Supplementary information Box 1 | Towards appropriate levels of evidence
A regulatory science perspective on adaptive approaches to marketing authorization
Towards appropriate levels of evidence
A regulatory science perspective on adaptive approaches to marketing authorization.

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** Glossary **
The discussion paper *Towards appropriate levels of evidence; A regulatory science perspective on adaptive approaches to marketing authorization* is proudly presented by the Escher Project. The Escher Project is a partnership between academic institutions and pharmaceutical companies, supported by the Dutch government through Top Institute Pharma, and collaborating closely with regulatory authorities, especially the Dutch CBG/MEB. The Project aims to provide scientific evidence for reform of the regulatory system in order to address public health needs and improve the efficiency of medicine development. This discussion paper is partly based on the scientific work conducted by the Escher Project between 2007 and 2012.

The discussion paper will serve as input and as a starting point for discussion for a workshop organized by the Escher Project: “Towards Adaptive Marketing Authorization: How to Meet Conditions for Reform?” This workshop takes place on 6-7 December 2012 in Amsterdam with selected key persons from regulatory agencies, health technology assessment bodies, academia, patient organisations and pharmaceutical companies. Participants of the workshop will work towards an agenda with actionable proposals for improving the regulation of medicine development and a research agenda for regulatory science. The output of the workshop will be communicated through a report and journal publications.

The Escher Project hopes that this discussion paper and the workshop will also be the start of a sustainable platform that can continue to foster a ‘science driven’ dialogue on regulatory reform.

On behalf of the Escher Project,

Bert Leufkens
This discussion paper will serve as input and as a starting point for discussion for a workshop organized by the Escher Project: “Towards Adaptive Marketing Authorization: How to Meet Conditions for Reform?” The Escher Project is a Dutch public-private partnership under the TIPharma umbrella that has investigated three elements of the regulatory system: stakeholder interaction; methods for evidence generation and evaluating requirements; and the decision making process. In this discussion paper we provide a synthesis of the diverse insights and instruments on these topics generated by the Escher Project by focusing on the question: *How to achieve appropriate levels of evidence for marketing authorization?*

Many people believe that delays in the development of innovative medicines and a lack of meeting priority health care needs is caused by, amongst others, a high regulatory burden. A suggested road forward is that granting marketing authorization should be possible on the basis of more appropriate, or less, evidence than is currently required. An important concept in this debate is a so-called ‘adaptive’ approach to marketing authorization, which can be seen as an extension of developments such as Conditional Approval.

To provide a regulatory science perspective on adaptive approaches we address three relevant questions in this paper:

1) *How to optimize evidence generation and adjust evidence requirements?*

2) *How to systematize benefit-risk decision making?*

3) *How to strengthen the dialogue between regulators and companies?*

Based on evidence generated by the Escher Project we can identify various opportunities and challenges for improving the regulatory system, which can also pave the way for introducing more adaptive approaches to marketing authorization.

(1) Evidence generation could be optimized by: introducing innovative design features in clinical trials (e.g. adaptive study designs); accepting more surrogate endpoints (e.g. [multiple] biomarkers); better learning between (classes of) medicines; and aligning evaluations of clinical relevance. A key challenge is how to adjust evidence requirements in an appropriate fashion. In this light, the regulatory system can profit from impact assessments beforehand and evaluating the effects of requirements in practice, including cost-effectiveness assessments.

(2) Benefit-risk assessment could be improved, for example, by implementing quantitative instruments. These instruments can support more consistent decision making by: structuring and integrating information; making evaluations of data, uncertainties and clinical judgments explicit;
and by giving (visual) feedback. However, data on how these instruments affect the quality and time investment of decision making is currently lacking. Furthermore, although quantitative instruments can make decisions for experts more transparent, communicating results to the public in a better way is a challenge that needs to be addressed.

(3) The scientific dialogue between companies and regulators currently revolves around getting assurances for ongoing development plans and interpretation of guidelines. It is suggested that the dialogue can be more constructive by prospectively discussing development plans. This might require binding agreements about development plans, a timelier and more continual dialogue and the involvement of patients and health technology assessment bodies.

Based on the discussions during the workshop The Escher Project will present an agenda with actionable proposals for improving the regulation of medicine development and a research agenda for regulatory science. This agenda will be communicated through a report and journal publications.
This chapter describes: (1) the world of Escher; (2) the multidisciplinary approach of the Escher Project; (3) the results of the Escher Project; and (4) the approach of this discussion paper.

1. The world of Escher

The current system that regulates the development, marketing authorization and market access of medicines has been very successful for bringing valuable medicines to the market, promoting the development of safe and efficacious medicines and contributing to public health. However, there are also important challenges. For example, regulations that cover pre-clinical and clinical development are perceived as important drivers for the high costs and long timelines of medicine development. At the same time, there is an opportunity to develop a more efficient and effective regulatory system, with more transparent and structured decision-making, by including recent scientific and technical developments and by strengthening stakeholder dialogue. Furthermore, alignment between marketing authorization and reimbursement decision making is perceived by many as suboptimal. To meet these challenges and identify solutions, a multidisciplinary, comprehensive and evidence-driven assessment of the regulatory system is essential.

2. The multidisciplinary approach of the Escher Project

Against this background, The Escher Project has been launched in 2008 as a public-private partnership based in The Netherlands, under the TI Pharma umbrella. The aim of the Escher Project is to provide evidence-based solutions that can support reform and fuel stakeholder discussion. It accomplishes this by offering a multidisciplinary and comprehensive perspective; by identifying bottlenecks that hamper efficient pharmaceutical innovation; and by developing new instruments and methods. The Escher Project is a collaboration between Utrecht University, University Medical Centre Utrecht, University Medical Centre Groningen, Erasmus University Rotterdam, GlaxoSmithKline, Amgen, the Royal Dutch Association of Pharmacists and Merck. In addition, Escher is working closely with several regulatory authorities in the Netherlands, the EU and globally. Principal Investigator is Prof. Dr. H.G.M. Leufkens.

The Escher Project is structured around 16 multidisciplinary subprojects focusing on the steps of development, approval and post-approval (Figure 1). These subprojects address many different topics and bring together a wide variety of expertise in e.g. trial design, epidemiology, health economics, technology assessment and research ethics.
3. Results of the Escher Project

The Escher Project has resulted in many publications and PhD theses, a list of publications can be found at the end of this discussion paper. Through its subprojects, the Escher Project has developed evidence on three elements of the regulatory system:

1. **Stakeholder interaction**: Communication and alignment between parties involved in the regulatory process contributes to an efficiently functioning regulatory system.

2. **Evidence requirements**: Knowledge generation is dependent on adequate development plans and the regulatory requirements at certain development steps.

3. **The decision making process**: At various steps of the medicine development process regulatory bodies and companies make decisions, based on a rational assessment of knowledge on the product.

Although many insights from subprojects will be discussed in this discussion paper, other valuable insights of the Escher Project are outside the scope of this discussion paper. This includes the work on the ethics of trials\(^1,2\), decision making by health technology assessment bodies\(^3\), patient reported outcomes, the relation between regulatory warnings and medicine use\(^4\), non-inferiority trials\(^5-7\).

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\(^{a}\) The strategic agenda’s from regulatory agencies in members states, at the EU level, and in other regions have all identified challenges and a need for reform concerning these topics. See, for example, the EMA Roadmap to 2015, CDER/initiatives at www.fda.gov and Strategic Business Plan 2009-2013 of the Dutch Medicines Evaluation Board.
4. The approach of this discussion paper

To be able to fuel an evidence-based discussion on current topics in regulatory reform, we provide in this discussion paper a synthesis of the diverse insights on these three topics by focusing on the following main question:

**How to achieve appropriate levels of evidence for marketing authorization?**

Because the possibilities of granting marketing authorization based on less evidence than is currently required is a much debated issue, especially within the context of visions for ‘adaptive’ approaches to marketing authorization, we have taken this debate as a source of inspiration and a steppingstone for our discussion of insights from the Escher Project (the concept of ‘adaptive’ approaches will be explained in the next chapter).

