be introduced into the benefit-risk process. As Israel accepts products that have been approved by mature agencies such as the US FDA, EMA and Swissmedic, bias may be introduced to the regulatory system (ie, if it was approved by mature regulatory authorities it must be safe and effective). But it should be remembered that in certain instances one agency may reject an application that is accepted by a different agency for registration. Since local experts are exposed and affected by decisions made by other regulatory agencies or by participating in the product's early stage clinical trials; this may also introduce bias into the system. To address this challenge, a "consensus" decision must be achieved by the Israeli advisory committee in order for a product to be deemed safe, efficacious and of good quality and given a positive opinion. Consensus decisions reduce bias as they allow an open discussion in which all members of the committee can express their opinions and influence the process.

The ability to use relative and real-world evidence and experience may reduce the uncertainty when approving new products. In an ideal world, products are approved with the highest level of evidence based on long-term data. However, the availability of such information changes from product to product. The data used in the benefit-risk assessment process should be context related, as the uncertainty surrounding new medicines will be variable and is likely to be much higher with innovative products compared with generic medicines, making the use of a uniform template important for evaluation.

Finally, a flexible and continuous risk dynamic approach should be used to achieve an even higher degree of certainty in benefit-risk assessment, Because only limited information may be available when a new medicine is evaluated and registered, benefit-risk evaluation processes should include the flexibility to incorporate emerging new evidence such as adverse events, additional results from clinical trials or real-world data. This evidence may, in some cases, affect a decision which was made at earlier stages of the evaluation process or the benefit-risk assessment

may change altogether. The altered benefit-risk assessment may positively affect the medicine, resulting in the approval of new or additional indications or the removal of limitations on the medicine's use, or negatively affect the product, resulting in the addition of a warning to its label or the medicine's withdrawal from the market.

Communicating regulatory balance and benefit-risk assessment – final thoughts

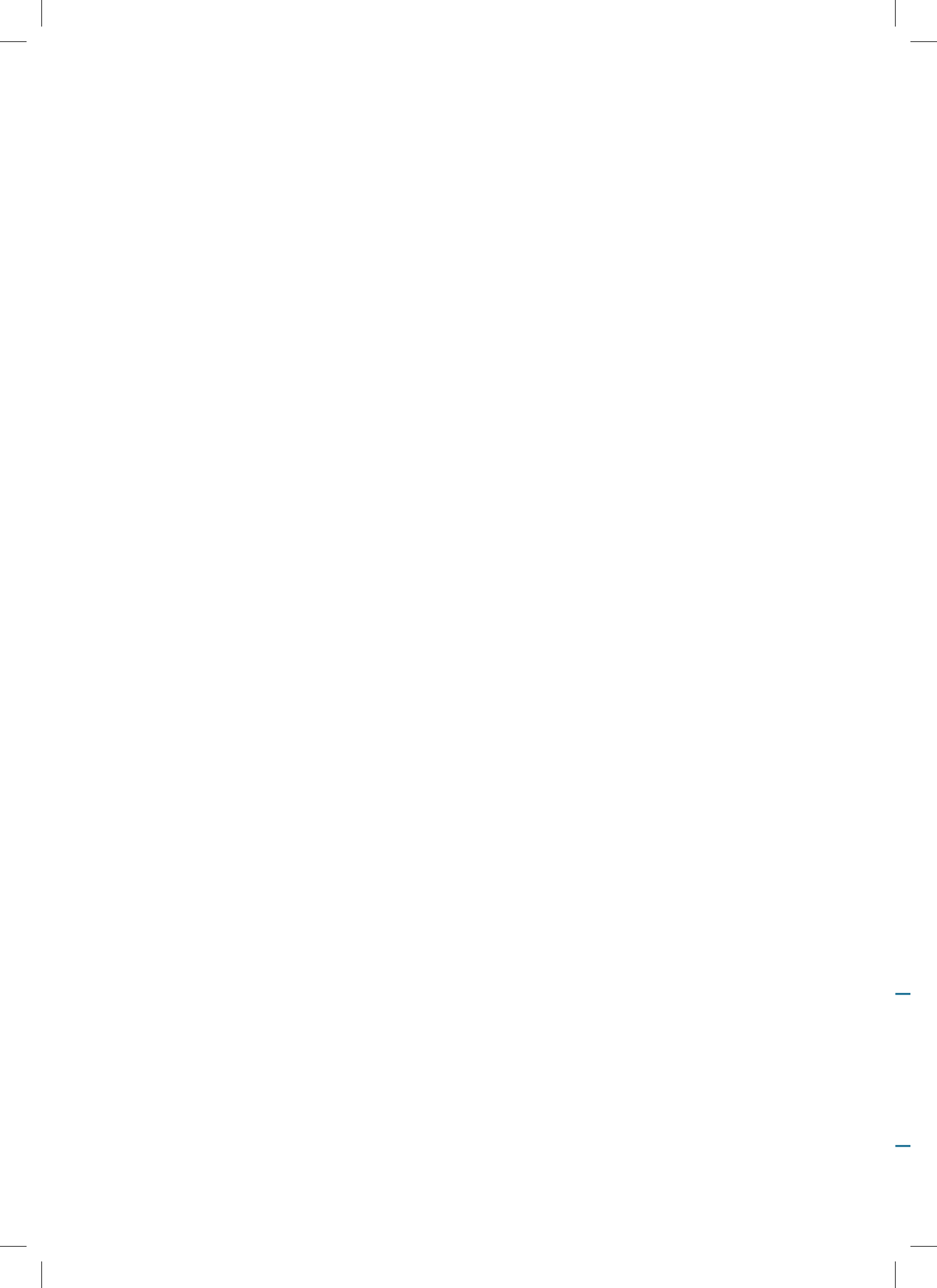
For regulators and other stakeholders involved in the benefit-risk assessment in the drug approval process it is clear that in spite of all the data available at the time of drug registration, many issues will be resolved only during the post-approval period. Much information, especially regarding special populations, long-term effects and other issues, is often missing at the time of drug approval. However, from the patient's point of view, drug approval by the regulatory authority may indicate that the drug is perfectly safe and can cause no harm to the user.

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Thus, it is highly important to efficiently communicate to healthcare providers and to the general public that each medicine has its benefits and risks and those drugs that are approved are based on a positive benefit-risk balance and not on a lack of adverse events. This approach should be an integral part of any benefit-risk module used by a regulatory agency.

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CHAPTER 14

THE IMPLEMENTATION OF STRUCTURED BENEFIT-RISK FRAMEWORKS IN AGENCY DECISION MAKING

“The work of the New Chemical Entity Working Group on Benefit Harm Uncertainty Assessments has facilitated a better understanding of factors considered in the decision-making process of respective regulatory authorities within the Consortium.”



Catherine Parker

Director General

Biologics and Genetic Therapies Directorate, Health Canada



Introduction

Regulatory agencies today cannot work in isolation from one another. Even well-resourced agencies can benefit from opportunities to access and use the expertise and resources of credible agencies. Moreover, providing small agencies with the capacity to work in close collaboration with larger agencies can serve as an important and critical capacity-building activity. In this chapter, an international collaboration is described that is being used to enhance agency decision making and communication.

The Australia, Canada, Switzerland, Singapore (ACSS) Consortium

The ACSS Consortium (formerly called Heads of Agencies (HoA) Consortium) was established in 2007 and consists of health regulatory agencies from Australia's Therapeutic Goods Administration (TGA), Canada's Health Products and Food Branch of Health Canada (HPFB), Singapore's Health Sciences Authority (HSA) and Switzerland's Swissmedic, Swiss Agency for Therapeutic Products. The Consortium was established as a means to foster regulatory collaboration and synergy to address emerging scientific and regulatory issues regarding health products and to leverage resources and expertise (work sharing) to enable regulators to draw on additional insight and expertise on various scientific and technical data, review process, best practices and standards to make better informed regulatory decisions, and possibly enhance the effectiveness of authorities' regulatory processes.

It would be natural to question why these four particular agencies would choose to work closely with one another since other than Singapore's HSA and Australia's TGA, they are not geographically close together. It was because all of these agencies are facing the same challenges, as medium-sized agencies. With the globalisation of the industry sectors, the rapid emergence of new technologies, increasing product complexity, demands by patients for faster access to new medications and the increasing expectations regarding agency performance, the pressure on the financial and human resources of individual agencies continues to grow. Whilst these pressures are not unique to these four agencies, they become magnified when an agency is smaller in size. Hence these four agencies share many challenges that are similar in scope and with a similar impact on their operations.

How does the ACSS Consortium work?

The Consortium was created as a voluntary network intent on building synergies, enhancing the effectiveness and efficiency of each participant's domestic regulatory systems and capitalising on each agency's area of strength. Participants are allowed

flexibility with regard to participation and can choose to opt-in or opt-out from any work plan activities. The chair and secretariat of the meeting is rotated among the four agencies.

The Consortium established a number of key objectives, from which specific work activities would be generated. These are:

- › Providing an effective and efficient alternative to participating regulators working independently on similar scientific and regulatory work;
- › Enabling participating regulators to draw on the very best scientific and technical data, information, expertise, resources and best practices to better inform regulatory decisions;
- › Improving each participant's effectiveness and efficiency as a regulator (domestically);
- › Creating or complementing existing communication networks and increasing dialogue and,
- › Exploring new initiatives and regulatory concepts.

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STRUCTURED BENEFIT-RISK: ACSS CONSORTIUM

The last of these objectives listed, namely exploring new initiatives and regulatory concepts, provides a prime example of the benefits of regulatory collaboration for medium-sized agencies. While each may not be ready or resourced to explore them independently, the prospect of exploring these as a group with shared resources can be an incentive to take on new activities that can potentially benefit each participating agency.

The ACSS Workplan

Up until 2010, regulatory collaboration under the Consortium had focused on information sharing between agencies. In 2010, HPFB drafted a "Proposal to Enhance Collaboration" to explore interest and stimulate discussion on potential initiatives for enhanced cooperation. Since then, the Consortium has moved beyond information sharing to actual work sharing where working groups were created to stimulate work sharing on important issues.

The Consortium's Workplan is a strategic document. It is continually evaluated, discussed and amended as needed based on the mutual interests and resources available among the four participating agencies. The proposed targeted activities for enhanced collaboration focus on current and existing work and activities. Bringing these activities under the Consortium provides a framework for and facilitates information and work sharing, without requiring or implicating significant resources within participating authorities.

Four main targeted activities serve as the basis of the Consortium's Workplan.

These are:

- › Discussion of issues related to premarket applications of special interest, in queue or under review, including first in class, new technologies, complex applications and applications of high public health significance;
- › Sharing the results of the CIRS pilot "Universal Methodology for Benefit-Risk Assessment (UMBRA)" template and methodology to assess benefit -risk associated with product reviews;¹
- › Establishing an ongoing dialogue on the use of foreign assessment reports and on the exchange of marketing authorisation assessment reports, and
- › Sharing "workload" participation in ICH technical working groups.

Four working groups have been created under the Consortium: New Chemical Entities, Generic Medicines, Complementary Health Products, and Information Technology. For the rest of this chapter the New Chemical Entities (NCE) Working Group and its work with respect to facilitating decision-making for benefit-harm-uncertainty (BHU) assessments will be presented.

The NCE Working Group

The NCE Working Group is co-chaired by HPFB and TGA. The Working Group meets primarily through teleconference meetings held every two months, supplemented by face-to-face meetings when possible, often on the margin of another meeting. The initial activities of the Working Group focused on establishing a common understanding of each agency's regulatory frameworks, processes and reviewer tools, with a particular focus on those used for Benefit Harm Uncertainty (BHU) assessments. The factors that were looked at in these analyses included, for each agency, the:

- › Definition of a New Chemical Entity
- › Legislative basis
- › Processes and procedures
- › Technical requirements (including application of Modules 2 to 5 of the International Council on Harmonization Common Technical Document)
- › Alternate processes
- › Appeal processes and "track record", including number of decisions that may have been overturned
- › Method of risk analysis
- › Data exclusivity parameters and patent periods
- › Management of submissions, including operational and logistical management and review time frames
- › Submission fees

- › Communication of decisions

A summary document was prepared of the BHU frameworks of the four agencies. Additionally, a summary of the tools and templates that were available for reviewers in each agency for use in BHU assessments was produced. These analyses instilled confidence in each of the other's processes. As a result, each of the agencies was very confident sharing their specific review tools with one another and using each other's tools to fill in gaps in their own processes.

