Benefit-risk methodology project: work package 1 report: description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network

Report
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Benefit-risk methodology project

Work package 1 report: description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network

Report by the EMA Benefit-Risk Methodology Project Team

Introduction

During the March 2008 plenary meeting, the Committee for Human Medicinal Products (CHMP) adopted the Reflection Paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use (EMEA/CHMP/15404/2007). One of the main recommendations for the CHMP was to explore further methodologies for benefit/risk analysis, including a wide range of quantitative and semi-quantitative tools, and involving experts and assessors. A consequence of this was the initiation of the EMA Benefit-Risk Methodology Project in which the five National Competent Authorities (NCAs) of France, The Netherlands, Spain, Sweden and UK volunteered to participate. A project team was formed involving experts in the field of decision theory.

The main objective of the EMA Benefit-Risk Methodology Project is the development and testing of tools and processes for balancing multiple benefits and risks, which can be used as an aid to informed, science-based regulatory decisions about medicinal products. This project is planned to be concluded in 5 consecutive work packages. The present report constitutes the deliverable of the first work package that was intended to describe the current practice of benefit-risk assessment for centralised procedures in the EU regulatory network. Included in the report are suggested opportunities for improvements and a list of criteria for assessing the usefulness of available tools and processes in the second work package.

Potential tools and processes for regulatory benefit-risk assessment must be adaptable to the current practice within the EU regulatory network. This is the reason why the first step of this project was to observe how the centralised drug approval process is implemented within each of the five participating agencies.

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Methods and procedure

Between June and September 2009, members of the project team were invited to visit five participating agencies (Sweden, France, The Netherlands, UK and Spain) for 2-3 days each. The purpose of the visits was purely observational, with the aim to extract an overall view of how B/R assessments are made Europe-wide. Care was taken to ensure that the visits did not interfere with the agencies' procedures.

In order to explore each agency's practice of evaluating and balancing benefits and risks, and to obtain a better understanding of the agency's decision making process, a number of people with a key role in the benefit-risk assessment and the regulatory decision making process were interviewed, primarily upon suggestion of the agency's host (CHMP member). The team was also invited to attend a number of meetings and observed how the process works in practice.

The project team interviewed 42 people across the five agencies (5 in Sweden, 6 in France, 9 in the Netherlands, 12 in the UK and 10 in Spain), encompassing a variety of roles: agency chairmen and directors, heads and co-ordinators of units, CHMP members, statisticians and a number of senior and junior assessors with different backgrounds and expertise (e.g., pharmacokinetics, toxicology).

Interviews were conducted individually for about an hour, with the exception of Spain where group interviews were conducted upon suggestion of the Agency's host. At the beginning of each interview, all interviewees were informed that our goal was to understand how they viewed benefits and risks, and what broader factors might influence the B-R assessment in their agency, within the scope of the centralized drug approval process. They were further assured that all views were anonymous and treated confidentially.

Interviews followed an observation protocol which was devised in May 2009 by the project team, and piloted with some internal EMA staff members. Following the first agency visit (Sweden), the protocol was subsequently revised and shortened. The observation protocol contained questions under the following eight summary headings:

Interview protocol
1) Agency's history and purpose 2) Agency's relationships with governmental and non-governmental organisations 3) Agency's organisational structure 4) Information flow 5) Meaning of "benefits" and "risks" 6) Benefit-risk assessment process 7) Consistency 8) Existence of models *(see Annex 1 for the full protocol and sub-questions)*

Findings

Our findings are summarised based on the previous eight summary headings.

1. The Agency's history and purpose frame the benefit-risk assessment process.

In all five countries, the NCAs were set up in the 1990s, except for The Netherlands, where the NCA dates back to 1963. The thalidomide tragedy provoked legislation that led to the founding of separate agencies in several countries, though some form of regulation had existed before, most notably in Sweden, whose agency history goes back to 1663 when pharmacy inspections began. All agencies are charged with ensuring that approved medicinal products work and are safe, but that requirement can be interpreted in different ways, which allows latitude for interpretation on issues of benefits and risks.