In chapter III we will introduce the system of marketing authorization of medicines, its challenge (the delay in approval of important new medicines), and a possible solution (the vision of ‘adaptive’ marketing authorization). In the chapters after that we will discuss our main question - how to achieve appropriate levels of evidence for marketing authorization - in light of the discussion about ‘adaptive’ approaches. We have divided our main question in three sub questions that together help answer the main question:

1) **How to optimize evidence generation and adjust evidence requirements?** (Chapter IV)

2) **How to systematize benefit-risk decision making?** (Chapter V)

3) **How to strengthen the dialogue between regulators and companies?** (Chapter VI)

Each of these chapters contains three sections (figure 2). For each topic we will first (1) describe the current situation. Next, (2) we discuss how the topic is related to an ‘adaptive’ approach to marketing authorization and then, (3) we analyze with the help of, amongst others, evidence generated by the Escher Project how progress could be made in reform. In chapter VII we propose discussion points concerning the main questions and the three sub questions.

**Figure 2** – Approach of discussion paper: three chapter sections leading to discussion points
Note to readers

Some readers may have considerable knowledge of the current system of marketing authorization of medicines. We suggest that they skip the background sections in chapter IV, V, and VI. Chapter III and the sections ‘adaptive approaches’ in chapter IV, V, and VI describe the vision of adaptive approaches. The ‘Escher analysis’ sections in chapter IV, V, and VI contain recent important developments in regulatory science (amongst others, results of the Escher Project) and a discussion of those developments in light of adaptive approaches.

A variety of sources was used in this discussion paper to support the analysis, including: the scientific output from the Escher Project (throughout the discussion paper we have highlighted relevant findings of the Escher Project); other academic research; and other sources such as regulatory reports (including strategic reports of the FDA, Dutch MEB/CBG and EMA), regulatory websites, interviews with key stakeholders and legal sources. We have tried to indicate where evidence was available and where we provided our own analysis.
Supplementary Information

Marketing Authorization and the discussion about ‘adaptive’ approaches

This chapter describes: (1) the current system of marketing authorization and its challenges; (2) ‘adaptive approaches to marketing authorization’ as a vision for reform; (3) the discussion about adaptive approaches; (4) this discussion paper’s main question: how to achieve appropriate levels of evidence for marketing authorization?

1. Current system of marketing authorization and its challenges

The purpose of the regulatory system for marketing authorization of medicinal products is to ensure that patients gain access rapidly to medicines that are safe and effective, while being protected from medicines that are not. Regulations for medicines were initially mainly driven by concerns about safety and aimed to protect patients from potentially harmful medicines. Later this has been complemented by an increasing need for efficacy data, and, more recently, by discussions about how data generated during development can meet the needs of health technology assessment bodies.

Public trust in the current system is frequently challenged by the controversy over timely access to new medicines, medicine withdrawals, and post-approval modifications to labels. This has put an even greater demand on pharmaceutical companies to generate the appropriate data for marketing authorization, leading to large investments and long timelines for medicine development. Many people believe this delays the development of innovative medicines and hampers meeting priority health care needs. Furthermore, it is not known to what extent these data are an effective and efficient investment of resources for the promotion of public health.

2. Vision for reform: ‘Adaptive’ approaches to marketing authorization

The regulatory system can fail in two ways: by being overly cautious (e.g., unreasonably delaying the approval of life-saving medicines) or by being insufficiently cautious (e.g., approving drugs that are ineffective or cause great harm). The latter failure mode gets the most publicity, but the former can be just as serious. How could the system accelerate the flow of innovative and important medicines? The possibilities of granting marketing authorization on the basis of less data than is currently required is a much debated issue, especially within the context of ‘adaptive’ approaches to marketing authorization.

In the last decade, several ‘adaptive’ approaches to marketing authorization have been proposed by the European Medicines Agency, the Food and Drug Administration and other parties under various names (e.g. staggered approval, managed entry, adaptive approval, progressive authorization, and adaptive licensing). These adaptive approaches are all based on the premise that knowledge
about medicines is not binary but continues to evolve over time. They propose to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation.  

Adaptive approaches can be seen as a holistic vision on the future of the regulatory system, but also as a combination and elaboration of existing pathways. In the European Union this includes the regulations/guidelines for Conditional and Exceptional Marketing Authorization, the introduction of Risk Management Plans and the recent pharmacovigilance legislation (Figure 3). In the United States this includes the Accelerated Approval pathway and the recent proposal for regulations concerning Special Medical Use.

The basic principles of adaptive approaches are: facilitating early access by approving medicines early, with acknowledged uncertainty about the favourable and unfavourable effects. The appropriate level of uncertainty can be decided on a case by case basis depending on considerations about the therapeutic area, medical need and willingness of stakeholders to accept more uncertainty. After initial approval, uncertainty is managed progressively. Uncertainty is reduced by collecting post-marketing data, and by adapting the approval status accordingly.

3. The discussion about adaptive approaches

Although adaptive approaches are attractive visions, they also have to confront several challenges. For example, appropriately defining and targeting the label population during the initial phases of approval to avoid safety issues, would require systematic restrictions on prescribing, monitoring of utilization, and interventions to ensure appropriate drug use, including support for patient...
III. Adaptive approaches

adherence. These steps would need to be strong enough to influence the behavior of patients, physicians and reimbursement authorities. Otherwise, serious safety issues could emerge, which could lead to liability claims by patients and also could affect public trust in the regulatory system.

Furthermore, ensuring that companies appropriately conduct post marketing studies could be challenging. Having proper evidence of favourable and unfavourable effects later in the life cycle of a medicine is crucial for being able to allow more uncertainty early in the life cycle. However, a critical issue here is what the regulatory action will be in the event promised studies are not (adequately) performed: restriction of the label could affect patient groups currently taking the medicine and taking no action would undermine the foundation of adaptive system. Recent EU pharmacovigilance legislation could help in this respect.

4. How to achieve appropriate levels of evidence for marketing authorization?

A third challenge for adaptive approaches concerns the main question of this discussion paper:

How to achieve appropriate levels of evidence for marketing authorization?

Although this question is not exclusive for an adaptive approach – in the current marketing authorization system deciding about the appropriate level of evidence is also an important challenge - in an adaptive approach this question is even more relevant for several reasons. (1) Adaptive approaches require iterative decision making on a product, which makes consistency between these decisions very important. (2) Decisions to require less evidence should be predictable and transparent to companies, allowing them to adapt their development plans. (3) Decisions to require less evidence should be transparent and communicated clearly to the public and practitioners to retain trust. (4) Requiring less evidence involves knowing how to adapt evidence generation and adjust current evidence requirements. (5) The appropriate level of evidence can be decided on a case by case basis. This complexity requires increasingly systematic decision making. (6) Decision making in an adaptive approach can involve the entire life cycle of a medicine, which means that besides efficacy also ‘real world’ effectiveness and safety are relevant to complicate decision making. This also calls for more participation of health technology assessment bodies and patients in decision making.

In next three chapters we will analyze this challenge - how to achieve appropriate levels of evidence for marketing authorization- by discussing three sub questions that together help answer the main question (Figure 4):

1) How to optimize evidence generation and adjust evidence requirements? (Chapter IV)

2) How to systematize benefit-risk decision making? (Chapter V)
3) How to strengthen the dialogue between regulators and companies? (Chapter VI)

**Figure 4** – Three chapters analyze the discussion paper's main question: How to achieve appropriate levels of evidence for marketing authorization?

We focus in this paper mainly on appropriate levels of evidence in relation to (initial) marketing authorization because (1) this is where decisions about early access to the market are made and (2) because the system for marketing authorization is in many ways distinct and separated from the systems for health technology assessment (HTA) and reimbursement, which would make a proper analysis including HTA too complex for this paper. However, although a proper analysis of HTA is out of scope for this discussion paper, the outcomes of the discussion here are of importance to developments in HTA as well, since the decision-making process about the marketing authorization of new medicines provides one of the key initial inputs for the HTA process and close interaction between these fields is necessary as the discussion about more adaptive forms of marketing authorization moves forward.