A common BHU Assessment template?

An early deliverable of the NCE Working Group was to develop a common template for use in conducting BHU assessments of NCE submissions. However, following the work to compare our existing frameworks and processes, the four participating agencies mutually agreed not to proceed with that next phase. There were a number of reasons for that decision. It was viewed that as the comparison had revealed that each had very mature processes for performing BHU assessments, the value of a common template was no longer evident.¹

Furthermore, the development of a common template that met the needs of the four agencies would have been very labour intensive, hence a quality-based decision not to proceed with a common template and not to put the resources into its development was made. More value was envisioned in moving toward work sharing rather than trying to have a common template for BHU assessments.

Outcomes of the work to date

The work to date of the NCE Working Group and the ACSS Consortium has yielded many benefits. It has provided an opportunity for more informed decision making as a result of peer discussion and contributed to the efficiency of the review processes. It has served as a potential basis for enhanced collaboration, including parallel or "real time" exchange of information or assessment. It has aided the participating agencies in identifying issues and challenges and sharing views on how to best express BHU assessments. It has served to provide additional insight regarding the review process, practices and standards of participating authorities.

This collaboration initiative has advanced work to address common enablers and tools that help the participating agencies speak a "common language", hence facilitating a better understanding of factors considered in the decision-making process. This will therefore also serve to promote regulatory transparency.

The next phase – moving toward work sharing

With the foundation of a common understanding of and confidence in each agency's BHU assessment processes, the NCE Working Group has been actively screening NCE filings to identify suitable candidate submissions for work sharing. Subsequent to the Workshop described in this book, concrete timelines and deliverables for the development of a work sharing framework for joint-review are now in place. The next step will be a joint HPFB and TGA review pilot with Swissmedic and HSA observation. A second pilot is being explored in parallel between HSA and Swissmedic. The Working Group is also developing a communications strategy to raise the profile of this work sharing initiative. Some examples of this strategy would include presentations at pharmaceutical industry and regulatory conferences and meetings and initiating targeted letters to key global sponsors and partners with valuable information about the proposed pilot.

All Consortium Working Groups are active in pursuing other objectives, including discussing how to best integrate and make use of foreign information and reports in domestic regulatory review processes and sharing participation in ICH Technical Working Groups based on respective expertise and interest in order to capitalise on each participant's area of strength and expertise and leverage resources.

Summary

The ACSS Consortium is a long-standing and successful collaborative initiative that has received continued high-level support and attention from the heads of the participating agencies. Work sharing has been the focus from the beginning of this initiative and is seen as providing the ultimate benefit for the partners. Ad hoc exchanges and information sharing among the Working Groups provides additional benefits including the sharing of lessons learned and best practices.

The work of the NCE Working Group on BHU Assessments has facilitated a better understanding of factors considered in the decision-making process of respective regulatory authorities within the Consortium. Activities have been useful in identifying gaps in our respective existing templates and processes and in leveraging best practices from multiple jurisdictions as well as the ready access to global expertise and resources gained through consultations in complex issues within submissions. With the completion of these activities, which laid the foundation, work-sharing pilots are now being initiated.

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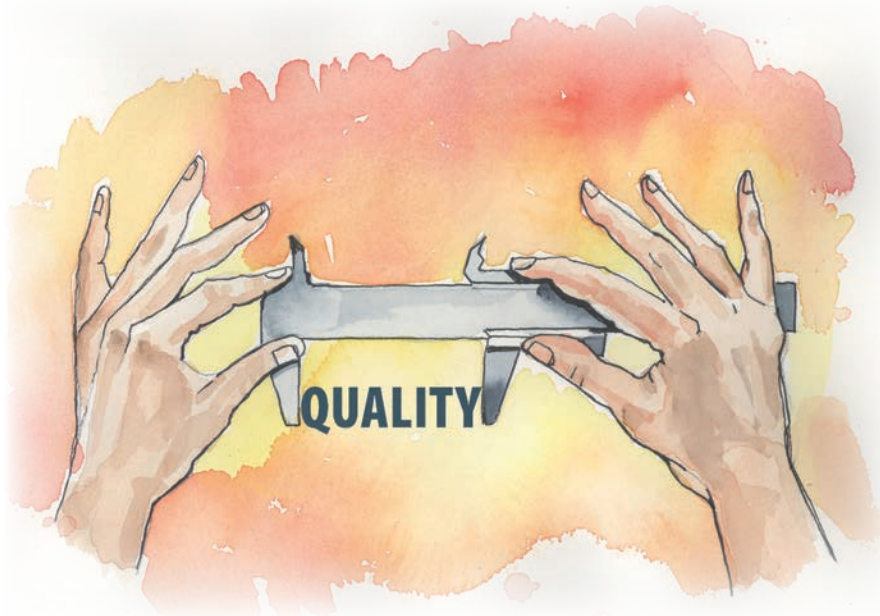




CHAPTER 15

THOUGHT LEADER DISCUSSIONS AND RECOMMENDATIONS INCORPORATING AND MEASURING THE PROCESSES AND OUTCOMES OF QUALITY DECISION MAKING WITHIN COMPANIES AND AGENCIES

"Quality decision-making practices should play an important role throughout the life cycle of medicines and decision makers should be aware of the crucial decision points where their use may be of critical importance... It is also important to understand the potential of a framework and of quality decision-making practices to accelerate critical decision making."



Prof Stuart Walker, Founder
Dr Neil McAuslane, Director
Magdalena Bujar, Project Manager
Patricia Connelly, Manager, Communications and
Dr Lawrence Liberti, Executive Director

Centre for Innovation in Regulatory Science



Workshop Discussion Groups

Breakout groups at the June 2017 CIRS Workshop discussed three different aspects of quality decision making within companies and agencies:

- › What are the practical challenges to measuring the quality of decision making within companies and agencies and what are potential solutions? Is there a role for external assessment of decision-making processes and outcomes to eliminate inherent internal biases?
- › How should companies and agencies practically incorporate quality into their decision-making processes, as defined by the ten Quality Decision-Making Practices (QDMPs)? What are practical approaches for reducing biases in decision making?
- › Measuring the outcome – how do we know if we have improved? What markers or measures could a company or agency instigate to ensure that a quality decision-making process is embedded? How could these measures ultimately be correlated to the outcome of the decision?

Discussion background

As an organisation seeks to improve its effectiveness and efficiency, it should also routinely measure the quality of its decision-making process. One way to determine whether quality decisions are being made is to assess the outcome and consequences of the decision. However, this is not often practical and measurement can be extremely difficult as decisions made under conditions of uncertainty may be more appropriately judged by the quality of the decision making, rather than by the quality of the consequences of that decision. Indeed, it is perfectly possible to make a good decision that has poor consequences and, equally, to make a bad decision that results with a good outcome. However, on balance, the long-running use of good systems for making decisions will generally result in better outcomes.

Results from a survey of pharmaceutical companies and regulatory agencies conducted in 2015 indicated that less than half the companies (41%) and only 20% of the agencies have formal assessments in place to periodically measure the quality of their decision making. These assessments included re-evaluation based on the outcome, feedback from stakeholders and audits of the decision making. In the same survey, company and agency survey respondents indicated that there are ways of measuring the quality of decision, with companies suggesting measures that related to evaluating the actual practices as well as the outcomes, whereas agencies identified measures relating to the practices of decision making only, such as assessing adherence to a validated standard or guideline for decision making.¹ However, these methods of measurement suggested by companies and agencies are not always incorporated. If the quality of decision making is truly key to

ensuring that organisations are making good decisions and in building trust in those decisions, the challenges that stand in the way of the measurement of decision making should be determined and ways to meet those challenges proposed.

As discussed by Professor Walker in Chapter 8, ten Quality Decision-Making Practices (QDMPs) were identified through research undertaken by CIRS to identify important issues that influence quality decision making. In this research, semi-structured interviews were carried out with 29 key opinion leaders from regulatory agencies and pharmaceutical companies, resulting in the identification of a number of overarching themes in quality decision making as well as decision-making practices that underpin a quality process that were considered relevant by both pharmaceutical companies and regulatory agencies. This set of holistic practices can be mapped against the key frameworks used during medicines' development, particularly in the area of benefit-risk assessment as well as the science of decision making. The QDMPs can also be organised into four areas, namely, *Structure and Approach, Evaluation, Impact and Transparency* and *Communication*.

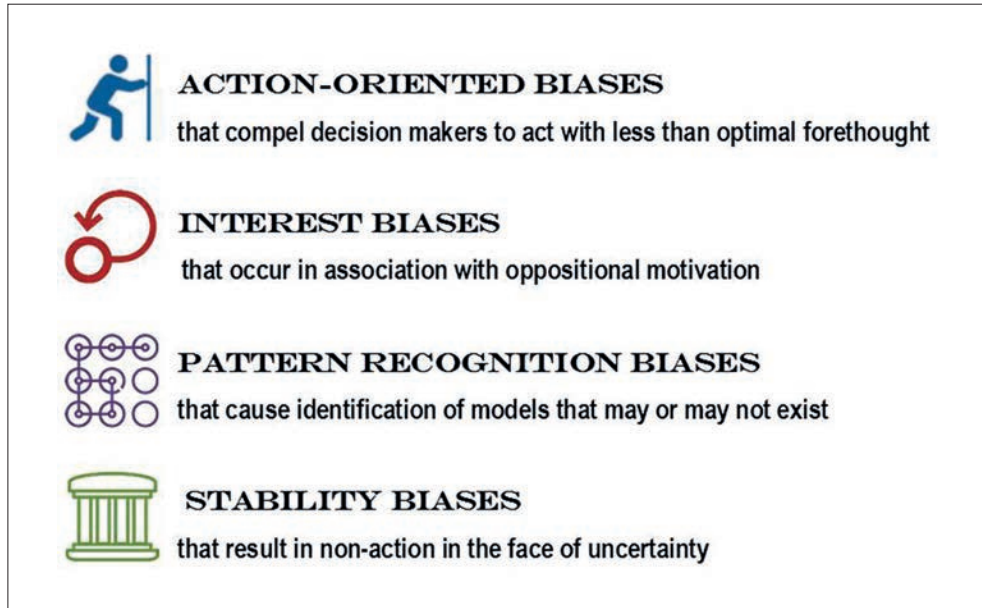
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DISCUSSION AND RECOMMENDATIONS

One way to measure decision making could be based on a pre-specified agreement regarding what a successful decision would look like, including an anticipated positive result. Indeed, one of the QDMPs specifies the performance of an impact analysis of the decision, but as previously mentioned, this may not be a good measure of the total decision-making process. However, despite the challenges to the direct measurement of the quality of the decision making and its outcome, by understanding the components of quality decision-making practices, it may be possible to build a methodology to measure performance against each practice to ensure that practice is embedded within organisational and individual processes. Could this in turn be tied to an outcome associated with the good decision-making practice?

In *The Case for Behavior Strategy*, Lovallo and Sibony identified four common bias types (Figure 15.1)². The study carried out by CIRS in 2015 indicated that companies and agencies both considered the occurrence of biases or their influence within their organisation as pertinent to decision making, but the perceived frequency of their recognition varied for both groups according to the type of bias. For companies, action-oriented bias, characterised by overconfidence and intuition, was perceived as the most frequently occurring bias or the bias that most influenced decision making. For agencies, however, action-oriented bias was considered less relevant, and instead stability bias, characterised by the preference for the status quo, was perceived as the most commonly occurring. Discussion participants were invited to suggest practical approaches for reducing each of these types of bias in companies and in agencies.