All agencies are now independent bodies, free of political or commercial pressures. Marketing authorisation is the final step of the national procedure in all the countries we visited except France, where a temporary authorisation for use can be issued. This possibility relieves some of the pressure for an early drug approval. The scope of the agencies differs; some are focussed only on human medicines, others deal also with medical devices or veterinary medicines. National and/or regional decisions about funding are handled in separate organisations (such as the National Institute for Health and Clinical Excellence in the UK).

The Medicines Evaluation Board in The Netherlands is the first regulatory agency to receive an ISO 9000-2001 certification for its quality management system, which covers the entire approvals process, including the people involved.

2. All the Agencies maintain extensive relationships with governmental and non-governmental organisations.

Most of the agencies we visited are increasing their relationships with external health-related bodies. Some make their expertise available to other organisations and may even be involved in their decision making process as required. They have established working relationships with universities, hospitals and scientists. All agencies often consult external experts for input in their procedures and maintain regular contacts with patient and consumer organisations. In the UK a patient representative attends the Commission on Human Medicines meetings and in Spain a consumer representative attends the Committee for the Evaluation of Medicines (CODEM) meetings.

To varying degrees, all five agencies consider their role beyond national borders. For example, the Swedish Agency's charter recognises the importance of linking to Europe and the Spanish Agency is also involved in Hispano-speaking areas of South America. All recognise a role in a larger European network, and they wish to achieve and influence a common view throughout Europe on benefit/risk issues.

3. Agency organisational structures vary greatly, some directly affecting benefit/risk assessment, others doing so more indirectly.

It was sometimes difficult to discern the on-the-ground, operating organisation structure of some agencies, though all said that the structure affects benefit/risk assessment activities. Sweden and France made it clear that they operate a matrix structure, separating the scientific and administrative functions; the latter has no accountability for benefit/risk decisions. Separate organisational units in

each agency cover some combination of therapeutic areas, safety, quality, pharmacovigilance, herbal medicines, novel foods, information processing, generics, OTCs, and veterinary medicinal products. It is clear that the structures are more formal in some agencies than in others. In Sweden, for example, anyone can talk to anyone else, and the two CHMP members don't appear at all on the organisation chart. Weekly meetings of assessors and this open climate, plus everyone located in one building, makes it easy to discuss any issue with whoever has the knowledge. The climate is even easier in Spain, where informal contact is the main vehicle for communication. The Dutch, on the other hand, are dispersed at three locations, The Hague, Groningen and Nijmegen, so their contact is more formal in meetings, which also satisfies the requirements of the ISO process. It is these variations in geography and culture that have led to differences in the structures, but all are aimed at ensuring the right information and advice is provided to enable benefit/risk judgements to be made.

4. Information flows differ considerably in the agencies, varying from the formal to the informal.

Dossiers received are usually distributed directly to teams, with the exception of France, where they are disseminated to individuals. In France, the clinical assessor receiving the dossier is in charge of the efficacy assessment and of assembling the whole assessment report, in close collaboration with quality, preclinical, and pharmacovigilance assessors. Informal peer review operates during the preparation of the CHMP assessment report.

In Sweden, the dossier is distributed to five relevant function/task groups: pharmacy/biotech, toxicology, pharmacokinetics, clinical and pharmacovigilance. The outputs of each are peer-reviewed and then combined into an overall assessment which goes to the Quality Assurance Committee. The QAC is advised by an Advisory Group, and the QAC-agreed-assessments are then input to the CHMP.

A similar process operates in the Netherlands, but with the dossiers going to therapeutic groups, each of which assembles a team of internal assessors, plus some external experts. The Product Leader ensures that functional area input is provided: quality, pre-clinical, pharmacovigilance, etc. Informal peer review, similar to France, operates during the preparation of the report to the CHMP and at the end of the finalisation of the report. Each group is certified ISO, and is responsible for its post-certification report.

The groups receiving the dossier in Spain are functional: quality, non-clinical, clinical, pharmacovigilance and Quality Review of Documents. Sometimes in Spain the Rapporteur may convene a meeting of all relevant parties, but in other cases it is not necessary because a view has been formed just through the process of interaction that includes consultations via telephone and email.