"Doubt is an uncomfortable condition, but certainty is a ridiculous one."

Voltaire
This chapter describes: (1) current evidence generation and regulatory requirements; (2) the need to optimize evidence generation and adjust regulatory requirements; and (3) ways to optimize evidence generation and adjust regulatory requirements.

1. BACKGROUND: Current evidence generation and regulatory requirements

Evidence about medicines is the result of two major forces: (1) the supply of evidence by companies through development plans, ‘evidence generation;’ (2) the demand for evidence by regulators through regulations and other requirements, ‘evidence requirements.’ Because both evidence generation and regulatory requirements are very complex, diverse and detailed we discuss them in this chapter from a regulatory systems perspective.

Evidence generation

Evidence about medicines is not a singular entity, but a complex phenomenon consisting of several steps in which evidence is generated. We have visualized these steps in a model (figure 5). Evaluating the evidence and uncertainties within each of these steps is the core activity of the regulatory assessment and should be based on scientific methods. In the first step, preclinical and clinical data, accompanied by a degree of statistical uncertainty, are gathered to form the ‘dossier’ for a product. Together with other sources of data these data constitute the input for an assessment of the (internal and external) validity of the data, resulting in aggregated information on a product’s multiple ‘favourable and unfavourable effects’ and quality aspects. In the following step, the (clinical) relevance of available information on effects is evaluated and combined into an overall picture of the product’s quality and ‘benefit-risk balance’. Because the next step (evaluation by health technology assessment bodies) takes place after (initial) marketing authorization, it will not be discussed here as a way for optimizing evidence generation for marketing authorization.b

b In this step, health technology assessment (bodies) evaluate the effectiveness of a product in a real world setting, also taking into account the costs involved, leading to insight in the ‘therapeutic value’ of a product.
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Regulatory requirements

In the European Union, public health is promoted by ensuring access to medicinal products that are of high quality, safe and efficacious. Several Regulations and Directives provide a framework for the evaluation of medicinal products by regulatory authorities, and specify mandatory requirements for companies to provide evidence demonstrating a product’s quality, safety and efficacy. The Directives also state that companies shall also take into account the requirements in the detailed scientific guidelines from the Committee for Medicinal Products for Human Use (CHMP). Although scientific guidelines do not have legal force, they are “soft laws”: deviation from them is possible provided that this is appropriately justified. Besides contributing to public health, scientific guidelines also aim to: support the regulatory decision making process; ensure consistency of regulatory decisions within the EU; facilitate access to the market for companies.

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They “provide advice to authorities on the best... way to fulfill obligations laid down in... legislation”...and “facilitate assessment.”[EMEA 42731/2008]

They ensure “harmonization of how EU Member States and the [European Medicines] Agency... require... demonstration of quality, safety and efficacy.”[EMA website]

Guidelines “give guidance to applicants and/or sponsors in planning the overall pharmaceutical product development”[EMEA/P:24143/2004 Rev. 1] and “help applicants prepare marketing authorisation applications” [website] to “facilitate... approval.”[EMEA 42731/2008]
The last decade has witnessed a sharp increase in the development of guidelines resulting in more than 600 (draft) guidelines for specific therapeutic areas, for biotechnological products and for advanced-therapy medicinal products. New guidelines originate from input of the CHMP, Member States and interested parties (e.g. companies, health care professional groups, academia, patient associations). The input consists of frequently encountered problems with requirements, questions brought forward by scientific advice, need for international harmonization, or the development of new technologies, practices or therapeutic indications. The CHMP drafts the guideline and releases it for consultation to relevant interested parties. Furthermore, the applicability of existing guidelines can also be reviewed based on input from the CHMP, Member States and interested parties. Guidelines will be considered for revision after five years. However, when knowledge is fast evolving or major problems with the application of the guideline come to light, review may be initiated earlier.

Companies generally appear to comply with applicable scientific guidelines for planning and executing the overall development of a product, also because deviations are not encouraged. As is discussed in chapter VI, companies have the opportunity to ask for ‘scientific advice’ to prospectively discuss development plans and (deviations from) guidelines. However, to what extent and in what cases companies deviate from guidelines is not known. The EMA and national regulatory authorities use scientific guidelines to evaluate marketing authorization applications to effectuate the obligations laid down in applicable legislation. However, how regulators use scientific guidelines in practice is not adequately communicated to the public.

2. ADAPTIVE APPROACHES: the need to optimize evidence generation and adjust regulatory requirements

As discussed in the chapter III, adaptive approaches to marketing authorization require a more flexible approach to the required level of knowledge about a product and allow initial marketing authorization based on less evidence than is currently required. This in light of the need to shorten development timelines and allow early access. Adaptive approaches also require that after initial marketing authorization, the level of knowledge will be raised by stepwise evidence generation and regulatory evaluation. However, although the concepts of adaptive approaches to marketing authorization specify to some extent what criteria (e.g. medical need) can be used to justify a (lower) required level of evidence for a product, they are essentially neutral with regard to how the appropriate level of evidence is realized.

As said earlier, evidence about medicines is the result of two major forces: ‘evidence generation;’ and ‘evidence requirements.’ So there appear to be two general ways to efficiently realize an appropriate level of evidence: optimize evidence generation and adjust regulatory requirements. On the basis of the model for evidence generation (Figure 5) we have identified three ways to...
optimize evidence generation: (1) Optimize data generation; (2) reconsider the validity of data; (3) reevaluate clinical relevance of information. Furthermore, we will also discuss (4) ways to adjust regulatory requirements for evidence.

3. ESCHER ANALYSIS: ways to optimize evidence generation and adjust regulatory requirements

Way 1. Optimize data generation

Uncertainty about a product’s value can stem from a complete lack of data on an aspect (e.g. safety issues) of a medicinal product. Although many types of studies are required for marketing authorization, regulators do not explicate how important a study is for the body of knowledge about a product. Obviously, refraining from conducting studies that contribute little to the body of knowledge could help to reduce the generation of upfront data. However, this requires insight in the added value of different types of studies. For example, recent publications show that appropriate preclinical and early Phase I and II studies contribute significantly to reducing attrition rates\(^{18}\). On the other hand, data from animal (toxicology) studies are of limited value to detect safety issues\(^{19}\).

Knowledge about a product is also determined by the level of statistical uncertainty which is a result of the studied sample size. Reducing the sample size could reduce timelines and resources required. However, the relationship between sample size and statistical precision also depends on methods used, i.e. how the sample size is used to extract data (e.g. trial design) and on the statistical analyses used. The Escher Project provides innovative methods that could serve as ways to optimize data generation (Box 1).
Box 1 – Reducing sample size: innovative study designs

Adaptive trial designs can reduce the sample size without reducing the statistical power. They can achieve this by performing interim analyses and then optimize the design of the trial (e.g. by altering randomization, sample size or patient characteristics). The Escher Project has investigated adaptive trial designs that enrich the study population during the trial on the basis of pharmacogenetic characteristics. This approach can lead to a smaller trial and can reduce the number of patients unnecessarily exposed to the medicine.

A related approach that can reduce sample size requirements and increase success rates of clinical trials is the ‘sequential parallel comparison’ design. This design consists of two consecutive placebo-controlled comparisons of which the second is only entered by placebo non-responders from the first. An Escher study suggests that this design is a highly efficient alternative to a conventional RCT in indications where placebo response is high and substantial treatment effects are established after a relatively short follow-up period, e.g. in antidepressant trials.

Furthermore, the sample size of a study can also be reduced by reporting continuous outcomes instead of dichotomous outcomes. An Escher study has shown that in case of bimodally distributed outcomes (such as in antidepressant studies), dichotomization decreases study power and does not address the heterogeneity of the outcomes optimally. Dichotomization only provides superior power when bimodality is extreme and the two groups that result from dichotomization coincide with the grouping in the underlying distribution. Reporting of the full outcome distributions in individual trials could reveal possible heterogeneity and corresponding grouping of patients.