Figure 15.1. Lovallo and Sibony outlined the types of biases that can affect decision making.²



Each group was requested to identify challenging issues and strategies to mitigate those issues as they related to the ten QDMPs. Participants were also asked to develop several recommendations to advance progress in the area of measuring and incorporating good decision-making practices. After the individual group discussions, Rapporteurs related the results to all Workshop participants and the topics were further explored by the group at large.

Discussion

Practical challenges

In addition to the basic barrier of the natural human resistance to change, differing and sometimes clashing cultural perspectives and considerations regarding the decision-making process within and among organisations and geographic areas represent important challenges to measuring the quality of decision making. These cultural differences can include a disparity in the levels of organisational readiness for the increased transparency that is required to measure quality decision making. Organisations will also vary as to their ability or willingness to identify and implement objective measures to assess quality decision-making practices and the availability and acceptance of the tools and the training to use them. There may even be a latent organisational opinion that decision quality has, in fact, already been achieved.

Even in organisations that recognise that quality decision-making practices are important, quality processes may not be implemented because of many competing business priorities or because of the perception of the administrative or bureaucratic burden associated with implementing a decision-quality programme. This may be particularly true when considering the ongoing decision making within the complex project matrix structure that exists within most pharmaceutical companies. The management of and communication about decision quality, under the crisis conditions that sometimes occur during the development and regulation of medicines, is an additional consideration.

Finally, despite knowledge of the fact that good-quality decision-making practices may not result in positive outcomes, the tendency of data-driven organisations to link outcomes to quality of processes may need to be overcome (Table 15.1).

Potential solutions

A champion or champions are required to overcome organisational resistance to change. Discussants emphasised that it is important to differentiate between a champion, who assumes ownership of a quality decision-making programme and strives to convince colleagues of its applicability and effectiveness and an external expert, who might be more expected to be objective. Whilst an external champion for quality decision making practices can be used, they would need to be combined with an internal champion at a managerial level who would have the influence to drive change. A combination of internal champions at the operational and managerial level, that is, a combined bottom-up and top-down approach, can also be effective. Programmes to build quality decision-making practices may be

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Table 15.1. Practical challenges to developing a quality decision-making programme

-
- › Cultural perspective/considerations for decision-making process
 - › Company champion needed to overcome resistance
 - › Opinion that QDMPs have already been achieved
 - › Organisation identifies QDMPs as important, but they are not widely implemented
 - › General resistance to change as part of human nature
 - › Competing resources and priorities
 - › Linking QDMPs to outcomes in order to gain buy-in
 - › Administrative/bureaucratic burden to implement QDMPs
 - › Management and communication of QDMPs occurs under crisis conditions
 - › Complexity of QDMPs implementation in project matrix structure
 - › Organisational readiness for increased transparency under QDMPs
 - › Availability and/or acceptance of QDMPs tools and training
 - › Identification and implementation of objective measures to assess QDMPs
-

QDMPs = Quality Decision-Making Practices.

adversely affected, however, with organisational shifts that result in the removal of the managerial champion (Table 15.2).

To mitigate individual and organisational resistance, it is important for the programme champion to have a value proposition in place that includes the identification and highlighting of dissatisfaction with the status quo and “selling points” for the quality decision programme’s ability to increase predictability and efficiency in decision making. Clear communication regarding the necessary separation of the quality of the decision-making practices from the decision outcome is essential, as is the establishment of clear decision-making roles and responsibilities and the use of an established decision-making framework.

Managerial or organisational buy-in to programmes for quality decision-making practices should include the development of quality decision training and the integration of that training into the employee competencies managed by human resource departments, including structured and scheduled “lessons-learned” exercises and non-conformity reporting.

Measuring success

Citing the peer review of decisions in place at the European Medicines Agency (EMA), discussants recommended the use of independent review teams within organisations to conduct separate evidence-based evaluations of those decisions.

Table 15.2. Solutions and success factors for developing a quality decision-making programme

-
- › Independent teams to review (EMA example) – peer review
 - › QDMPs value proposition – selling points to mitigate resistance to QDMPs
 - ↑ probability in decision making
 - ↑ efficiency in decision making
 - › Champions for QDMPs – management commitment
 - › Training in QDMPs – integration into employee competencies
 - › Identify/highlight dissatisfaction with status quo
 - › Structured, regular lessons-learned exercises
 - Integration of QDMPs into quality management system
 - Change management
 - Non-conformity reporting and assessment
 - › Benchmarking/comparative data
 - In-industry
 - Comparable industries
 - › Independent assessment of decision process – blind to the outcome
 - › Define clear roles + responsibilities in the decision-making process
 - › Consider external accreditation opportunities – ISO9001
-

QDMPs = Quality Decision-Making Practices.

Baseline decision-making data should be established through status quo analysis of individual organisations and data accrued for purposes of comparison, from both within industry and comparable business models. Case studies can be created for organisations that have already implemented decision-quality programmes and external accreditation opportunities similar to ISO9001 could also be considered. Any assessment of an organisation's decision process should be blind to outcomes of decisions.

When to use a decision framework

Not all decisions require the use of a decision framework in its full context and the development of a guide for use of the framework that explains the rationale for its application would be beneficial. Quality decision-making practices should play an important role throughout the life cycle of medicines and decision makers should be aware of the crucial decision points where their use may be of critical importance, such as occurs before a compound is given the green light to enter first-in-man studies, when sponsors and investigators must decide what kind of exposure to a drug can be given to humans based on the data from nonclinical studies. It is also important to understand the potential of a framework and of QDMPs to accelerate critical decision making.

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DISCUSSION AND RECOMMENDATIONS

Communication and collaboration

Discussants agreed that decision making relies on data but also on compensatory factors such as early interaction and communication among all stakeholders. In particular, pharmaceutical decision-making processes should incorporate the perspective of patients and payers as early in the life cycle as possible. In fact, patients should be considered as research partners throughout medicines' development, regulation and reimbursement and in addition to well-designed studies, patient-generated data from new technologies may be an important resource in this regard.

Likewise, to manage expectations before the submission of a marketing authorisation application, the sponsors of new medicines should request early consultations and ongoing meetings at key product developmental milestones with regulators as well as with health technology assessment agencies where possible. This approach to early, joint collaborative communication could benefit internal and external alignment and decision making.

Identifying and mitigating internal and external influences and biases

Because the term *bias* has a negative connotation, it may be more helpful to consider the impact of internal and external behavioural influences on decision making. Practical approaches to mitigate these influences should be based on

the goals of individual decisions (Table 15.3). Categorisation of the influences introduces order to their discussion and awareness and discussion could potentially create equilibrium in influencing the ultimate decision. Decision makers need to examine and discuss the criteria for and documentation of decision making, establishing a clear scope and ensuring that good practices are incorporated. Because transparency underpins trust in decision making, stakeholders should openly state their perspectives at the beginning and throughout the process. The establishment of decision committees will bring in external views and introduce objectivity into decision making. Decisions should be made through consensus and negative decisions should be accompanied by a re-examination of the decision.

Workshop discussants reorganised the ten Quality Decision-Making Practices, grouping them as those that

- › Establish who, why and how decisions are made (Practices 1,2 and 3),
- › Ensure decision quality, relevance and importance (Practices 4, 6 and 7),
- › Consider decision alternatives and impact (Practices 5 and 8) and
- › Involve decision transparency and communication (Practices 9 and 10) (Figure 15.2).

Participants further agreed that documentation is a key marker of quality decision making and specified that documentation for practices 1,2 and 3 should include documentation of the decision-making framework and weighting criteria and the decision-making standard operating procedures (SOPs), including a rigorous documentation of the roles and responsibilities of decision makers. These decision makers should be accountable for adherence to the SOPs and decisions should reflect their perspectives. Documentation of practise 4, 6 and 7 should include documentation of the framework used for evaluating biases, uncertainties that were considered and fully defined triggers for the re-evaluation of the decision.

Table 15.3. Approaches to mitigate biases in decision making and the goals of those approaches.



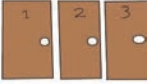

Approaches to mitigate biases	Goals of approach
› Discuss and categorise influences	› Introduces order and awareness and potentially create equilibrium
› Examine and discuss the criteria for and documentation of decision making	› Determines a clear scope and ensures incorporation of good practice in decision making
› Openly state perspectives throughout the decision-making process	› Establishes trust and transparency needed for decision making
› Establish decision committees, make decisions through consensus and re-examine negative decisions	› Brings in internal views and introduces objectivity into decision making

Documentation for practices 5 and 8 should include documentation of the alternatives to the decision that were considered and the template that was used to perform an analysis of the impact of the decision. Finally, documentation for practices 9 and 10 should include a template to be used for the communication of the decision.

Perspectives on the outcomes of decision making

Whilst there is a shared desire among decision makers in the development, regulation and reimbursement of medicines for the ultimate overall outcome of their

Figure 15.2. Workshop participants reorganised Quality Decision-Making Practices according to their goal and specified documentation as a clear marker of quality in decision-making practices.

Quality Decision-Making Practices	Goal of the practices	What should be documented
<ol style="list-style-type: none"> 1. Have a systematic, structured approach to aid decision making 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) 3. Assign values and importance to decision criteria 	 <p>Establish who, how and why</p>	<ul style="list-style-type: none"> • Rigorous process defined by SOPs • Decision template with decision framework and weighting criteria
<ol style="list-style-type: none"> 4. Evaluate both internal and external influences/biases 6. Consider uncertainty 7. Re-evaluate as new information becomes available 	 <p>Ensure information quality, relevance and importance</p>	<ul style="list-style-type: none"> • Framework used to evaluate bias • Uncertainties that were considered • Clearly defined triggers for re-evaluation
<ol style="list-style-type: none"> 5. Examine alternative solutions 8. Perform impact analysis of the decision 	 <p>Consider alternatives and impact</p>	<ul style="list-style-type: none"> • Alternatives that were considered • Template for impact analysis
<ol style="list-style-type: none"> 9. Ensure transparency and provide a record trail 10. Effectively communicate the basis of the decision 	 <p>Communicate clearly and openly</p>	<ul style="list-style-type: none"> • Template for decision communication

decision making to be the improvement of public health, perspectives differ as to whether individual decisions have been successful (Figure 15.3).

Regulators may view their decisions as appropriate inasmuch as the outcomes of those decisions achieve the regulatory objectives of ensuring access to treatment and avoiding the release of dangerous medicines into the marketplace and in fact, if regulatory decisions achieve those objectives, regulators may consider them to be correct and not subject to challenge. This viewpoint may make some regulators resistant to changes in their decision-making practices.

In evaluating the outcome of their decisions regarding medicines, industry asks if those decisions facilitated the approval of label that was sought in a timely way, if the scope of that label was appropriate in terms of the designated population and dosage, and if the post-marketing commitments and manufacturing specifications and limitations were as expected.

The affordability of medicines is also an important outcome of decision making that may not be considered as early or as often as necessary by all decision makers.