The MHRA's six Product Lifecycle Assessment Teams (PLAT) are organised by therapeutic area: cardiovascular and diabetes; respiratory, ear, nose & throat, endocrine and dermatology; central nervous system, and anaesthetics; gastrointestinal & nutrition, and blood; anti-infective, obstetrics & gynaecology, and urinary tract; musculoskeletal and malignant disease. Each team has its own clinical assessors, while the non-clinical assessors, including the quality assessors, go around to different PLATs. The reports from PLATs form the basis for the final benefit-risk assessment by the Commission for Human Medicines.

In all the participating agencies, a highly interactive process occurs, with peer review taking place informally by senior people guiding junior people, or more formally with separate peer reviews. In most agencies the assessors are mainly internal with the exception of Spain where there is a mixture of internal and external assessors. External expertise is involved in France, UK and Sweden. Interestingly, the Dutch agency uses clinical assessors with diverse scientific backgrounds (not only medical doctors). Occasional scepticism was expressed by some assessors about university-based

experts who lack clinical experience because they tend to give clear recommendations as if there is no uncertainty. In most agencies statisticians advise upon request, with the exception of UK and Sweden where statisticians work full time in the agencies and advise all the teams.

5. The meanings of "benefit" and "risk" are very fluid.

Many interviewees found it difficult to define precisely what is meant by a "benefit". Most interviewees in all agencies agreed that benefits are clinically meaningful improvements to a patient, an improvement in health state or quality of life. Others said it was an improvement over a placebo, or at least "non-inferior to comparators; a statistically significant effect; a change in the disease management of a patient; a better way of delivering a drug; or even a safety improvement. Clearly, these definitions go beyond traditional views of efficacy in their concern for effectiveness and, as Annex 2 shows, they varied across interviewees within and across agencies.

An even greater variance within and across agencies was observed when asked to define what is meant by a "risk", which was found more difficult and challenging to answer compared to "benefit". Risk could mean many things: absence of benefit; dangers/hazards for the patient, adverse events, direct or indirect harm to the patient, frequency and severity of a side effect; harm to non-patients and to the general public; unacceptable damage to the patient; what is lost compared to current therapy; the negative aspects of a drug; the inverse of safety; pharmacokinetic interactions; insufficient duration; probability of an adverse event or harm; negative impact on quality of life; failure to meet endpoints; intolerability; uncertainty surrounding the risks; mortality; "a concept of gambling which includes perception". Many felt that while benefits are objective, risks are not and are more difficult to define (See Annex 2 for the list of different definitions of what is a "benefit" and "risk"). Overall, more varied definitions were given for risks than for benefits.

At this point in our interview, we explained to our interviewees that, from a decision-theoretic perspective, any drug decision could be decomposed into two broad components: Firstly, the favorable ("good things") or unfavorable ("bad things") effects for the patient; secondly, the level of uncertainty surrounding each of them.

These two aspects are illustrated in the following 2 by 2 matrix/table, where the first column represents the "values" and the second column represents associated "uncertainties". The strength of this representation is that it is backed up by solid decision theory[1].

GOOD THINGS	Uncertainty of good things
BAD THINGS	Uncertainty of bad things

[1] *Goodwin P, Wright G. Decision Analysis for Management Judgment, 4th edition. Chichester: John Wiley; 2009.*

We asked if this four-fold way of thinking could encompass all aspects of benefits and risks, and typically the interviewee agreed. Some raised the question about the placement of the adequacy of an experimental design in this table, and we explained that it would impact uncertainty about the good or bad things, or even both.

We then asked most of the interviewees to allocate 100 points to each of the four quadrants to reflect the time and effort devoted to analysing each cell, on average, for the centralised procedure. A few people felt they couldn't manage this task, either because different contexts would yield different distributions of points, or because their expertise was too specialised to know what was happening in all four quadrants. However, 25 people gave specific point distributions (2 managed to give only qualitative answers) about the relative time and effort spent on top vs. bottom row or left vs. right column.