These examples show that besides simply allowing a higher level of statistical uncertainty, one of the ways to optimize data generation is to reduce the amount of generated data by using innovative methods, for example by optimizing the use of available data in novel methods for trial design and statistical analysis. However, an important point to consider in accepting new methods is that they can involve a trade-off between statistical precision and validity and thereby introduce another type of uncertainty: decreased validity. In the words of the CHMP: adaptive designs could render ‘confirmatory’ trials to be considered merely ‘exploratory’.

Way 2. Reconsider validity

Validity can be subdivided in internal and external validity. Internal validity is ensured in clinical trials by a number of central design features, including randomization, blinding (of allocation,
IV. Evidence generation and requirements

Although it is possible to give up some of these design features, this is problematic for three reasons: (1) it can lead to systematic error (of unknown source) and render results simply untrue; (2) it is unlikely to shorten or reduce the size of studies and therefore does not help early access to the market; (3) it is unethical to enroll research subjects in less rigorous studies because it means that their efforts do not contribute to the body of knowledge about a medicine. Nevertheless, a current route that sacrifices internal validity is conducting single-arm and observational studies instead of trials. This has been the basis for the conditional marketing authorization for some cancer and orphan medicines. Still, even for orphan medicines, randomized controlled trials are preferred by regulators and are in fact supplied in almost 60% of the dossiers.

However, besides the general design features of trials, the use of alternative outcome measures is also a way to optimize evidence generation. The Escher Project has contributed to the ongoing discussion about the validity of so-called “surrogate outcome measures” (Box 2). Although surrogate outcome measures can turn out to be inadequate predictors of clinical effects, they hold great promise to shorten development timelines, especially for diseases with long-term outcomes.

**Box 2 – Validity of data: biomarkers**

The Escher Project has conducted studies that focus on validating biomarkers as surrogate endpoints. The time to marketing authorization could be shortened considerably by accepting surrogate endpoints instead of clinical endpoints as the basis for marketing authorization. However, although a biomarker may have superior prognostic ability, therapeutically changing such a biomarker does not necessarily improve long-term outcome. It is therefore of key importance that after initial marketing authorization on surrogate endpoints, further studies confirm an effect on relevant clinical endpoints. This concept is especially useful for products for renal and vascular conditions, for which RCTs on clinical endpoints take many years.

Because medicines can affect multiple biomarkers the Escher Project has also studied the predictive performance of a combination of biomarkers. Off-target effects (e.g. certain biomarkers) of medicines are often not systematically considered when evaluating medicine efficacy. However, an integration of on-target and off-target effects in a so-called “multiple parameter risk response outcome” (PRO) score could have a profound impact on the evaluation of efficacy. The Escher Project currently investigates how the applicability and generalizability of the PRO score can be strengthened, and aims to fuel discussions with regulators, developers, and policy makers about how medicine efficacy should be established.
Reconsidering external validity also seems a promising avenue to optimize evidence generation, which fits recent EMA thinking about ‘extrapolation.’ According to a concept guideline, ‘extrapolation’ can occur between: population subsets; diseases; animals and humans; healthy volunteers and patients; and medicines, within and between classes. Several Escher studies support this concept (Box 3). Although these ways to optimize evidence generation appear promising, further research is needed to assess the resulting level of external validity in the context of other knowledge about a product (see section way 4).

### Box 3 – Extrapolation: ‘learning’ studies and medicine classes

A first form of optimizing evidence generation concerns extrapolation between medicines. This can be done within and between medicine classes. The Escher Project has shown this could be a valuable way to reduce uncertainty without requiring additional data generation. One study focused on learning between same class medicines during marketing approval and found that adverse drug reactions of first in class medicines were not always included in the Summaries of Product Characteristics of second in class medicines. Another study showed that for HIV medicines, safety issues were taken into account in the approval process of other medicines in the same class. Improving this kind of learning could help to achieve a proper level of safety knowledge while requiring less data to be collected pre-approval.

A second form of extrapolation investigated within the Escher Project concerns relying more on preclinical and early clinical data. One study distinguished ‘confirmatory’ studies (late-stage trials) and ‘learning-phase studies’ (e.g. mode of action, proof of concept, pharmacokinetics, dose finding and safety pharmacology), and found that both types of studies are important for marketing authorization. Analysis of the ‘learning-phase studies’ showed that in cases where outcomes of efficacy studies were problematic, sufficient evidence on the mode of action, proof of concept and dose finding studies were important factors for successful marketing authorization. The study suggests that assessors might rely more on extrapolation of the results of early clinical studies (in healthy individuals) to increase the degree of confidence about ‘real’ clinical effects in patients. This could be a way to optimize evidence generation in the confirmatory phase.

### Way 3. Reevaluate clinical relevance

The body of knowledge about a medicine also depends on the evaluation of the clinical relevance of different pieces of information. Therefore, reevaluating the level of clinical relevance attributed to effects could be a way to optimize evidence generation. This line of thinking is also present...
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in adaptive approaches: they let the required level of knowledge depend on the product, the therapeutic area, medical need and willingness of stakeholders to accept more uncertainty. For example, a high medical need would be a good reason to attach more clinical relevance to favourable effects in relation to unfavourable effects. This could lead to (initial) marketing authorization based on an incomplete safety record.

Such considerations of medical need affect the evaluation of the benefit-risk balance consisting of the sum of favourable and unfavourable effects. However, the Escher Project shows that the evaluation of individual effects can differ between regulators and between regulators and non-regulators. This suggests that aligning the evaluations of regulators with those of patients could lead to less (or more) need for evidence (see also chapter VI).

Way 4. Adjust regulatory requirements for evidence

We have now discussed three ways to optimize the generation of evidence. A fourth and complementary way to efficiently realize an ‘appropriate’ level of evidence would be to alter the standards for evidence generation. As the standards for evidence are to a considerable degree laid down in scientific guidelines, this would imply a more flexible approach to guidelines. However, because guidelines are considered ‘soft law’ and are generally followed, this requires regulators and industry to have a ‘change of attitude’: they should acknowledge (and communicate) that guidelines are in fact just that – guidance- and exist to help make the best decisions within the context of other considerations.

A complementary approach would be to refrain from developing guidelines in the first place. Currently, stakeholders only have influence on the development of a guideline in a later stage. The EMA acknowledges the value of evaluating the need for developing a guideline beforehand and therefore requires an ’impact assessment’. However, in practice this leads to an uninformative formula which does not describe a comprehensive assessment of pros and cons and a resulting ‘go/no go’ decision for the development of a guideline. A possible solution for this situation is that companies, academics and patients are involved in the early stages of guideline development, which is in line with recent EMA thinking.

Furthermore, a more flexible approach to evidence requirements could also be supported by having (more) insight in the effects of existing requirements and guidelines. This idea is in line with the WHO’s report ‘Effective Drug Regulation’ which states that “ideally, an assessment of drug regulation should begin by studying regulatory outcomes to judge overall performance”. However, this report also concluded that “outcomes are often not readily measurable.” The Escher Project has made progress in this respect by conducting studies that provide insight in the effects

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6 e.g. “It is expected that the “Guideline … provides guidance for pharmaceutical companies with respect to methodology, assessment tools, measurements, clinically relevant outcomes, etc. for clinical investigation in … Furthermore, the guidance should ensure uniformity and comparability of the performed clinical studies for the indication … in the European Union.” [EMA website]
IV. Evidence generation and requirements

of evidence requirements (Box 4). These studies show that promising instruments exist to adjust regulatory requirements, also for the case by case evaluations of the need for evidence in adaptive approaches.

**Box 4 – Measuring effects of evidence requirements**

An Escher study investigated whether Exceptional Circumstances or Conditional Approval pathways for marketing authorization lead to more safety issues. The study found that despite limited data at time of conditional approval, new medicinal products were not associated with an increase in the risk of serious safety issues emerging after marketing approval.

A second study looked at results of post-approval commitments for biosimilars and found that the safety profiles of biosimilars seem comparable to those of innovator products. The study concluded that, following a successful comparability exercise, the benefit-risk profile of the comparator product could be extended to the biosimilar and that biosimilar risk management should be limited to those products with known or expected risks of clinically relevant immunogenicity associated adverse events.