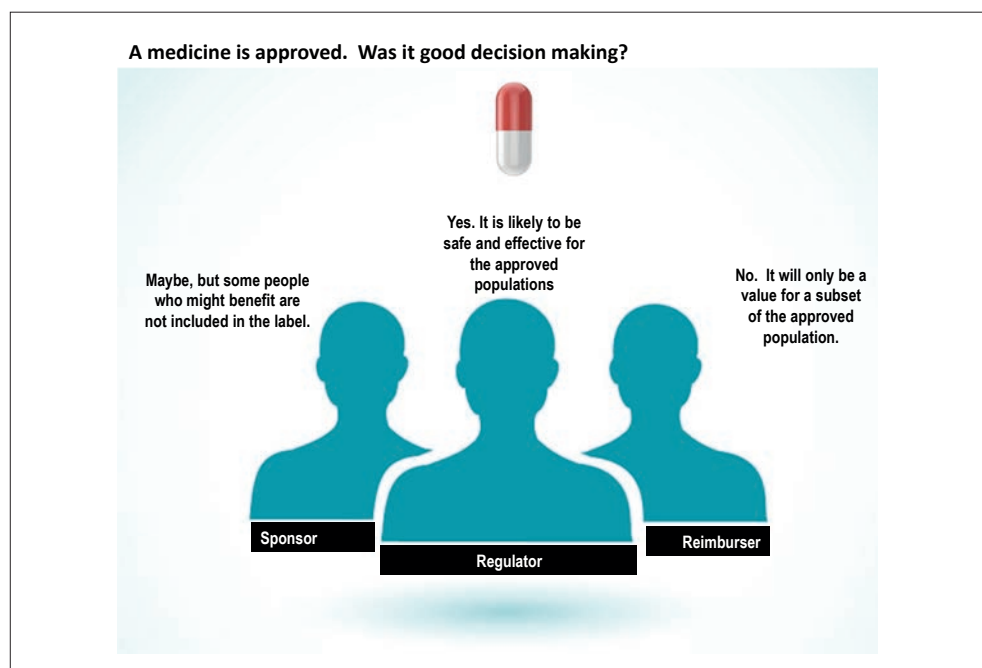
Re-evaluating decision making

The ability to look back and evaluate the quality of past decision making can inform future decisions, but this typically occurs when there has been an unfavourable outcome such as a lack of regulatory approval or the withdrawal of a drug for safety concerns and is less common when the outcome of decisions has been favourable or as anticipated, when such a discussion may be considered by some to be a waste of resources.

There are some natural opportunities to evaluate decision making such as is anticipated will occur in Australia, where provisional approvals that are scheduled to begin in 2018 will include a time-bound directive to re-examine decisions. It is envisioned that building the requirement for re-examination into the legislation for provisional approvals will ensure that labelling is as broad or restricted as appropriate and that post-marketing commitments are fulfilled.

Re-evaluation of a decision can also be part of an appeal or dispute resolution process with a regulatory agency such as the US FDA when new or different information that may impact a decision has emerged. It may be valuable to examine a case in which a regulatory agency issued a different decision as the result of such an appeal.

Figure 15.3. Perspectives regarding the outcomes of decision making.



The re-evaluation of decision making quality may prove more challenging around health technology assessment where negotiation and advocacy are part of the decision-making process in addition to scientific evaluation. HTA bodies are also subject to additional economic and political external pressures that may affect decision making and add to the complexity of its evaluation. Finally, it should be recognised that the quality of decision making can rarely be isolated and evaluated as a single decision, but must be more typically considered as a continuum.

Recommendations from the Syndicate Discussions

Building the evidence around quality decision-making practices

- › Accrue benchmarking data on existing organisational decision quality for industry and regulators
- › **Generate** case studies of organisations where decision-quality programmes have been implemented
- › **Consider** a controlled pilot in which agencies and companies compare the results of decision making with and without a structured framework and the ten QDMPs
- › **Organise** an exercise among agencies and companies to determine if use of the ten QDMPs improves communication and interactions

- › Analyse joint venture decision-making processes

Internal consideration for building quality into the decision process

- › Perform decision-making status quo analysis of individual organisations
- › Create a value proposition/business case for decision quality that includes the provision of more clear and transparent articulation of decisions
- › Clarify that the outcome of good decision making may entail better decisions, specific regulatory action, developmental progress or even project termination
- › Define clear organisational decision-making roles and responsibilities
- › Develop a new model of *bias* mitigation starting with a change in terminology to *behavioural influences*; create appropriate motivational incentives and an environment to balance the internal and external influences
- › Conduct post-decision-making discussions between industry and regulators

Measuring the process and outcome

- › Ensure the availability of quality documentation at the time of decision making
- › Examine and highlight the importance of the rationale for quality decision making not just the methodology
- › Document the expected outcome at the time of the decision so there is a basis for comparison
- › Resolve to assess the quality of decision making across multiple decisions
- › Identify ways in which quality decision-making practices and decision quality (see Spetzler, Chapter 3) may intersect

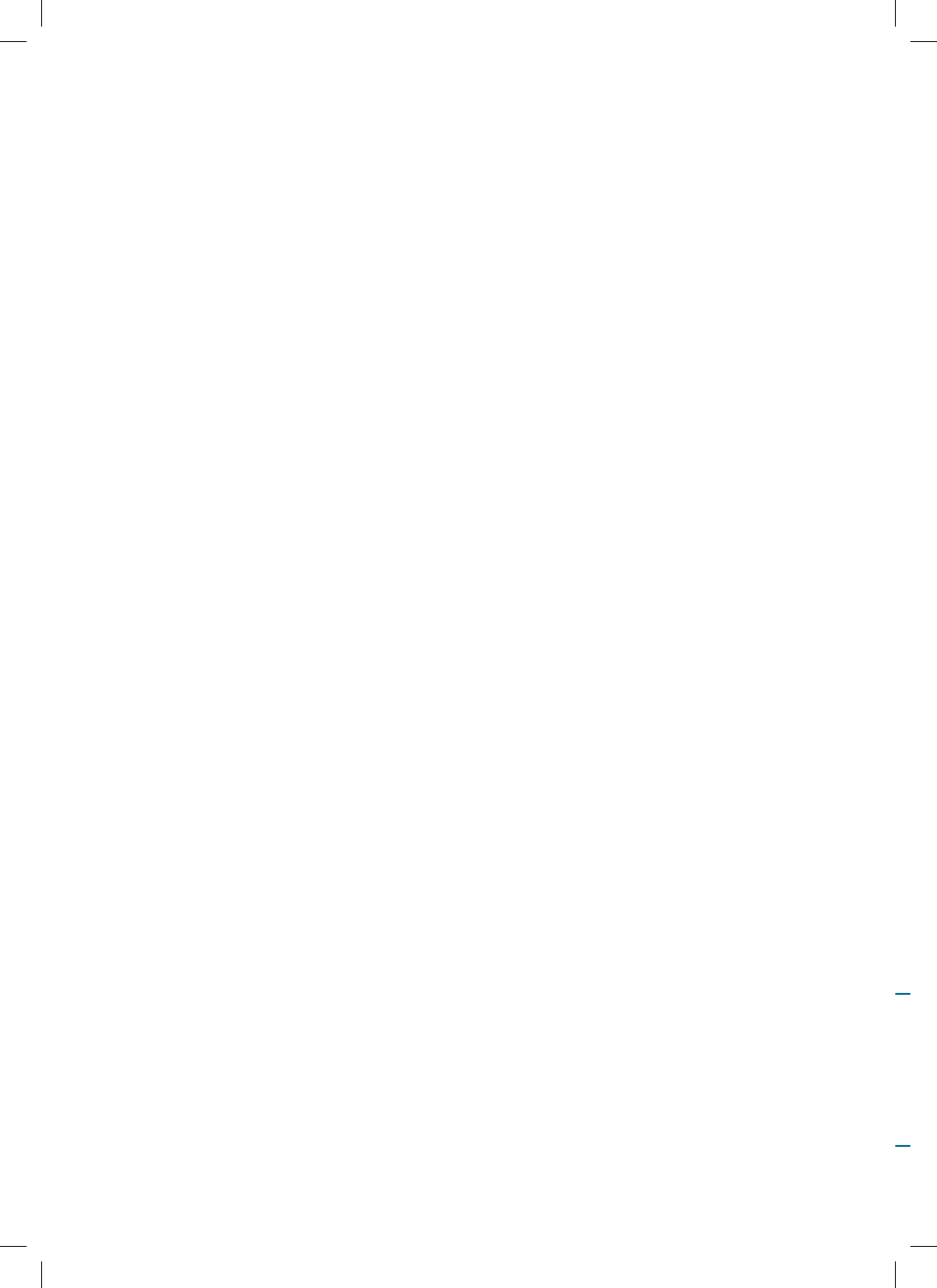
Syndicate Chairs and Rapporteurs

Chair	Catherine Parker, Director General, Biologics and Genetic Therapies Directorate, Health Canada
Rapporteur	Dr Ashley Preston, Head of Regulatory Science, Process, Compliance & Training, EMD Serono, USA
Chair	Prof Sam Salek, Professor of Pharmacoepidemiology and Head, Public Health and Patient Safety Research Group, University of Hertfordshire, UK
Rapporteur	Renu Vaish, Associate Vice President, Regulatory Affairs, Oncology, Merck Research Labs, USA
Chair	Adj Prof Dr John Skerritt, Deputy Secretary, Department of Health, Australia
Rapporteur	Dr Patrick Brady, Vice President, Head of Regulatory Policy and Intelligence, Bayer, USA

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CHAPTER 16

CONCLUSIONS

“The Centre for Innovation in Regulatory Science will endeavour to create a value proposition or business case for decision quality and an environment that contributes to the awareness and importance of Quality Decision Making Practices in the development, regulatory review and reimbursement of medicines.”



Prof Stuart Walker

Professor of Pharmaceutical Medicine, Cardiff University and Founder
Centre for Innovation in Regulatory Science, UK



Decisions, ranging from the mundane to the critically important are constantly being made throughout the lifecycle of medicines and those decisions are often made under conditions of uncertainty and bias without an established, examined strategic process. As written by Lovallo and Sibony, “Companies cannot afford to ignore the human factor in the making of strategic decisions. They can greatly improve their chances of making good ones by becoming more aware of the way cognitive biases can mislead them, by reviewing their decision-making processes, and by establishing a culture of constructive debate.”¹

In 2011, the CIRS initiated a quality decision-making programme in order to build that necessary awareness cited by Lovallo and Sibony and to evaluate decision-making processes and substantially contribute to the discussion about decision making among all of medicines’ stakeholders. The programme represents a natural evolution of CIRS work in performance metrics, through good review practices to the key topic of the benefit-risk assessment of medicines. Through its programme, CIRS aimed to develop a framework for making quality decisions throughout medicine’s development, the regulatory review and reimbursement processes. In this case, a *decision framework* has been defined as a structured, flexible systematic and scientific approach to organising, evaluating and summarising information while ensuring its quality and re-assessing that information over time.

Many of the authors in this book have stated that because so many decisions are made during the lifecycle of medicines under conditions of uncertainty, it is particularly important that the principles of good decision making are followed. Magda Bujar presented some of the interesting results obtained in the CIRS research in quality decision making in 2015 and 2017. This research, evaluated the decision-making processes, the use of frameworks and formal assessments and the perceived occurrence of biases in regulatory and health technology assessment decision making by pharmaceutical companies, regulatory authorities and health technology assessment agencies. It demonstrated, that although most organisations do not carry out formal assessments of their decision-making processes, they believe that such evaluations should be performed.

These results supported the statement cited by Dr Carl Spetzler, “the requirements of good decision making may seem like common sense, but common sense is not common practice.” However, the use of tools, data and expert sources such as the Quality Decision-Making Practices (QDMPs) developed by CIRS or the six requirements for a good decision developed by Dr Spetzler and colleagues, can help to ensure quality measures are built into the processes of companies and agencies.

A literature review by Bujar and associates demonstrated that the tool developed by Dr Ronan Donelan together with the CIRS,² the Quality of Decision-Making Orientation Scheme (QoDoS), have been shown to be of significant value compared with other decision-making tools.³ Companies and organisation feedback included the identification of four major benefits to evaluating decision making with tools like QoDoS namely:

1. Increased awareness as to the practices that need to be considered when making decisions and identifies the strengths and weaknesses of an organisation
2. Reduced uncertainty around decision making and decrease the burden of recycling bad decision making or continuing with failing projects
3. Improved quality of the decision-making process within an organisation and across individuals for major decisions
4. The provision of a basis for discussion of the issues in decision making within teams and the broader organisation, as well as with other stakeholders

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CONCLUSIONS

Dr Joseph Scheeren reviewed his company's experience in working with QoDoS and the QDMPs, indicating that despite the fact that Bayer had been performing well above industry standard since 2008 according to the key performance indicator of first-cycle approvals, "these tools provided a platform not just to evaluate decision making, but also to animate a debate as well as to identify strengths and areas for improvement."