The data show great variation in people's perception of the distribution of time and effort, both within and between agencies. Sixteen of the 27 interviewees placed more points on the first column, good and bad things, many arguing that these things are clearer in the dossiers than uncertainty. Thirteen interviewees said that more time and effort was given to the first row, good things and their uncertainty, than the second row, though 9 gave the rows equal importance. Only 5 of the 27 interviewees gave more points to the bottom row, bad things and their uncertainty. We could not discern any consistent pattern that could be associated with the role of the interviewee, except for the statisticians, who spend more time and effort on uncertainty, as would be expected. We discovered that explanations for the point distributions were not very helpful, especially when we heard the same explanation given for opposite distributions. For example, some said that more time was spent on the left column because that information was clearer in the dossier than the uncertainties, while others said the opposite—because the uncertainties were not so clear presented in the dossier, they spent more time on the right column. Overall we were left with the impression that at the beginning of the assessment process attention is more concentrated on the left column whereas towards the end of the procedure the assessors focus more on the right column, since uncertainty is often highlighted during the CHMP discussions.

The mean number of points in each of the four cells, for the 25 interviewees who gave specific point distributions, is shown below.

GOOD THINGS Mean = 33	Uncertainty of good things Mean = 25
BAD THINGS Mean = 22	Uncertainty of bad things Mean = 20

So, on average, more time and effort is spent on favourable effects and their uncertainty than on unfavourable effects and their uncertainty. Most time is spent on favourable effects, least time on the uncertainty about unfavourable effects.

When we asked for the order in which the four cells were addressed in dealing with a dossier, nearly everyone started with the upper left cell, arguing if there is no favourable effect, there is no need to deal with the rest. But after that start, some interviewees proceeded clockwise around the matrix, others went anti-clockwise, and some proceeded left-right on both rows.

We are left with the impression that this diversity of viewpoint is related to the lack of agreed definitions of what represents benefits and risks. It was clear to us that the mental models of the interviewees are not structured as in the above 2-by-2 matrix. As Annex 3 shows, there is a great convergence in defining benefits as "good things" or favourable effects, as all but three definitions given fall in the top left cell of the matrix (with 3 exceptions defining a benefit as something uncertain, possible, to be supported by data and statistical tests). On the contrary, there is less convergence in the perception and interpretation of risks. The definitions given to "what is a risk" fall across all four quadrants, although the majority belongs to the "bad things" (or unfavourable effects) cell, 10 definitions belong to the "uncertainty of bad things" cell (e.g., frequency of side effect), one belongs to the "uncertainty of realizing a good thing" cell and 2 belong to the "good things" quadrant (counting risk as the lack of benefit).

The revised version of the Guidance for the CHMP Day 80 Assessment Report (AR)[2] overview uses this four-fold model, defining benefits as 'favourable effects' and risks as 'unfavourable effects'. It asks for the favourable effects to be described, and also the uncertainty about the knowledge of the favourable effects to be explained. Then it asks for the unfavourable effects and their uncertainty to be described. This update on the benefit-risk section of the AR was the result of our finding about the lack of agreement about the meaning of benefits and risks.

6. The benefit-risk balance is assessed mainly intuitively, the responsibility of an accountable senior assessor in some agencies or of a group in other agencies, as a result of extensive discussion.

Everyone agrees that the benefit-risk balance is a matter of expert judgement, and that this is the most difficult step in the approval process. Many pointed to the importance of context: the patient population, the severity of the disease, availability of a comparator, etc. The balance is particularly difficult to judge "when risks cannot easily be explained to patients", "when the drug is good on efficacy but has serious adverse events", "when the benefit is smaller than expected", "when there is high uncertainty", "when the endpoint is not well defined", "when there are differences of opinion in the agency", "when people may be unduly influenced by recent experience and their feelings may spread to the group", or "when the data aren't persuasive." These difficulties are met through further discussions, consultations and debate, rarely by a final vote.

In some agencies, the benefit-risk balance is concluded in a group meeting, and then it is presented by the Rapporteur to the CHMP. Feedback from the CHMP is typically reported back to the group. In other agencies, the aggregation is done by a senior assessor individually, after the input from the expert group discussion is taken into account.