Finally, this approach of studying the health effects of evidence requirements can also be extended to include considerations about costs. Currently, costs of evidence requirements are not prominent in regulatory thinking and hardly any evidence exists regarding the cost-effectiveness of regulatory requirements. Two Escher studies show that systematically evaluating the cost-effectiveness of regulatory requirements is feasible and could be part of a comprehensive impact assessment of regulatory requirements (Box 5). This could support a flexible approach to evidence requirements.

**Box 5 – The cost-effectiveness of medicine regulation**

An Escher study investigated the cost-effectiveness of guideline ICH E14 which requires QT/QTc studies for particular products. Costs and health effects of two scenarios were compared: the health effects and costs resulting from implementing ICH E14 vs. not implementing ICH E14. The additional costs of ICH E14 were €2.4 million per sudden cardiac death prevented and ~€187,000 per quality-adjusted life year (QALY) gained. The main driver of costs was electrocardiogram (ECG) monitoring. The study concluded that ICH E14 is not a cost-effective guideline.
Along the same lines, the cost-effectiveness of periodic safety update reports (PSURs) of biologicals was analyzed in an Escher study. This study revealed two urgent safety issues for biologicals: (i) distant spread of botulinum toxin and (ii) edema/fluid collection from off-label use of dibotermin-alfa. The cost-effectiveness of requiring PSURs was calculated to be €342,110 per quality-adjusted life year gained. The authors concluded that costs involved in PSUR reporting are unlikely to outweigh their health gains.

Although a flexible approach to evidence requirements (and guidelines) is attractive, it can also pose challenges. It could complicate the work of regulators and decrease consistency of decisions, although a more systematic benefit-risk assessment method could help in this respect (see chapter V). Furthermore, if companies do not get proper assurance of regulators that they do not have to comply with certain requirements, companies will comply with them anyway. A strengthened scientific dialogue could help to solve this problem (see chapter VI). Finally, using guidelines more flexibly requires regulators to justify deviations thoroughly. If their justification is not transparent this could decrease public trust in regulatory decisions.
This chapter describes: (1) Current benefit-risk decision-making; (2) the need for more consistency and transparency; and (3) instruments for more systematic benefit-risk assessment.

1. BACKGROUND: Current benefit-risk decision-making

The assessment of benefits and risks of new medicinal products is a central element of the evaluation of the marketing authorization application by regulatory authorities. Benefit-risk assessment also plays an important role in companies’ development strategies, in reimbursement decisions by health technology assessment bodies and in decision making on the ethics of research by research ethics committees. Although we focus on benefit risk assessment in the context of decision-making about marketing authorization by regulators, much of our discussion is also relevant to other decision makers.

Benefit-risk assessments consist of three ingredients: data about the favourable and unfavourable effects of a product; uncertainties about these effects; and judgements about the clinical relevance of effects based on data accompanied by uncertainty. A properly conducted benefit risk assessment should have two important qualities:

1. It should be a rational process of combining objective elements (data and uncertainties) with subjective elements (clinical judgement), leading to consistent decisions;
2. It should be a transparent process, making it communicable and accountable.

However, benefit-risk assessment is a complex, multi-person process that requires the evaluation of a large amount of data (10Gb) on multiple kinds of effects and a transformation into an overall balance, usually resulting in a simple ‘yes/no’ decision. In general, discussions and evaluations of a descriptive nature guide this transformation by regulatory agencies and most companies. The EMA has suggested that the consistency and transparency of the decision-making process by regulatory agencies could be improved. The need for improvements is illustrated by an Escher study that shows that differences exist in the assessment of risks between regulatory assessors (Box 6).
Box 6 – Differences in risk perception

An Escher study investigated the subjective aspects of risk evaluation of medicines by regulators. The study found that the risk evaluation of medicinal products is influenced by the harm associated with the medicine, the number of people affected and ethical concerns. However, assessors conflate these dimensions (e.g. they assess the beneficial effects of a medicine with risk of carcinogenicity differently from a medicine without that risk). This endangers rational decision making about benefits and risks. Furthermore, the evaluation of risks varied between individual assessors depending on the assessors’ individual characteristics such as age and sex.

To help increase consistency and transparency of benefit-risk assessments, many stakeholders, including companies and regulators, have developed frameworks to structure, standardize and simplify benefit-risk assessments. Examples are the PhRMA BRAT framework, EMA’s PrOACT-URL framework, IMI PROTECT and the benefit-risk projects of the Centre for Innovation in Regulatory Science (CIRS). Furthermore, the EMA has set up the Benefit Risk Methodology Project with the participation of, amongst others, the Escher Project. The Benefit Risk Project has investigated and developed instruments to aid benefit-risk assessment by regulators (Box 7).

Box 7 – The Benefit Risk Methodology Project

In 2009, the European Medicines Agency established the Benefit Risk Methodology Project to improve the transparency, consistency and communicability of marketing approval decisions of medicines by developing tools and processes for balancing multiple benefits and risks. The project has resulted in an improved conceptualization of ‘benefit’ and ‘risk’, replacing these words with four separate items: 1) favourable effects; 2) uncertainties about the favourable effects; 3) unfavourable effects; and 4) uncertainties about the unfavourable effects. The CHMP has incorporated this conceptualization in relevant guidance documents for assessment report. Furthermore, the project has endorsed a descriptive (‘PrOACT-URL’) framework for systematically evaluating the benefit-risk profile and proposed an ‘Effects Table’ to display a product’s relevant effects and uncertainties.
2. ADAPTIVE APPROACHES: the need for more consistency and transparency

Although assessing benefits and risks consistently and transparently is of growing importance in the current system, it is even more so in adaptive approaches. As described in chapter IV, an adaptive approach to marketing authorization implies a more flexible approach to evidence by deciding on a case by case basis which evidence is needed and where the level of knowledge could be lowered. These decisions should be based on a comprehensive overview of (possible) evidence and uncertainties in an overall benefit-risk balance.

However, if the decision making process is not highly systematic an increased flexibility about requirements could jeopardize consistent decision making. Furthermore, because a higher level of uncertainty is allowed in an adaptive approach, the decision making process becomes more complex which could also jeopardize rational decision making and lead to inconsistent decisions. Another reason why consistency is essential to adaptive approaches is that the multiple decisions during the life cycle of a medicine should be consistent. With the growth of knowledge during the life cycle of a medicine, it is important to have a precise and explicit record of the assessment of the initial benefit-risk balance, so that it is evident how new knowledge affects the balance leading to a widened or restricted label. Besides, in an adaptive approach, considerations on medical need also determine what type of marketing authorization pathway is deemed appropriate. However, incorporating medical need in benefit-risk assessments involves a careful adjustment of the clinical value attached to the effects of a medicine. Although this might seem straightforward, an Escher study showed that in practice the concepts of benefits and risks appear to be confounded in people's minds and lead to an erroneous belief that activities or technologies judged high in benefits are consequently low in risk and vice versa.

Transparency of decision-making is also of increased importance in adaptive approaches. A more flexible use of regulatory requirements, in order to allow more uncertainty requires a more elaborate justification of deviations from requirements, otherwise public trust in regulatory decisions might be at stake. Also, a flexible approach to evidence requirements could make the regulatory system less predictable to companies. To avoid that companies ‘play safe’ and comply with all possible requirements (i.e. guidelines) anyway, transparency and communication of regulatory requirements and decision-making should be a main priority (see chapter VI).

3. ESCHER ANALYSIS: instruments for more systematic benefit-risk assessment

Quantitative instruments promise more consistent and transparent decision making

Although currently no regulatory authority uses them, many authors and organizations (including the EMA) endorse ‘quantitative’ instruments to achieve more consistent and transparent
V. BENEFIT-RISK ASSESSMENT

The logic of quantitative instruments is to distinguish three steps in decision making: (1) decompose problematic situations into its constituent pieces; (2) make assessments about these pieces; and (3) recompose the pieces to a whole (Figure 6). The first step is descriptive (e.g. PrOACT-URL framework and Effects Table), but step 2 and 3 are ‘quantified’: in step 2 input elements (effects, uncertainties and value judgments) are translated to numbers or ranks on a common scale; step 3 consists of a formal model with an algorithm for integrating different input elements into a single output.