Regulatory and HTA agencies employ their own tools and methods for evaluating decision making in the area of benefit-risk assessment of medicines. For example, peer review can ensure quality decision making. In Canada, the CADTH Common Drug Review CDR evaluations undergo exacting internal and external peer review and patient input is evaluated by patient groups. Transparency and communication are important elements of quality decision making that the EMA implement through the use of the European Public Assessment Report and the Effects Table. The US FDA seeks to reduce uncertainty in decision making through the use of its Benefit-Risk Framework, allowing reviewers to analyse large amounts of data in a limited time in a consistent documented manner.

To ensure quality decision making, Australia's TGA employs experienced and competent staff for its evaluations, uses documented administrative processes and benchmarks their decisions with those of international regulators. Timeliness and predictability are also recognised as core components of the quality review at the agency. Dr Skerritt stated that the majority of regulatory agencies use templates or frameworks in their decision making and even if formal benefit-risk templates

are not used by regulators they will “invariably use guidance documents including international guidelines such those of the World Health Organization (WHO) and templates for component/module evaluations.”

Regulators also seek to enable quality decision making through collaboration. The Consortium of health regulatory authorities from Australia, Canada, Singapore and Switzerland was established to enable the participants to draw on the very best scientific and technical data, information, expertise, resources and best practices to better inform regulatory decisions and explore new initiatives and regulatory concepts. Among the initiatives of this group, the Consortium evaluated the use of the CIRS Benefit-Risk Template.⁴ Although the regulatory authority in Israel is not part of an official consortium, it currently expands its limited resources through collaboration and knowledge sharing with EMA and Swissmedic and looks toward establishing memoranda of understanding with other jurisdictions. In addition, the authority's recent incorporation of the use of the CIRS Benefit-Risk template into its review procedures, confers the quality advantages inherent in the use of a uniform and internationally accepted framework.

Currently, pharmaceutical companies are making unique internal and external contributions to advance quality decision making. Methodologies to assess and communicate benefit-risk as well as to incorporate the perspective of patients continue to be developed and strengthened at Amgen. At Eli Lilly, this concentration on organisational decision quality over the past 25 years has resulted in a consistent decision-making approach that includes an evaluation of alternatives, a mitigation of biases and the inclusion of multiple perspectives.

As part of its ongoing quality decision-making programme, CIRS will endeavour to identify markers and practices that build quality into decision making as recommended through the Syndicate discussions at the Workshop described in this book. Advice from these particular discussion groups included recommendations to create a value proposition or business case for decision quality and develop a new model of bias mitigation and create appropriate motivational incentives and an environment to balance both the internal and external influences. CIRS will also continue to build awareness as to the importance of quality decision making in medicines development through Workshops, presentations and publications. It is hoped that this publication will contribute to the debate and discussion on this very important topic.

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3. Bujar M, McAuslane N, Walker SR, Salek S. Evaluating quality of decision-making processes in medicines' development, regulatory review, and health technology assessment: A systematic review of the literature. *Front Pharmacol.* 2017 Apr 10;8:189. doi: 0.3389/fphar.2017.00189.
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APPENDICES

CIRS R&D BRIEFING 61: BUILDING QUALITY INTO
DECISION-MAKING PROCESSES IN MEDICINES'
DEVELOPMENT, REGULATORY REVIEW AND
HEALTH TECHNOLOGY ASSESSMENT

WORKSHOP PROGRAMME: CIRS WORKSHOP BUILDING
QUALITY INTO THE DECISION-MAKING PROCESS
15-16 JUNE 2017, TYSONS CORNER, US

WORKSHOP PARTICIPANTS: CIRS WORKSHOP BUILDING
QUALITY INTO THE DECISION-MAKING PROCESS
15-16 JUNE 2017, TYSONS CORNER, US





Background to quality decision making

“An organisation that seeks to improve its productivity should also routinely measure the quality of its decision making” (From Thinking Fast and Slow, Kahneman, 2011)

The various decisions made by pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies throughout the life cycle of medicines are critical for ensuring that appropriately safe and effective medicines become available in a timely and efficient manner. Despite this, there is a paucity of research into the quality aspect of decision making in medicines’ research and development.

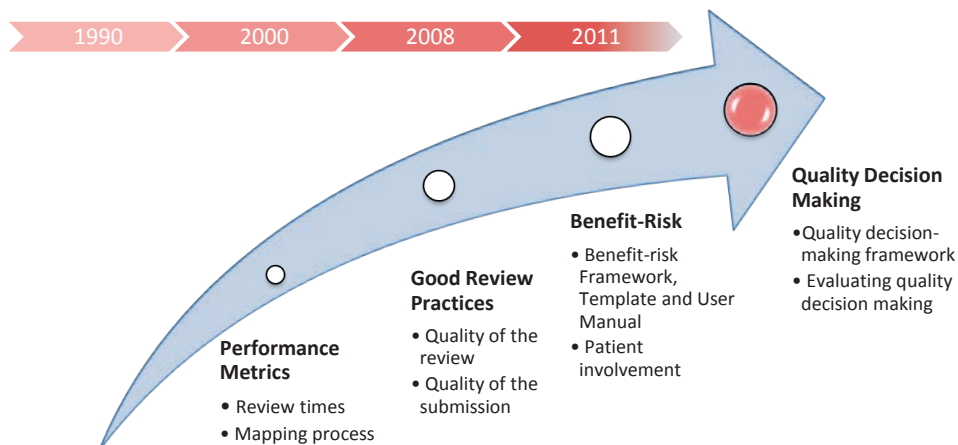
At a Centre for Innovation in Regulatory Science (CIRS) Workshop in 2004, Professor Larry Phillips, a Professor of Decision Analysis at the London School of Economics, discussed the “science of decision making” saying that “. . . In an uncertain world, it is perfectly possible to make a good decision that has poor consequences and, equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes.”

In addition, recent CIRS Workshop participants have recommended that the quality of the decision-making processes for these functions be considered separately from the decisions themselves.

“Delinking the regulatory review process from the process of making decisions should be explored. Although the quality of decision making is of equal importance to the quality of review process and procedure, methods for enhancing and measuring that quality have yet to be outlined.” (Recommendation from CIRS Emerging Markets Workshop December 2011)

“Explicitly explore quality in decision making separately from the quality of submissions and reviews and develop or identify an instrument to be used to assess the robustness of deliberative processes within HTA agencies” (Recommendation from CIRS HTA Workshop December 2013)

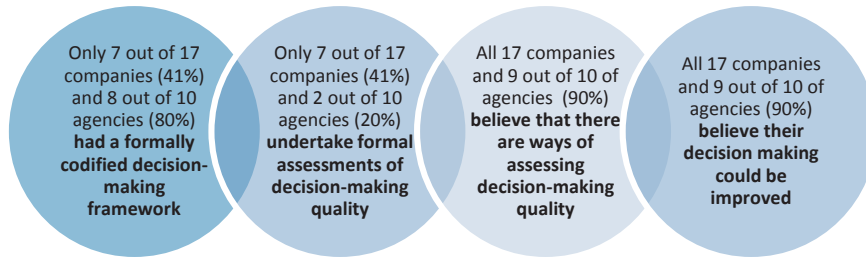
As a consequence, CIRS initiated a programme that aims to address the research gap in quality decision making in the area of medicines’ development, review and HTA assessment. This programme represents a natural evolution of CIRS work in performance metrics, good review practices and benefit-risk assessment. The overall aim is to develop a quality decision framework and evaluate quality decision-making practices in order to identify markers that build quality into decision making throughout medicines’ development, regulatory review and reimbursement.



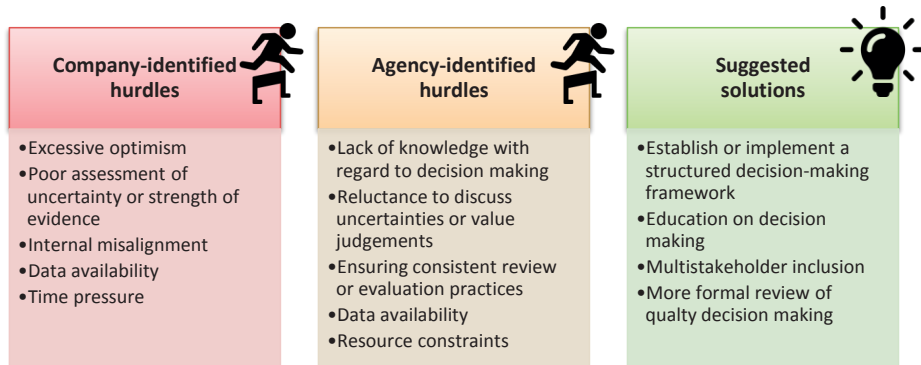
Background to quality decision making

As part of its programme in quality decision making, in 2015, CIRS conducted a study among 17 pharmaceutical companies and 10 regulatory agencies to identify current decision-making practices used by companies' in their decision to submit and by agencies' in their decision to approve a new drug application. It also looked to ascertain how they measure the quality of the decision-making process and the challenges and solutions¹.

Key results from the questionnaire indicated that:



Moreover, the majority of company and agency participants identified instances of decision-making biases within their organisation. *Other hurdles by companies and agencies to quality decision quality decision making, as well as suggested solutions are listed below:*



The study results demonstrated that the quality of decision making is influenced by the processes and procedures within companies and agencies. Organisations believe their decision making could be improved and the first step to achieve this, which CIRS has already initiated, would be to assess current practices and evaluate the quality of decision making within regulatory and HTA agencies as well as pharmaceutical companies. In addition, CIRS will be conducting a similar questionnaire to the above, but amongst HTA agencies and pharmaceutical companies to explore quality decision making in the area of medicines' reimbursement.

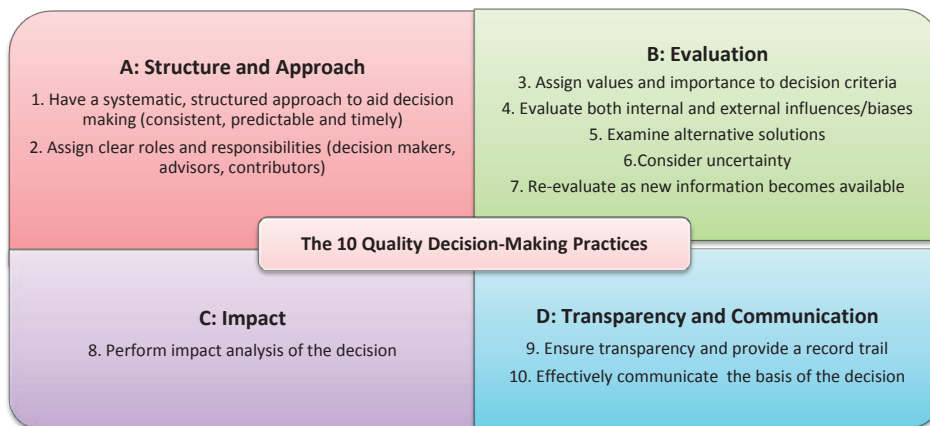
¹ Bujar M, McAuslane N, Salek S, Walker S. Quality of regulatory decision-making practices: issues facing companies and agencies. *Ther Inn Reg Sci*. 2016;DOI: 10.1177/2168479016628573.

Development of the 10 Quality Decision-Making Practices

In order to investigate and identify the important issues that influence quality decision making, semi-structured interviews were carried out with 29 key opinion leaders from regulatory agencies and pharmaceutical companies². The study participants were invited to discuss and review their perception of decision making within their organisation, its role in drug development and regulatory review, their awareness and use of decision-making techniques and the impact and monitoring of decisions. The analyses resulted in the identification of a number of overarching themes in quality decision making, which are exemplified below with quotations from interviewees.