[2] CHMP Day 80 AR Overview Guidance (as adopted in September 2010): http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004800

7. Consistency is important.

All agencies highlighted the importance and expressed concern about being consistent in their approvals. The EMA Guidelines are/were found useful, and help to create consistency at the European level. All agencies rely on the experienced assessors to preserve consistency. In the Netherlands and the UK, they look at previous cases to test whether their arguments in the current case are valid, but could go in a new direction if the evidence warranted it. In Sweden, their low turnover and the fact that everyone is placed in the same building help maintain an intact and accessible regulatory memory. In France, they have set up an internal group that discusses monthly cases found to be challenging with a view to ensure consistency in the national procedure. Nobody mentioned routinely consulting their organisation's databases for past similar cases.

8. There is no system or model currently used by any agency.

The only structured support currently used for B/R assessment is the Template-Guidance document for the CHMP Day 80 AR. Suggestions from the interviewees for improving the benefit-risk decision process included help in translating data to benefits and risks, a good template, spelling out/listing of criteria (both short- and long-term), prompts for efficacy, check lists of good and bad things, information on whether or not a comparator is important, better structure of the B/R discussion to avoid repetition, experienced clinical assessors, training courses, guidelines for the decision process, a model from the start (and at every stage) to help cope with the amount of information gathered in the assessment, scoring and weighting systems, and input from lay people. Many commented on how well the process works now, but all agreed it could be improved.

Discussion and Conclusions

In the five agencies visited, their history, purpose and current context all impact their organisation structure, which in turn affect the process of approving drugs. Some agencies are focused on human products, others deal also with animal products and other concerns; some are more self-contained, others rely on outside experts; some have adopted more formal procedures, others rely more extensively on informal communications; some hold individuals accountable for aspects of the regulatory process, others hold groups accountable. There is clearly not one 'best' structure or process, even though in all five agencies these are tuned to each organisation's objective of ensuring that medicinal products work and are safe.

A major finding is the variability of interpretations, both within and between agencies, given to 'benefit' and 'risk', particularly to the latter. This divergence of meanings suggests that the mental models regulators employ in balancing benefits and risks, in order to arrive at decisions to approve or not, may slow down the approval process and could lead to inconsistencies, both of which are concerns of regulatory agencies. On the other hand, group-oriented approval processes, as in the CHMP, can provide a means for exploring the differences so that a more robust consensus view can emerge.

Our suggestion of thinking about benefits and risks in terms of 'good things' and 'bad things' and the uncertainties associated with both, was accepted by all interviewees, and, we consider, could help toward clarifying the benefit-risk balance. At the very least, this should improve communication among regulators, and at best provide improved transparency and auditability of regulatory decisions.

In parallel with these findings there was a significant input from the project team to the B/R section of the revised template-guidance of the CHMP Day 80 Assessment Report. Based on the experience from the interviews with the assessors the team proposed the distinction of benefits and risks to favourable

and unfavourable effects, each one linked to its relevant uncertainty. This approach reflects the 2x2 matrix concept described above and was endorsed in the updated version of the guidance-template.

Overall, this work package has achieved our goal of gaining an understanding of how European regulatory agencies work. In all five agencies, the requirements of the centralised procedure are met, but in different ways. While there are many similarities among the countries, we observed substantial differences, making it clear to us that our next steps must take account of contextual differences. Any form of decision aiding must include a bespoke element, as off-the-shelf decision aids will not be universally helpful.

Next steps

Models could further support the process of making the B/R balance explicit, transparent and auditable. They can enhance communication among regulators and between regulators and pharmaceutical companies or the public. In exploring the potential usefulness of decision aids, we will focus on tools and processes that are fit for purpose, or 'requisite', neither overly complex nor too simple to be of use.

In taking account of agency differences, it will be necessary to look carefully at decision aids that can be helpful without disrupting the current effective flows of information. In addition, it is evident that the helpfulness of a decision aid might be different depending on whether the way of working in an agency is more formal or more informal.

Any decision model/tool has to be evaluated under specific criteria in order to verify its applicability for regulatory B/R assessment. Based on previously established knowledge and taking into account suggestions for improving the benefit-risk decision reported in paragraph 8, above, we composed a list of criteria for appraising tools and processes. This list below includes five major criteria and their sub-criteria.