Multi-criteria decision analysis as a quantitative instrument

Although many quantitative instruments might support benefit-risk assessments, we focus on multi-criteria decision analysis (MCDA) because it is one of the best developed instruments and has undergone field testing within the context of regulatory benefit risk assessment, e.g. within the EMA’s Benefit-Risk project. MCDA can incorporate a (1) logical, (2) coherent model, (3) different forms of data, (4) multiple objectives, (5) uncertainty, and (6) value judgements. This covers all elements of regulatory benefit risk decision making: working towards a (1) rational,
(2) overall benefit-risk balance of (3) different kinds of study results about the (4) multiple effects of a product, accompanied by (5) uncertainty about these effects, and evaluated by (6) clinical judgements. An additional feature of MCDA (and many other quantitative instruments) is that it can visualize how different elements contribute to the overall benefit-risk balance, comparing one product to another (Figure 7). Box 8 describes the MCDA instrument as it was developed and field-tested within the EMA’s Benefit-Risk project.

Box 8 – Field tests of an MCDA instrument

An MCDA approach was field-tested for a benefit-risk assessment of medicines that were at that time under review by the CHMP. At five member state agencies a one-day, facilitated ‘decision conference’, was organized to construct on-the-spot a benefit-risk model of the medicines and their comparators. The EMA’s PrOACT-URL framework guided the development of the model. Group discussions resulted in an Effects Table that included: the medicines and their comparators, relevant criteria (effects) with measurement scales, and data on effects. Each effect was then converted to a ‘preference value’ on a 0 to 100 scale to enable comparisons of dissimilar favourable and unfavourable effects (e.g., percentages of responders vs. mean QTc prolongation). Then, the units for the different preference value scales were compared by ‘weighting’ them on the basis of judgements about clinical relevance. Finally, the weighted effects were summed to give an overall benefit-risk balance. The model was created with a computer and projected so participants could see the model being created at each step. The computer also graphically displayed results: the overall result and the contribution of each criterion to the overall balance. Uncertainties in the data were explored with a ‘sensitivity analysis’: changing data input and ‘weights’ (clinical relevance) to see how this affected the overall balance. This provided a way to explore scenarios representing future developments. The group also discussed whether thinking and judgments had been consistent with past decisions. Although the project considered the field test a success, the most recent proposals for implementation of benefit-risk tools focus on introducing the Effects Table.

The field-tests showed that a quantitative approach is feasible within the context of regulatory benefit-risk assessment about a product. Assessors especially appreciated the feedback the quantitative model gave them on the impact of uncertainty in the data and of differences of opinion about clinical relevance. Limitations of the software instruments were that, besides sensitivity analysis (manually changing weights or varying input within the limits of confidence intervals)
instruments had limited capabilities to incorporate statistical uncertainty, an essential element of benefit risk assessment. Furthermore, building up the model through input of data and relevant criteria with measurement scales was time consuming. A software tool developed by the Escher Project addresses these limitations and provides additional opportunities to improve decision making (Box 9).

**Box 9 – Software for multi-criteria decision analysis**

The results of clinical trials are communicated mainly through text-based publications in scientific journals, which makes the process of gathering evidence to support decisions inefficient. The decision making process could be made more efficient, reproducible, and transparent if the data were available in a structured format. The Aggregate Data Drug Information System (ADDIS) developed by the Escher Project stores clinical trial information in a structured format, enabling it to be used in more flexible ways. It can also integrate data from studies that do not make direct comparisons between medicines, through automated network meta-analysis. Furthermore, ADDIS enables multi-criteria decision analysis (MCDA) models to be built on top of single trials or network meta-analyses. This framework supports benefit-risk assessment by incorporating clinical measurements and their associated statistical uncertainties, as well as making trade-off decisions between criteria explicit (e.g. efficacy versus the risk of an adverse event), also through visualization of results (Figure 7). ADDIS shows that more structured and transparent approaches to benefit-risk assessment are possible when data are available in a structured format. It is also clear that while ADDIS greatly facilitates working with the evidence, meta-analysis and benefit-risk assessment remain difficult topics that require a certain level of expertise from the user. ADDIS is free and open source software available from http://drugis.org.
Challenges and opportunities of quantitative instruments

Although many studies and instruments provide promising opportunities for the introduction of quantitative approaches, there exists little evidence about how quantitative instruments affect the quality of regulatory decision-making or public health. A starting point for gathering evidence could be to compare EPARs of currently available medicines to the outcomes of quantitative instruments. However, besides opportunities, quantitative instruments might also be challenging for regulators through requiring additional skills and time investment. Decision conferences are time intensive, although standardizing models, an intensified preparation and using models to facilitate efficient communication could save time. It might also be possible to decide on a case by case basis how much quantitative modeling is needed. However, a first step here would be to study the time investments involved.

Nevertheless, it seems probable that quantitative approaches can increase consistency of decisions between products, and of repeated decisions about the same product, as is required in adaptive
approaches. Quantitative instruments could help to (re)align judgments about clinical relevance because they force systematic explication of judgements and allow exploring discrepancies between personal intuitions and computer results. Also, explication of judgements about clinical relevance could help communicating the rationale of benefit risk decisions to the public and so promote trust in the regulatory system. However, explication can also pose challenges because the regulator’s value judgements might be different from those of patients, and also because communicating what the numbers and graphical output mean for actual patients could be challenging.

Still, an explication and exploration of value judgments could be especially valuable in cases where high medical need can form the basis for adjusting evidence requirements, as is the case in adaptive approaches. Furthermore, quantitative instruments can instantly play-back the results of the model. Regulators could explore how changes in value judgments or (uncertainty about) data affect the overall benefit risk balance by simulating scenarios. This feature of quantitative instruments is especially valuable for adaptive approaches because it allows regulators and companies to have a constructive and prospective discussion on what evidence is needed (chapter VI). It can also help to get insight in how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients) and how (new) real world data could affect the balance. Having insight in the robustness of decisions could also support the confidence of regulators for approving medicines on the basis of adjusted evidence requirements. Furthermore, as we described in Box 9, a quantitative approach can incorporate statistical uncertainties about effects and also (possible) effects without data (knowledge gaps). However, other forms of ‘uncertainty’ such as different levels of validity (chapter IV) can currently not be accounted for.

Quantitative models could also be used for efficient communication between regulators and between regulators and companies, especially if the results are visualized. However, proper visualization is still a challenge. Companies could be encouraged to submit benefit-risk models in support of their application or for discussing their development programs to support a constructive dialogue between regulators and companies (chapter VI). The EMA currently looks, in collaboration with the European Network for Health Technology Assessment, into how the information on benefits and risks of medicines in European public assessment reports (EPARs) could better contribute assessments by HTA bodies17. Quantitative instruments might support this harmonization, especially because an Escher study showed that transparency of reimbursement decision-making could be improved14.

“Models are not designed to describe how man ordinarily behave, but rather to help them behave more like they would like to behave.”
Becker and McClintock58
Scientific advice: towards a constructive dialogue between companies and regulators

Openness of possibilities is an opportunity, and doubt and discussion is essential to progress into the unknown... doubt is not to be feared, but welcomed and discussed.” — Richard P. Feynman

This chapter describes: (1) current forms of interactions between companies and the EMA, especially ‘Scientific Advice’; (2) the need for a constructive scientific dialogue on medicines; and (3) how the scientific dialogue could be strengthened.

1 BACKGROUND: interaction between the EMA and companies on scientific issues

Current forms of interactions between companies and the EMA

Interaction between the EMA and companies about medicines can concern regulatory (interpretation of legislation), administrative (how to submit an application) or scientific issues. The scientific interaction concerns what data need to be generated to demonstrate the quality, safety and efficacy of a medicine. Scientific interaction can concern a particular medicine or can be of a more general nature. Examples of scientific interaction that are not related to a particular medicine, and are thus more general, are workshops, information days, and guideline consultation procedures. These activities are organized by the EMA in order to discuss scientific issues such as new methodologies and study designs. How guideline consultation procedures could be reformed is discussed in chapter IV.