Theme 1
<i>“There is a difference between the organisational decision-making process and that of the individual. We have a good understanding of how a committee makes a decision, but we do not necessarily understand how individuals on that committee have made their own decision”</i> Regulatory agency
Theme 2
<i>“Transparency, the justification for decisions, and understanding why a decision has been made need to be documented, it is good practice”</i> Regulatory agency
Theme 3
<i>“It is important that we are trained in decision making. We also need an understanding and practical application of the tools which can assist our decision making”</i> Pharmaceutical company

A major outcome of this study has also been the identification of the *10 Quality Decision-Making Practices (QDMPs)* that underpin a quality process and that were considered as relevant by both pharmaceutical companies and regulatory agencies. This set of holistic practices can be mapped against the key frameworks used during medicines’ development, particularly in the area of benefit-risk assessment as well as the science of decision making. The 10 QDMPs are organized into four areas, namely, ‘Structure and Approach’, ‘Evaluation’, ‘Impact’ and ‘Transparency and Communication’



² Donelan R, Walker S, Salek S. Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiol Drug Saf.* 2015;24: 319-328.



Development of the 10 Quality Decision-Making Practices

As a result of the discussion from CIRS Workshops in June 2015 and February 2016³, the following Guidance Notes were produced to describe the 10 QDMPs in more detail.

QDMP 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely)

- Establish the decision context, objectives and assumptions made.
- Employ frameworks, guidelines and tools for structuring the decision-making process.
- Such an approach should ensure that the process is systematic, which in turn would enable better consistency compared with similar past decisions, as well as predictability and timeliness.

QDMP 2. Assign clear roles and responsibilities (decision makers, advisors, information providers)

- The roles and responsibilities should be clearly defined in terms of individuals who provide information (including external input), compared with those who advise on the decision or make the final decision.
- The roles and responsibilities of each stakeholder (regulatory authorities, HTA agencies and companies) should be transparent and well communicated, which should help manage expectations.

QDMP 3. Assign values and relative importance to decision criteria

- The relevant criteria for the decision must be determined to ensure that these are in line with the decision context and overall objective. The criteria should be weighted, for example, by ranking or rating their relative importance.

QDMP 4. Evaluate both internal and external influences/biases

- Stakeholders need to be aware of personal considerations, subjective influences and biases, acknowledge them and minimise where possible. Potential biases that need to be considered⁴:
 - Action-oriented bias: excessive optimism, overconfidence in own judgement and gut-feeling
 - Interest-oriented bias: inappropriate attachments and misaligned incentives
 - Pattern recognition: generalising based on recent events and seeking out information that supports a favoured decision, which could lead to perpetuating previous mistakes
 - Stability bias: preference for status quo and tendency for inertia in the presence of uncertainty

QDMP 5. Examine alternative solutions

- Decision makers should actively explore possible options during the decision-making process.
- The alternatives need to be assessed, for example using a SWOT analysis, against the relevant decision criteria in order to determine the best outcome.

QDMP 6. Consider uncertainty

- The extent and limitations of available information need to be judged for each decision criterion in relation to the alternative options.
- Stakeholders must be explicit regarding acceptability of benefits and harms and how this affects their approach.

QDMP 7. Re-evaluate as new information becomes available

- This should be actively carried out at all stages during the lifecycle of medicines' development.
- This may be a safeguard against plunging in or procrastination and/or perpetuating previous mistakes as well as identifying cultural/organisational/hierarchical influences (e.g. individual vs. organisational, group successes and group failures).

QDMP 8. Perform impact analysis of the decision

- The impact of the decision needs to be considered on both internal and external stakeholders.
- The analysis must relate to present situation, but also to the future and should take into account elements of quality/validity of data, political/financial/competitor influences and procedures for similar decisions.

QDMP 9. Ensure transparency and provide a record trail

- It must be clear how the decision was made and details must be consistently documented in a manner that can be easily followed or audited by appropriate stakeholders.

QDMP 10. Effectively communicate the basis of the decision

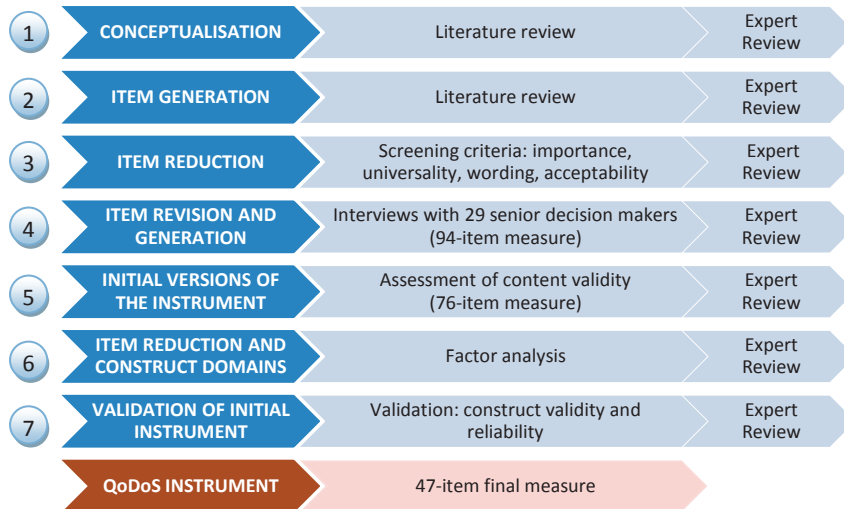
- The basis of the decision needs to be appropriately communicated to the relevant stakeholders, both internally and externally.

³ The Centre for Innovation in Regulatory Science. *Publications*. Available at: <http://www.cirsci.org/past-workshops-and-publications/>

⁴ Lovallo D, Sibony O. *The case of behavioral strategy*. McKinsey Quarterly. Available at: http://www.mckinsey.com/insights/strategy/the_case_for_behavioral_strategy.

Development of the Quality of Decision-Making Orientations Scheme

Recognising the importance of quality of decision making as well as the paucity of information and available instruments, CIRS in collaboration with Cardiff University, initiated a study to develop and validate an instrument for evaluating quality of decision making⁵. This collaboration is now being continued with the University of Hertfordshire. The instrument, named the Quality of Decision-Making Orientation Scheme (QoDoS) was developed and validated using a standardised approach and qualitative as well as quantitative techniques. A flowchart representing the stages in the development of the QoDoS is shown below.



The QoDoS items were generated from 29 face-to-face semi-structured interviews with key opinion leaders from the pharmaceutical industry (n=10), contract research organisations (n=10) and regulatory agencies (n=9). The thematic analysis yielded a 94-item initial version of the QoDoS with a five-point Likert frequency scale response option.

Content validity was established using an expert panel to confirm that the emphasis and the focus of the QoDoS is fit-for-purpose. The experts rated the language clarity, completeness, relevance and scaling of each item on a four-point scale (Strongly agree, agree, disagree and strongly disagree) and the agreement among the panel members was high with an intra-class correlation coefficient value of 0.89 (95% confidence interval = 0.056, 0.99).

Factor analysis was performed on the resulting 76-item instrument and produced a 47-item measure (QoDoS) organised into four sections namely, organisational decision-making approaches, organisational decision-making culture, individual decision making competencies and individual decision-making style.

The 47-item QoDoS showed high internal consistency (n = 120, Cronbach's alpha = 0.89), high reproducibility (n = 20, intra-class correlation = 0.77) and a mean completion time of 10 minutes. This suggests that the QoDoS is a practical instrument possessing strong psychometric properties of validity and reliability. Moreover, the QoDoS items can be mapped according to the 10 Quality Decision Making-Practices (page 4) and consequently, the degree of incorporation of these 10 QDMPs into agency and company processes can be evaluated. The full instrument is shown on pages 7 and 8.

⁵ Donelan R, Walker S, Salek S. The development and validation of a generic instrument, QoDoS, for assessing the quality of decision making. *Frontiers Pharmaceutical Medicine and Outcome Research*. 2016; 7: 180.

The QoDoS instrument for evaluating quality decision making

The Quality of Decision-Making Orientation Scheme (QoDoS)®

The statements in the questionnaire relate to your views on your personal and your organisation's *decision-making processes for major strategic choices within your organisation*.

Please mark clearly one box for each statement. Assume that Not at all = 0% of time; Sometimes = 25% of time; Frequently = 50% of time; Often = 75% of time; Always = 100% of time. If not sure, please tick the box that you feel is the most appropriate.

No data that will identify an individual or an organisation will be reported, or details made to a third party.

Background questions

Gender: Male Female Other

Job title: _____

How many years of professional experience have you to date? _____

Organisation: Regulatory Agency Pharmaceutical Industry HTA Academia Other

Part I: Organisational-level influences

	Not at all	Sometimes	Frequently	Often	Always	Not applicable
A. Decision-Making Approach						
1. My organisation evaluates the impact of the decisions it makes						
2. My organisation's decision making is transparent						
3. My organisation's decision making is consistent						
4. My organisation uses a structured approach in its decision making						
5. My organisation's decision making is influenced by external stakeholder's demands						
6. My organisation assigns qualitative values to its decision-making criteria						
7. My organisation assigns quantitative values to its decision-making criteria						
8. My organisation is open to using better alternatives in its decision making						
9. My organisation encourages innovative decision making						
10. My organisation considers uncertainties in relation to its decision making						
11. My organisation provides training in the science of decision making						
12. My organisation re-examines its decision making as new information becomes available						
B. Decision-making culture						
13. My organisation has suffered a negative outcome due to slow decision making						
14. My organisation's culture has resulted in its inability to make a decision						
15. My organisation's decision making is influenced by organisational politics						
16. My organisation's decision making results in making the same mistake as in the past						
17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest)						
18. My organisation underestimates problems which adversely impact its own decisions						
19. My organisation continues with projects/products which should be terminated at an earlier stage						
20. My organisation's decision making is influenced by similar organisations or competitors						
21. My organisation's decision making is influenced by incentives or penalty payments						
22. My organisation effectively communicates the decisions it makes						
23. My organisation provides clear and unambiguous instructions for decision making						



The QoDoS instrument for evaluating quality decision making

Part II: Individual-level influences

	Not at all	Sometimes	Frequently	Often	Always	Not applicable
A. Decision-making competence						
24. My decision making is knowledge based						
25. My decision making is consistent						
26. I consider uncertainty and unknowns in my decision-making approach						
27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making						
28. I present contingencies or achievable options as part of my decision making						
29. My decision making is transparent						
30. I understand the context of the decision I am being asked to make						
31. I understand the importance of the decisions I make						
32. I use a structured approach in my decision making						
33. I assign qualitative values to its decision-making criteria						
34. I assign quantitative values to its decision-making criteria						
35. I receive training in the science of decision making						
36. I use intuition or “gut-feeling” in my decision making						
37. My professional experience is important when having to make challenging decisions						
B. Decision-making style						
38. Emotion is part of my decision making						
39. I have experienced “paralysis by analysis” caused by my slow decision making						
40. I have experienced a negative outcome by a decision not being made						
41. In my decision making, I make the same mistakes as in the past						
42. Recent or dramatic events greatly impact my decision making						
43. My procrastination has resulted in a negative outcome						
44. My decision making could be improved by assigning relative importance to decision criteria						
45. I underestimate problems which adversely impact my decision making						
46. I continue with projects/products which should be terminated at an early stage						
47. I feel that I could make better quality decisions						

Confidentiality

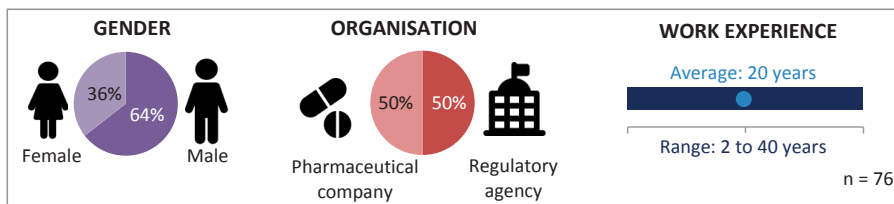
If an organisation was to use this survey, it should be noted that all information collected from individual agencies and companies will be kept strictly confidential. No data that will identify an individual agency or company will be reported, or detail made to a third party. External reports or presentation of the data will include only anonymous figures and any appropriate analytical interpretation. Agency or company data will only be provided to the relevant organisations concerned.