1. Logical soundness

- The overall benefit-risk evaluation is decomposed into separate elements that are demonstrated theoretically and/or empirically to be meaningful.
- The elements are recombined according to a theoretically sound rule.
- The approach is coherent, that is, it ensures that related decisions based on the approach do not contradict each other or the objectives that are to be met.
- The approach aids rational thinking about benefits and risks.
- The approach gives results that do not change relative evaluations when alternatives are added or removed.

2. Comprehensiveness

- The approach can handle any form of data, continuous or discrete, qualitative or quantitative data, objective or subjective.
- The approach can accommodate uncertainty and value judgements, time preferences and risk attitudes.
- The approach makes multiple objectives and trade-offs explicit.

3. Acceptability of results

- The approach provides consistency checks that identify inconsistencies in the data and in people's judgements.
- The outputs of the approach should be understandable and interpretable in the user's terms, readily understandable and in quantitative form to facilitate comparison between options.
- The approach should be 'scrutable' in that it should make sense to anyone using it and be seen as a realistic way to evaluate benefits and risks.

4. Practicality

- Implementation of an approach should be economical in the use of participants' time.
- The approach should be easy to teach and easy to use.
- The approach should be adaptable to either formal or informal agency structures.
- Additions or deletions to the approach should be possible without having to re-do existing inputs.
- Extending a model based on the approach should grow linearly with its inputs.
- Computer support should be available for any approach, enabling the user to make changes quickly and provide immediate feedback. The functionality of the software should include clear and effective graphical displays, and support for sensitivity analyses.

5. Generativeness

- The output of the approach should link clearly to action.
- The approach should provide a clear audit trail so that all aspects of the benefit-risk evaluation can be traced.
- The approach should develop insight and promote learning about benefit-risk evaluation.
- The approach should transform a fragmented, covert benefit-risk evaluation into an overt structure and set of rational processes.
- The results should be readily communicable and easily understood.

In the second work package we will assess the applicability of existing tools and processes that have appeared in the literature and can potentially aid the regulatory B/R assessment. The above list of criteria will be the basis for this evaluation.

Disclaimer

This report was sponsored by the European Medicines Agency in the context of the Benefit-risk methodology project and the views expressed are those of the authors.

Annex 1: Interview protocol used in the cross-agency comparison.

Observation Protocol

Agency: _____

Date of visit: _____

Interviewers: _____

_____

Interviewee's role_____

The general aim of this questionnaire is to gather information about different practices and to extract an overall view of how B/R assessments are made Europe-wide. All views are kept anonymous and will be treated confidentially.

Impact on B/R assessment of:

1 Agency's history and purpose

We expect that the purpose for which the agency was set up has an impact on how you view benefits and risks.

Why was your agency set up and when?

What is it supposed to do?

2 Agency's relationships with governmental and non-governmental organizations

What relationships do you have with other organizations, both within and outside your country and how might they have an impact on B/R assessments?

Do these "external" perspectives enter in the B/R assessments?

Who holds the final authority for approving a drug in your country?

3 Agency's internal structure

Does your internal organizational structure reflect or affect how B/R are assessed (pre- and post-marketing approval).

Is there an organizational chart available? If so, use it to explain structure as given on the chart.

Does the agency actually work this way?

4 Agency's information flow

What is the "flow of information" to and from the EMEA in the process leading to the CHMP?

Is this standard, or does this further depend on unit/therapeutic area?

5 How is information for the B/R decision processed?

What does your agency/you think of as "benefit"?

What does your agency/you think of as "risk?

Do you think different people in your agency are agreed on what they mean by benefit and risk?

If the answer is: no, what does this variety of views depend on?

Any drug decision can lead to good things and bad things for the patient. Both have some uncertainty surrounding them.

GOOD THINGS	Uncertainty of good things
BAD THINGS	Uncertainty of bad things

Imagine you have a pot of 100 points. Please allocate them according to the time and effort devoted to analyzing each cell, on average, for the centralized procedure.

Is there a specific order in which you assess info in the “4 quadrants”?

How do people make the B/R balance?

Are there situations in which the B/R balance is difficult to derive? If so, explain.