In this chapter we focus on the medicine-specific interactions about scientific issues during medicine development. This kind of interaction takes place in all phases of a medicine’s life cycle: before marketing authorization, during the marketing authorization procedure, and in the post-marketing phase (Figure 8).
VI. Scientific dialogue

Most of these interactions, such as pre-submission meetings, CHMP list of questions and clarification meetings, concern how additional information and justification can be provided in the dossier\textsuperscript{60}. These types of interaction all concern interpretation of available evidence about a medicine, not evidence generation. However, in the scientific advice procedure the EMA can interact with companies about development plans before data are generated, in the form of the EMA Scientific Advice procedure\textsuperscript{61}. In this chapter we will explore opportunities to expand the scientific advice procedure in the light of the possibilities to shorten development timelines and introduce adaptive approaches to marketing authorization. We will first discuss the (1) objectives of scientific advice, (2) its (legal) status, (3) the timing and (4) stakeholder involvement.

**Objectives of scientific advice**

The scientific advice procedure was reformed by the EMA in 2006 to enable companies to discuss development plans with regulators. Since then, an increasing proportion of applications for marketing authorizations has been preceded by scientific advice: in 2011 76\% of applications\textsuperscript{62}. During scientific advice, issues related to all phases of medicine development can be discussed, e.g. quality (manufacturing, chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests) or clinical issues (early and confirmatory clinical studies pre- and post-approval), and also opportunities for conditional or exceptional approval\textsuperscript{61}. According to the EMA, such advice is particularly useful to companies in cases where guidelines appear to provide insufficient details about how to set up the development plan or in cases where companies want to deviate from guidelines. The EMA emphasizes that scientific advice aims to discuss development plans prospectively and not to pre-evaluate study results to support a marketing authorization application\textsuperscript{34,61,63}.

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**Figure 8 – Interactions about scientific issues during medicine development**
VI. Scientific dialogue

(Legal) status of scientific advice

Although a large proportion of companies receive scientific advice, companies are not obliged to follow the advice: scientific advice is not legally binding, for companies nor for authorities with regard to a future marketing authorization application. However, compliance with scientific advice is associated with successful marketing authorization. Companies have to justify deviations from scientific advice to the CHMP when applying for marketing authorization, for example when the company decided to use a different study design than recommended during scientific advice. Similarly, the CHMP has to explain during the review of a marketing authorization application why it deviates from previous advice.

Timing of scientific advice

The EMA does not specify timelines for scientific advice but companies can seek scientific advice as many times as necessary and in all phases of the product lifecycle: either during the initial development of the medicine or during the post-marketing phase, e.g. related to risk management plans.

Stakeholders involved in scientific advice

The parties involved in current scientific advice procedures are the companies that request scientific advice and the EMA Scientific Advice Working Party (SAWP) which arranges and provides the advice and is supported by expertise from CHMP working parties and scientific advisory groups. The CHMP formally adopts the scientific advice.

2. ADAPTIVE APPROACHES: the need for a constructive scientific dialogue

As explained in chapter III, an adaptive approach to marketing authorization involves stepwise learning with iterative phases of data gathering and regulatory evaluation. To be a viable approach, adaptive marketing authorization requires a strong scientific dialogue on all aspects mentioned above:

- **Objectives:** adaptive approaches involve optimization of evidence generation in relation to adjusted (lowered) regulatory requirements. This means that the scientific dialogue should be constructive: developments plans should be based on a discussion about the need for evidence.
- **Status:** it also means that the data generated through these adapted development plans should be considered acceptable by regulators in a later stage. So, some sort of binding agreements about development plans might be required.
• **Timing:** adaptive approaches require an *early* scientific dialogue because they require a discussion before evidence is generated. Furthermore, in an adaptive approach a *continual* scientific dialogue is required because collecting post marketing data is essential for being able to proceed from ‘initial’ to ‘full’ approval.

• **Stakeholder involvement:** adaptive approaches require that health technology assessment bodies and patients are also included in an *inclusive* dialogue.

Furthermore, besides in discussions about adaptive approaches, a strengthened dialogue between companies and regulatory authorities has also been recommended as a strategy to support innovative medicine development. In the following sections we will analyze to what extent the current scientific dialogue could be strengthened and reformed towards a more *constructive, binding, early, continual, inclusive* interaction (Figure 9).

**Figure 9** – *Design of a strengthened scientific dialogue*
3. ESCHER ANALYSIS: strengthening the scientific dialogue

New objectives: constructively discuss development plans

The Escher project has investigated the current practice of the scientific advice procedure and found that companies request scientific advice primarily to get assurance that ongoing development plans comply with regulatory requirements and guidelines. To a lesser extent was scientific advice used to discuss development plans in cases where guidelines provided insufficient detail (Box 10).

Box 10 – Objectives of scientific advice in practice

The Escher Project conducted qualitative and quantitative analyses of scientific advice to gain insight in how companies and regulators interact in practice, especially concerning development plans. An analysis of scientific advice questions to the scientific advice committee of the Dutch Medicines Evaluation Board showed that most questions aimed to get assurance about the total package of (ongoing) phase III clinical studies. Furthermore, detailed questions were asked about specific issues concerning the various studies, such as study design, endpoints, study population and special safety issues. A subsequent study of scientific advice by the European Medicines Agency focused on questions about study design, in particular non-inferiority designs and found scientific advice to be complementary to existing guidelines. Specific questions related to non-inferiority designs were asked in cases the non-inferiority guidelines provided insufficient detail.

This current practice of scientific advice is not in line with the EMA’s aim that scientific advice can help to set up a development plan, nor with adaptive approaches that require a constructive dialogue about how much and what kind of evidence is required for a particular medicine. Companies could be more strongly encouraged to request scientific advice before evidence is generated. (see section on timing). Furthermore, a more open and explicit discussion about evidence requirements could be supported by benefit risk assessment instruments (chapter V).

Change status: more binding agreements

Current scientific advice is not legally binding, although deviations by both parties should be explained. However, to support a constructive discussion about the need for evidence, companies...
VI. Scientific dialogue

might need to be able to reach some sort of binding agreement with regulators about the development plan. If regulators want to assess development plans more on a case by case basis, (for example in the context of an adaptive approach) and allow companies to deviate from guidelines, companies should feel confident that the evidence generated on the basis of their development plan is still acceptable at time of marketing authorization application. If this is not the case, companies will be inclined to ‘play safe’ and comply with all available guidelines. On the other hand, reaching ‘binding’ agreements on developments plans could become problematic due to scientific progress or regulatory innovation indicating that the development plan is suboptimal.

The FDA already allows formal agreement on plans for phase III studies in the procedure ‘Special Protocol Assessment’\textsuperscript{69}. Also, ethical review of study protocols by research ethics committees is prospective and binding. However, agreement on the development plan of a medicine is currently not possible at the EMA (except for orphan drugs and medicines for children through ‘paediatric investigation plans’), although the recent ‘qualification of novel methodologies and biomarkers’ procedure is a step in this direction. This procedure can lead to formal approval of new methodologies and biomarkers for a therapeutic group\textsuperscript{70}. For example, the multiple biomarker score described in chapter IV could be approved through this procedure.

*Better timing: an early and continual dialogue*

As discussed earlier, a dialogue on the need for evidence requires a constructive discussion before evidence is generated. Furthermore, the scientific dialogue should not only start early but should also be continual. Collecting and evaluating post-marketing data is a very important step in protecting public health, and essential to adaptive approaches. Although agreements about post-marketing studies can in principle be made before first approval, adaptive approaches require continual reevaluations of plans for these studies on the basis of previous experiences with the medicine. However, studies by the Escher Project indicate that current scientific advice does not take place very early nor continual. An analysis of the national and European scientific advice procedures showed that most questions are asked about the later stages of the pre-authorization phase, e.g. discussion on the interpretation of Phase III guidelines when Phase III studies are already ongoing (Box 10). Advice concerning early medicine development post-marketing is less frequent.