COPYRIGHT This questionnaire should not be reproduced without the permission of M.S. Salek m.s.salek@herts.ac.uk and S. Walker swalker@cirsci.org.



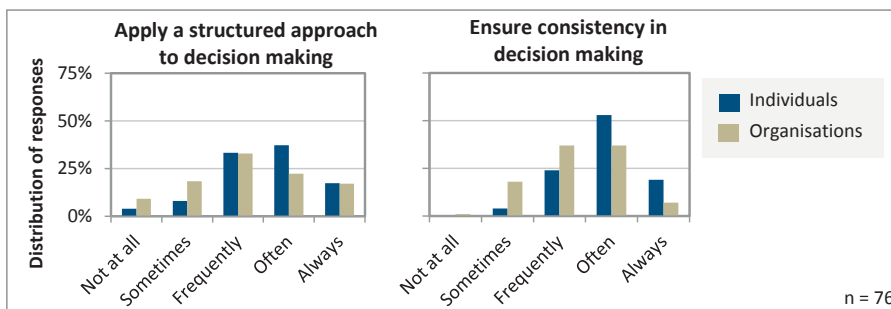
Practical application of the QoDoS instrument

One of the objectives of the CIRS programme is to utilise the QoDoS to assess the quality of decision-making process and evaluate the level of incorporation of the 10 Quality Decision-Making Practices within companies, regulatory and HTA agencies. In order to demonstrate the practicality and applicability of the QoDoS for evaluating quality decision making, a study was initiated with 76 participants from 12 regulatory agencies and 23 international pharmaceutical companies, who were asked to complete the tool⁶. The demographics were as follows:



Study results: Organisational and individual decision making

The QoDoS enables an evaluation of decision making across both individuals and the perspective of individuals on the organisation as eleven of the QoDoS items are analogous for the organisational and individual parts of the instrument. The results for two common QoDoS items, 'Apply a structured approach' and 'Ensure consistency in decision making' indicate that both were incorporated more at the individual level rather than organisational level of decision making.



Although in practice the two scores should be similar as people make up an institution, individuals tend to score themselves more highly and be more critical of an organisation. While this could be a potential sign of bias, areas of disparity between the two could also indicate areas for improvement for the individuals, which should translate into better practices within the organisation.

Study results: Pharmaceutical company and regulatory agency organisational decision making

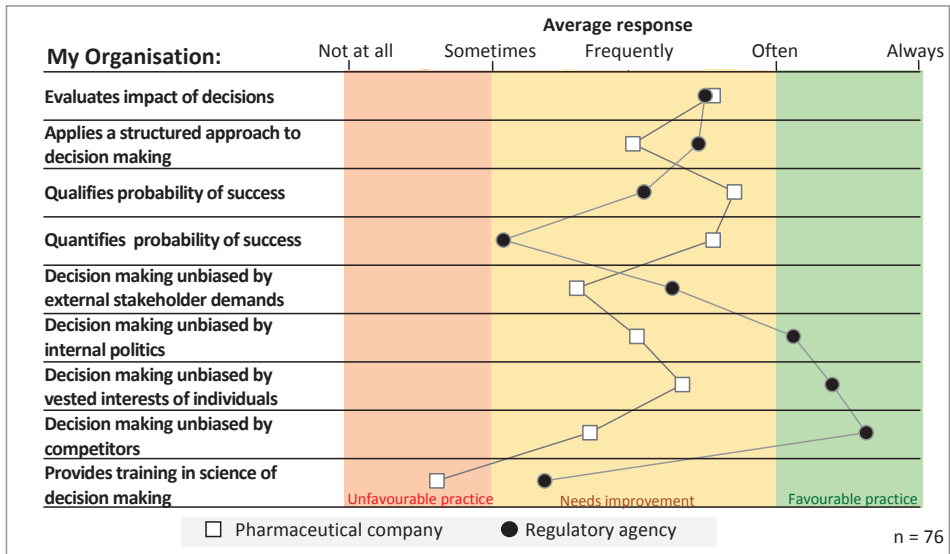
An assessment of regulatory agency and pharmaceutical company organisational-level responses identified differences between the two stakeholders. Both considered evaluating the impact of the decisions as important, with agencies using a structured, systematic approach to decision making more frequently than companies. Conversely, there was a general tendency for biases due to politics, competitors or incentives to have more impact on company decision making compared with agencies.

⁶ Bujar M, Donelan R, McAuslane N, Salek S, Walker S. Assessing quality of decision making in medicines' development and the regulatory review: Identifying biases and best practices. *Ther Inn Reg Sci.* 2016; doi:10.1177/2168479016662681



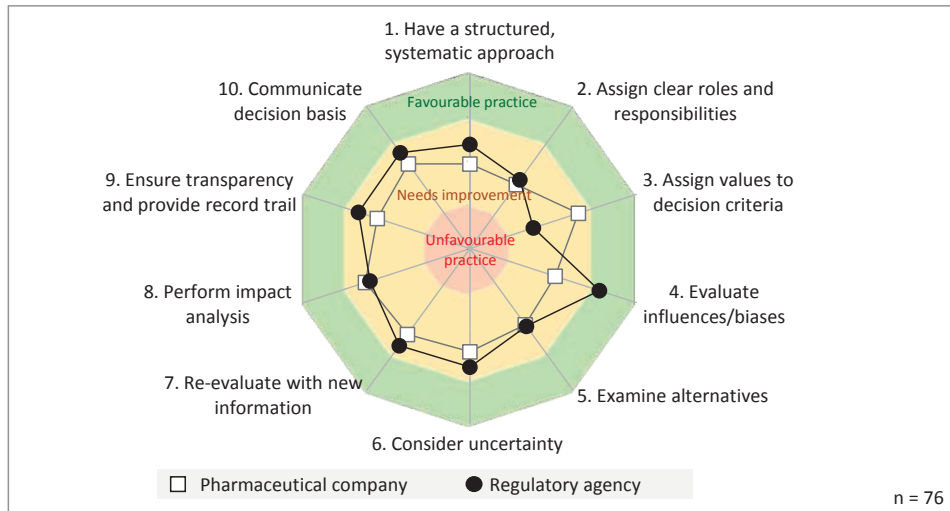
Practical application of the QoDoS instrument

Whilst it was recognised that the science of decision making is important, training in this area was rarely provided. All responders from agencies and 92% from companies felt that they could improve the quality of their decision making. Nine selected organisational-level QoDoS items are shown below:



Evaluating the 10 Quality Decision-Making Practices

Finally, the organisational level agency and company responses were mapped against the 10 QDMPs, demonstrating key differences between company and agency practices and confirming the need for improvement and training in decision making for both stakeholders.



Transparency • Predictability • Consistency

The potential impact of evaluating decision making with the QoDoS

The applicability of the QoDoS for evaluating decision making

The findings of the study with pharmaceutical companies and regulatory agencies demonstrate that the QoDoS has the ability to identify differences in decision making between individuals and their organisation as well as differences between companies and agencies.

The potential impact for evaluating quality decision making with the QoDoS in association with the 10 Quality Decision Making Practices



Individual knowledge: Simply completing the instrument can increase an individual's awareness of the issues in decision making, different biases and influences that need to be considered when making decisions, as well as best practices that should be incorporated into an organisation's decision-making framework.



Internal Monitoring: The QoDoS can be used by organisations to internally monitor and visualise decision making within and across different teams and divisions to identify strengths and weaknesses. This should facilitate raising sensitive issues by individuals relating to decision making, help with relationship building and ultimately increase trust within the organisation. The QoDoS could also provide the ability to measure change over time in order to determine the impact of training and other improvement initiatives in order to ultimately improve effectiveness across teams, increase productivity in R&D decision making, reduce uncertainty and result in more consistent outcomes for organisations.

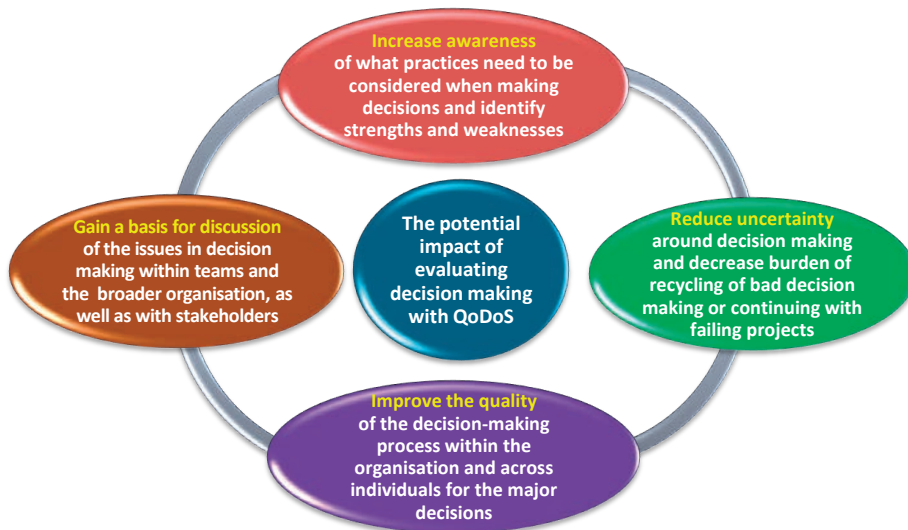


External Benchmarking: The QoDoS can be utilised to externally benchmark an organisation's decision-making practices and performance compared with other organisations. This in turn could provide a basis for discussion of the issues in the quality of the decision-making processes, thereby encouraging a level of trust and partnership and helping to identify areas for improvement and collaboration. Ultimately, the QoDoS should enable organisations to build quality, transparency and consistency into the critical decisions that are undertaken during the lifecycle of medicines.

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APPENDICES

Routine assessments with the QoDoS may offer a number of benefits to organisations and individuals.



Conclusions

In 2015, CIRS initiated a programme in Quality Decision Making with the following aims and activities:

ACTIVITIES	AIMS
<i>Surveys and other research projects</i>	<ul style="list-style-type: none"> Evaluate the current decision-frameworks and understand the characteristics of different decision-making processes Assess the quality of decision-making processes and practices that need to be considered when making a decision, as well as influences and biases that may impact the process
<i>QoDoS studies</i>	
<i>International Workshops</i>	<ul style="list-style-type: none"> Develop the principles of a quality decision framework and identify markers and practices that build quality into decision making

An enhanced understanding of how to identify and apply quality decision-making practices may facilitate decision-making approaches and subsequently will enable improved practices for both the individual and the organisation. Ultimately, this will enable improved transparency, predictability and consistency in critical decisions in medicines' development, review and health technology assessment.



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About CIRS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics, formerly the IP & Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science.

CIRS achieves its mission of advancing regulatory and HTA policies and processes by means of the aligned activities of its Health Technology Assessment and Global Development programmes – activities that include international Workshops, Insight Seminars, research projects, publications and presentations and the identification of and advocacy for best international practices. Through these activities, CIRS regularly interacts with international pharmaceutical companies, regulatory agencies and HTA and coverage bodies to address the overlapping themes of metrics, to manage uncertainty and improve predictability; quality of process, to improve the development of development, regulatory and health technology assessment processes and ultimately the quality of decision making and alignment, promoting convergence within and across organisations and stakeholders.

Website: www.cirsci.org

If your organisation would be interested in participating in a QoDoS study, please contact one of the authors listed above.

Appendix 2

Workshop Programme: CIRS Workshop Building quality into the decision-making process
15-16 June 2017, Tysons Corner, US

Session: Quality of Decision Making – Can the quality of decision-making practices improve decision outcome?