How do you come up with an evaluation of the desirability of good and bad things?

How do you deal with uncertainty of good and bad things?

So far we have focused on the benefits and risks of the drugs themselves as patients might experience them. Considering now the perspective of your agency, are any other criteria considered in the decision to approve or not? If so, what are they?

How do you reconcile conflicting views?

Is consensus required and how is it achieved?

Have issues of consistency come up and how do you address them?

What would help the agency to improve the benefit-risk decision?

6 Is the national agency procedure different? If yes, how?

7 Is there anything else you would like to contribute?

Annex 2: Definitions of Risk and Benefit by NCA

NCAs	Benefits	Risks
1	1. everything good 2. improvement in health state 3. effectiveness in the real world 4. efficacy in clinical trials (equivalent to positive effect) 5. clinical relevance 6. improvement of illness 7. potential good effects	*1. all that is negative* *2. inverse of safety* *3. adverse events* *4. loss of efficacy (e.g.) a company's inability to keep quality intact)* *5. kinetic interactions* *6. hurt to patients, variable depending on context* *7. side effects* *8. serious adverse effects* *9. reduction in quality* *10. bad effects*
2	1. "drug works" 2. positive action of a drug 3. unmet medical need 4. positive improvement in health state that is perceived by patient 5. everything that improves health or reduces problem of safety, efficacy in clinical trial 6. safety improvement 7. improvement of convenience/quality of life for patient	*1. danger for the patient* *2. adverse events* *3. likelihood of negative event* *4. inverse of benefit* *5. harm* *6. long term and short term safety profile* *7. frequency and severity of side effect* *8. direct harm on patient* *9. indirect harm through misuse by patient* *10. harm on non-patients/general public*
3	1. efficacy for the patient, supported by data, externally validated and clinically relevant 2. patient's function and survival 3. value compared to the placebo 4. non-inferior to comparators 5. efficacious 6. an improvement that is meaningful to the patient 7. depends on context	*1. more difficult to define* *2. more difficult to draw hard conclusions about* *3. not objective* *4. diverse* *5. linked to benefits* *6. frequent but harmless or infrequent but serious* *7. how patients tolerate a drug compared to serious side effects like death*

NCAs	Benefits	Risks
	8. more than pharmacological activity 9. pre-defined efficacy for a pre-defined population 10. for vaccines, prevention of disease; for antibiotics, elimination of the microbe; for metabolic disease, maintenance; less adverse effects 11. positive effects 12. a statistically significant effect 13. changes in the management of a patient re disease progression	*8. effects observed after a drug is approved* *9. serious events* *10. withdrawal* *11. impact on pregnancies* *12. severity of side effects* *13. chance the benefit won't be realised* *14. the inverse of short-term and long-term safety* *15. for vaccines, reactogenicity (e.g., fever); development of resistance; vaccine failure* *16. possible negative effects (or probability)* *17. frequency and severity of side effects* *18. what we don't want in this compound* *19. depends on the disease* *20. unacceptable damage to the patient*
4	1. an improvement to the patient, quality or quantity of life, survival 2. amelioration of symptoms 3. suffering reduced, 4. preventative improvement in health and well-being 5. social benefits, 6. a measurable change in the right direction in a parameter that matters 7. a parameter that everyone agrees about 8. something positive 9. a good medicine, safe, efficacious 10. a decent primary endpoint translated to the patient being better off.	*1. harms* *2. adverse reactions* *3. severity* *4. duration* *5. quality of life* *6. probability of an adverse event or harm—trivial or serious* *7. negative impact on quality or quantity of life* *8. detriments to health* *9. failure to meet endpoints* *10. not as expected* *11. tolerability* *12. potential or theoretical risks (there is still a lot unknown after clinical trials; a signal may have been obtained from pre-clinical studies)*