The EMA has recently recognized that interaction with companies during the life-cycle of medicines should be improved, especially during early drug development and during post-approval about Risk management plans\textsuperscript{71}. We suggest that EMA could encourage a scientific dialogue at predefined, crucial time points in medicine development (post- and pre-approval). Relevant time points could be before the start of the non-clinical development, before start of first in human studies, before start of the confirmatory clinical studies and post-approval.
More stakeholder involvement: including health technology assessment bodies and patients

Alignment of requests for evidence by marketing authorization agencies and health technology assessment bodies is of key importance for adaptive approaches, and is also a major topic in strategy documents from various regulatory authorities (CBG, FDA, EMA). Without some form of alignment, health technology assessment bodies might decide that proper information is lacking for granting reimbursement of new medicines. This could lead to the situation that medicines would be granted early access to the market (e.g. within the context of adaptive approaches) but without the necessary reimbursement and user access. Furthermore, alignment of the requests to conduct post-marketing studies could contribute significantly to an efficient regulatory system.

Although HTA is currently not part of the scientific dialogue concerning specific medicines, the EMA and EUnetHTA have begun to explore how Scientific Advice could be harmonized with advice given by HTA bodies, and to establish the evidence that both groups need.

The EMA has recognized the need to involve patients in the scientific dialogue. Patient involvement will in particular be relevant in adaptive approaches to help define acceptable levels of risk and uncertainty. Studies by the Escher Project show that preferences of patients can indeed differ from those of regulators (Box 11).

**Box 11 – Patient and regulator preferences**

Several Escher studies have investigated the preferences of patients and regulators in relation to benefits and risks. One study demonstrated that patients weigh the influence of adverse effects on their daily lives heavily: according to diabetes patients, control of glucose and a small risk of cancer were considered less important than adverse effects affecting daily life (e.g. gastro-intestinal problems). By contrast, another study showed that regulators consider severe, but infrequent adverse drug events very important, and that they are less willing to trade higher risks on adverse drug events for more benefits. These studies show that although regulators evaluate the benefit-risk profile of medicines on behalf of patients, the preferences of regulators are different from those of patients.

Furthermore, one of the commissioned projects of the Escher Project plans to investigate how patient perspectives could be incorporated in regulatory decision making. Open questions are what an appropriate setting is for patient involvement, what the status of patient preferences should be, what an appropriate moment for patient involvement is, and in what cases/dossiers patient involvement is most valuable.
“[T]here are known knowns; there are things we know that we know.
There are known unknowns; that is to say there are things that, we now know we don’t know.
But there are also unknown unknowns – there are things we do not know we don’t know.”
Donald Rumsfeld

In this chapter we bring together our analysis about ‘how to achieve appropriate levels of evidence’ and suggest points of discussion concerning the topics of the preceding chapters: evidence generation and requirements, benefit-risk assessment and scientific dialogue. These discussion points presented here are tentative: not all these discussion points can or should be discussed within the context of the workshop on 6-7 December. Furthermore, we encourage readers to bring their own discussion points to the table. The main aims of the workshop are to propose (1) an agenda with actionable proposals for improving the regulation of medicine development and (2) a research agenda for regulatory science. To help shape these agendas, four types of question will be discussed during the workshop:

**Agenda for action:**

1. What can we do tomorrow to improve the regulation and development of medicines?
2. What is the long-term strategy to reform the regulatory system?

**Research agenda:**

3. What knowledge and instruments do we currently lack to solve issues?
4. What new concepts and visions might be worth developing?

**General discussion points concerning adaptive approaches (Chapter III)**

- How to safeguard public trust in a system that approves medicines with more uncertainty?
- Does current legislation provide sufficient flexibility to allow more (initial) uncertainty about medicines? For example, does current legislation on conditional approval need adaptation?
- Under what conditions is having early access to the market for companies worth giving up some of the predictability of the regulatory system?
- Besides adaptive approaches, what are attractive visions on the future of the regulatory system?
Discussion points concerning evidence generation and requirements (Chapter IV)

- What are the most promising ways to optimize evidence generation? (e.g. skip studies, more extrapolation, adaptive study designs, surrogate endpoints) And what are challenges in incorporating them in regulatory decision making?

- What role should regulators have in shaping new methods to optimize evidence generation? Could they take a more pro-active and leading role during the development of methods?

- What is needed to proceed from an approach to regulatory requirements and guidelines driven by compliance towards a more flexible approach?

- How to set up proper checks and balances for the development and evaluation of regulatory requirements/guidelines? What are proper methods for evaluation of requirements and how can these methods be implemented?

Discussion points concerning quantitative benefit-risk assessment (Chapter V)

- Are quantitative benefit risk instruments the way forward to improve consistency and transparency of decision making? Under what conditions? Or, what are alternatives?

- In what situations should benefit risk instruments be used: for internal regulatory decision making, for discussions with companies, for accountability to the public, for harmonization with HTA?

- What are challenges for the implementation of quantitative benefit risk assessment instruments?

- What are the key research objectives for further development of quantitative benefit-risk instruments?

Discussion points concerning scientific dialogue (Chapter VI)

- Is formal agreement about (elements of) the development plan of specific products the way forward? And under what conditions?

- What are proper moments for scientific dialogue? Should they be predefined by regulators?

- How, when and to what extent should patients be involved in the scientific dialogue?

- How, when and to what extent should health technology assessment bodies be involved in the scientific dialogue?


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**SUPPLEMENTARY INFORMATION**

**List of publications by the Escher Project**


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List of publications by the Escher Project


The authors gratefully acknowledge the support of Andre Broekmans, the board of the Escher Project, the Escher Project researchers and TIPharma.
**Applicants:** parties (e.g. pharmaceutical companies or academic groups) that intend to submit or have submitted a marketing authorization application.

**Benefit-Risk assessment:** evaluation of benefits (favourable effects) and risks (unfavourable effects) of a medicinal product.

**Committee for Medicinal Products for Human Use (CHMP):** committee of the European Medicines Agency responsible for conducting the initial assessment of medicines for which an EU-wide marketing authorization is sought. The CHMP is also responsible for several post-authorization and maintenance activities, including the assessment of any modifications or extensions (‘variations’) to an existing marketing authorization.

**Conditional approval:** procedure to grant marketing authorization to (i) medicinal products for treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or (ii) to medicinal products to be used in emergency situations or (iii) orphan medicinal products, on the basis of less complete data than is normally the case and subject to specific post-approval obligations.

**European Medicines Agency (EMA):** The European Union regulatory authority committed to the recommendation about marketing authorization of medicinal products.

**Food and Drug Administration (FDA):** The United States regulatory authority committed to the recommendation about marketing approval of medicinal products.

**Health Technology Assessment (HTA) bodies:** Health Technology Assessment bodies provide recommendations on medicinal products and other health interventions that can be paid for or reimbursed by the healthcare system in a particular Member State. Their recommendations are based on comparing the ‘relative effectiveness’ of medicines and taking into account their financial costs.

**Marketing authorization:** the (first) approval of a medicinal product by a regulatory authority, leading to access to the market

**Marketing authorization application:** the submission of a dossier for marketing authorization.

**Pharmacovigilance regulation:** regulation aimed at the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products for human use after they have been placed on the market.
**Glossary**

**Regulatory authorities:** authorities committed to the marketing authorization of medicines on a European or a national level; also called **competent authorities or regulatory agencies.**

**Regulatory system:** the system that regulates the development, marketing authorization and market access of medicines

**Risk Management Plans:** A Risk management plans contains a specification of risks associated with the medicinal product, important missing information and specifications of the obligation to conduct a post-authorization safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product

**Scientific advice:** the opportunity for applicants to discuss scientific and regulatory aspects of the marketing authorization application with a regulatory authority.

**Scientific guidelines:** guidelines on the studies of a medicinal product to demonstrate a product’s quality, safety and efficacy.