Chair's welcome and introduction	Dr Peter Honig , <i>Senior Vice President, Worldwide Safety and Regulatory, Worldwide Research and Development, Pfizer Inc, USA</i>
A changing landscape – The need for agencies to have a quality decision process to enable trust and manage uncertainty	Adj Prof Dr John Skerritt , <i>Deputy Secretary, Department of Health, Australia</i>
Quality of decision making – The importance of measuring the process as well as outcome	Dr Carl Spetzler , <i>Chief Executive Officer, Strategic Decisions Group, USA</i>
What are the key issues for companies and regulatory and HTA agencies in their internal decision-making processes?	Magda Bujar , <i>Senior Research Analyst, Centre for Innovation in Regulatory Science</i>
The decision-making process: Stakeholder's perspectives on the key decision points and how they ensure the building of quality into the process?	
Industry viewpoint	Dr Paul Huckle , <i>Chief Regulatory Officer and SVP, GlaxoSmithKline, USA</i>
Regulatory agency viewpoint	Dr Theresa Mullin , <i>Director, Office of Strategic Programs, Food and Drug Administration, USA</i>
HTA viewpoint	Dr Trevor Richter , <i>Director of CDR and Optimal of Drugs, CADTH</i>
Awareness of the types of biases that affect decision making and potential ways to de-bias the process	Dr Carl Spetzler , <i>Chief Executive Officer, Strategic Decisions Group, USA</i>

Session 2: Measuring and embedding a quality decision-making process – How can this be best achieved?

Chairman's introduction	Dr Richard Moscicki , <i>Deputy Center Director for Science Operations, FDA, USA</i>
Development of 10 key Quality Decision-Making Practices (QDMP) for development and review of medicines by companies and agencies and the practicality and applicability of an instrument (QoDoS) for evaluating QDMP	Prof Stuart Walker , <i>Founder, Centre for Innovation in Regulatory Science</i>
Case study: Experience using QoDoS – What has been learnt and next steps	Dr Joseph Scheeren , <i>Head, Global Regulatory Affairs Pharma and Consumer Care, Bayer Consumer Care AG, Switzerland</i>
Building quality into the decision-making process within development – A company approach and case study	Charles Persinger , <i>Research Advisor, Decision Sciences, Eli Lilly and Company, USA</i>
How has the EMA benefited from the use of a structured decision approach: The use of the effects table in practice	Prof Hans-Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i>

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APPENDICES

Appendix 2. (continued)

Session: Syndicate Sessions

Topic A: What are the practical challenges to measuring quality of decision making within a company and agency, what are potential solutions and is there a role for external assessment of decision making processes and outcome to eliminate inherent internal biases?

Chair: Catherine Parker, *Director General, Biologics and Genetic Therapies Directorate, Health Canada*

Rapporteur: Dr Ashley Preston, *Head of Regulatory Science, Process, Compliance & Training, EMD Serono, USA*

Topic B: How should companies and agencies practically incorporate quality into their decision-making process as defined by the 10 QDMPs and practical approaches for reducing biases in decision making?

Chair: Prof Sam Salek, *Professor of Pharmacoepidemiology and Head, Public Health and Patient Safety Research Group, University of Hertfordshire, UK*

Rapporteur: Renu Vaish, *Associate Vice President, Regulatory Affairs, Oncology, Merck Research Labs, USA*

Topic C: Measuring the outcome - How do we know if we have improved - What could be the markers or measures that a company or agency could instigate to ensure that a quality decision-making process is embedded – how could these measures or markers ultimately be correlated to the outcome of the decision?

Chair: Adj Prof Dr John Skerritt, *Deputy Secretary, Department of Health, Australia*

Rapporteur: Patrick Brady, *Vice President, Regulatory Affairs, Head Regulatory Policy & Intelligence, Bayer Healthcare, USA*

Day 2, 16 June 2017

Chairman's introduction

Prof Sir Alasdair Breckenridge

Feedback of syndicate discussions and participants viewpoints

Panel discussion - reflections: Measuring the quality of decision making

Company regulatory viewpoint

Dr Felipe Dolz, *Head, Global Regulatory Affairs Policy, Sanofi, USA*

Company HEOR viewpoint

Dr Amitabh Singh, *VP, Internal Medicine Payer Insights and Access Lead, Pfizer Inc, USA*

Regulatory agency viewpoint

Dr Petra Dörr, *Head of Communication and Networking, Deputy Director, Swissmedic*

HTA agency viewpoint

Anne Lee, *Chief Pharmaceutical Adviser, Scottish Medicines Consortium, UK*

Session: Building Quality into the Decision-Making Process: Benefit-Risk Frameworks – are they achieving their promise?

Chairman's introduction

Are companies including a structured benefit-risk approach in their submission to regulatory agencies? How are companies preparing for the implementation of ICH M4(R4)?

Dr Meredith Smith, *Global Risk Management Officer, Amgen, USA*

Appendix 2. (continued)

Building quality into decision making through a structured approach to benefit-risk assessment and documentation within developing agencies

Viewpoint from Israel

Prof Eyal Schwartzberg, *Head of Pharmaceutical Division, Ministry of Health Israel*

Viewpoint from Brazil

Ana Carolina Marino, *Health Regulation Expert, ANVISA, Brazil*

Current implementation of structured benefit-risk frameworks in agency decision making – Has this improved both internal decision making and communication of the decision?

Pujita Vaidya, *Decision Support and Analysis Team, CDER, FDA, US Acting Director, Decision Support and Analysis Team, Office of Program and Strategic Analysis, CDER, Food and Drug Administration, USA*

FDA perspective

Four agency consortium perspective

Catherine Parker, *Director General, Biologics and Genetic Therapies Directorate, Health Canada*

Discussion on the future evolution of frameworks for building quality into decision making
Chairman summary and close of meeting



Appendix 3

Workshop Participants: CIRS Workshop Building quality into the decision-making process
15-16 June 2017, Tysons Corner, US

Regulatory agencies

Ana Carolina Moreira Marino Araujo	Health Regulation Expert - Advisor for Drugs Office	ANVISA, Brazil
Prof Sir Alasdair Breckenridge	Former Chairman	MHRA, UK
Dr Petra Dörr	Head of Communication and Networking, Deputy Director	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Dr Alyson Karesh	Director, Division of Clinical Trial Quality, Office of Medical Policy Initiatives	Food and Drug Administration, USA
Prof John Lim	Deputy Director of Medical Services and Executive Director, Centre of Regulatory Excellence	Ministry of Health, Singapore and Duke-NUS Graduate Medical School, Singapore
Tatiana Cambraia de Sá Lowande	Especialista Em Regulação e Vigilância Sanitária	ANVISA, Brazil
Dr Richard Moscicki	Deputy Center Director for Science Operations	Food and Drug Administration, USA
Dr Theresa Mullin	Director, Office of Strategic Programs, CDER	Food and Drug Administration, USA
Catherine Parker	Director General, Biologics and Genetic Therapies Directorate	Health Canada
Dr Tomas Salmonson	Chair, CHMP	European Medicines Agency
Prof Eyal Schwartzberg	Head of Pharmaceutical Division	Ministry of Health, Israel
Adj Prof Dr John Skerritt	Deputy Secretary	Department of Health, Australia
Graham Thompson		Food and Drug Administration, USA
Dr Juli Tomaino	Deputy Director, Division of Clinical Trial Quality, Office of Medical Policy Initiatives	Food and Drug Administration, USA
Pujita Vaidya	Acting Director, Decision Support and Analysis Team, Office of Program and Strategic Analysis, CDER	Food and Drug Administration, USA

Pharmaceutical companies and consultants

Cristina Baratta	Regulatory Affairs – Operational Manager	Bayer Inc, USA
Virginia Beakes-Read	Executive Director/Special Counsel, Regulatory Strategy and Law	Eisai Inc, USA

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APPENDICES

Appendix 3. (continued)

Annetta Beauregard	Vice President, Regulatory Policy and Operations	Vertex Pharmaceuticals Inc, USA
Fabio Bisordi	Head, International Regulatory Policy	F.Hoffmann-La Roche, Switzerland
Patrick Brady	Vice President, Regulatory Affairs, Head Regulatory Policy and Intelligence	Bayer Healthcare, USA
Dr David Brott	Director of Safety Science Center of Excellence	AstraZeneca, USA
Tricia DeSantis	Vice President, Global Regulatory Policy	Biogen, USA
Felipe Dolz	Head, Global Regulatory Affairs Policy	Sanofi, USA
Prof Bruno Flamion	Vice President, Head Strategic Development	Actelion Pharmaceuticals, Switzerland
Dr Emily Freeman	Director, Risk Management Sciences	AbbVie, USA
Dr Scott Freeman	Lead, Regulatory Intelligence and Research	Shire, USA
Vibeke Hatorp	Senior Director	Novo Nordisk A/S, Denmark
Lauren Hetrick	Senior Director, Regulatory Policy and Intelligence	AbbVie, USA
Dr Peter Honig	Senior Vice President	Pfizer Inc, USA
Dr Paul Huckle	Chief Regulatory Officer and Senior Vice President of Global Regulatory Affairs and Quality Assurance	GlaxoSmithKline, USA
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations,, Public Affairs and European Product Safety	Eisai Europe Ltd, UK
Dr Alex Kiazand	Head Safety Science, Patient Safety	AstraZeneca, USA
Dr Carol Koro	Executive Director	Merck, USA
Dr Andrew Lee	Director, Value and Access	Biogen, USA
Andrea Masciale	Vice President, Regulatory Policy and Global Analytics	Johnson & Johnson, USA
Alexis Reisin Miller	Senior Director, Regulatory Policy and Intelligence, GRA	Eisai Inc, USA
Melissa Mudrick	Vice President, R&D Quality & Compliance	Biogen, USA
Dr Chris Pashos	Vice President, Global Outcomes Research	Takeda Pharmaceuticals International, Inc, USA
Charles Persinger	Research Advisor, Decision Sciences	Eli Lilly and Company, USA
Dr Ashley Preston	Head of Regulatory Science, Process, Compliance & Training	EMD Serono, USA



Appendix 3. (continued)

Dr Joseph Scheeren	Global Head, Regulatory Affairs Pharma and Consumer Care	Bayer Consumer Care AG, Switzerland
Dr Amitabh Singh	VP, Internal Medicine Payer Insights and Access Lead	Pfizer Inc, USA
Dr Meredith Smith	Global Risk Management Officer	Amgen Inc, USA
Dr Carl Spetzler	CEO and Chairman	Strategic Decisions Group, USA
Gretchen Trout	Head North America Policy and FDA Liaison	Novartis, USA
Renu Vaish	Associate Vice President, Regulatory Affairs, Oncology	Merck Research Laboratories, USA
Janet Vessotskie	Head of Americas, Regulatory Policy & Intelligence	UCB Inc, USA
Karen Weiss	Vice President, Regulatory Policy and Intelligence	Janssen Pharmaceuticals, USA
Greg White	Senior Director, Global Market Access Policy	Janssen, USA
Deborah Yarbrough	Director, Global Regulatory Affairs	Takeda, USA

Health technology assessment agencies

Anne Lee	Chief Pharmaceutical Adviser	Scottish Medicines Consortium, UK
Dr Trevor Richter	Director, CDR and Optimal Use of Drugs	CADTH, Canada

Academic institutions

Emel Mashaki	Doctoral candidate	University of Cardiff, UK
Prof Mamoru Narukawa	Professor, Laboratory of Pharmaceutical Medicine	Kitasato University Graduate School of Pharmaceutical Sciences, Japan
Prof Sam Salek	Professor of Pharmacoepidemiology and Head, Public Health and Patient Safety Research Group	University of Hertfordshire, UK

Centre for Innovation in Regulatory Science

Magda Bujar	Senior Research Analyst	
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prof Stuart Walker	Founder	
Tina Wang	Manager, HTA Programmes	