NCAs	Benefits	Risks
		13. *uncertainty surrounding the risks* 14. *side effects* 15. *mortality* 16. *a concept of gambling which includes perception*
5	1. easy to perceive 2. variable between people 3. dependent on the therapeutic area, can improve quality of life (hard to measure) 4. prolong life (easy to measure) 5. treat disease symptoms 6. hard to generalise from the individual to the population 7. useful to the patient 8. anything good for the patient 9. safety 10. efficacy and quality 11. something positive even if associated with risks 12. beneficial to the patient 13. added value of new therapy over the present one 14. more convenient way of delivering the drug	1. *anything harmful to the patient; related to quality, safety or lack of efficacy* 2. *worse in some respect to other medicinal products* 3. *what you lose compared to current therapy* 4. *any detrimental effect on the patient* 5. *side effects* 6. *no benefit* 7. *adverse reactions* 8. *no treatment* 9. *Linked to use of a drug after approval, when the risks may be different from those observed in the clinical trials, especially if the target population were to be different*

Annex 3: 2 x 2 partitioning of benefits and risks (in italic) listed in Annex 2.

Good things	Uncertainty of good things
1. everything good 2. improvement in health state 3. effectiveness in the real world 4. efficacy in clinical trials (equivalent to positive effect) 5. clinical relevance 6. improvement of illness 7. "drug works" 8. positive action of a drug 9. unmet medical need 10. positive improvement in health state that is perceived by patient 11. everything that improves health or reduces problem of safety, efficacy in clinical trial 12. safety improvement 13. improvement of convenience/quality of life for patient 14. patient's function and survival 15. value compared to the placebo 16. non-inferior to comparators 17. efficacious 18. an improvement that is meaningful to the patient 19. depends on context 20. more than pharmacological activity 21. pre-defined efficacy for a pre-defined population 22. for vaccines, prevention of disease; for antibiotics, elimination of the microbe; for metabolic disease, maintenance; less adverse effects 23. positive effects 24. changes in the management of a patient re disease progression 25. an improvement to the patient, quality or quantity of life, survival 26. amelioration of symptoms 27. suffering reduced, 28. preventative improvement in health and well-being 29. social benefits, 30. a measurable change in the right direction on a parameter that matters 31. a parameter that everyone agrees about	35. efficacy for the patient, supported by data, externally validated and clinically relevant 36. potential good effects 37. a statistically significant effect *51. potential or theoretical risks (there is still a lot unknown after clinical trials; a signal may have been obtained from pre-clinical studies*

Good things	Uncertainty of good things
32. something positive 33. a good medicine, safe, efficacious 34. a decent primary endpoint translated to the patient being better off. 52. *inverse of benefit* 53. *linked to benefits*	

Bad things	Uncertainty of bad things
1. *all that is negative* 2. *adverse events* 3. *loss of efficacy (e.g. a company's inability to keep quality intact)* 4. *kinetic interactions* 5. *side effects* 6. *serious adverse effects* 7. *reduction in quality* 8. *bad effects.* 9. *danger for the patient* 10. *adverse events* 11. *harm* 12. *long term and short term safety profile* 13. *severity of side effect* 14. *direct harm on patient* 15. *indirect harm through misuse by patient* 16. *harm on non-patients/general public* 17. *how patients tolerate a drug compared to serious side effects like death* 18. *effects observed after a drug is approved* 19. *serious events* 20. *withdrawal* 21. *impact on pregnancies* 22. *severity of side effects* 23. *for vaccines, reactogenicity (e.g., fever); development of resistance; vaccine failure* 24. *severity of side effects*	41. *frequency of side effect* 42. *likelihood of negative event* 43. *frequent harmless or infrequent but serious* 44. *chance the benefit won't be realised* 45. *possible negative effects (or probability)* 46. *probability of an adverse event or harm—trivial or serious* 47. *not as expected* 48. *uncertainty surrounding the risks* 49. *a concept of gambling which includes perception* 50. *hurt to patients, variable depending on context*

Bad things	Uncertainty of bad things
25. what we don't want in this compound	
26. depends on the disease	
27. unacceptable damage to the patient.	
28. inverse of safety	
29. the inverse of short-term and long-term safety	
30. harms	
31. adverse reactions	
32. severity	
33. duration	
34. quality of life	
35. negative impact on quality or quantity of life	
36. detriments to health	
37. failure to meet endpoints	
38. tolerability	
39. side effects	
40. mortality	

Annex 4: Visit to Paul-Ehrlich-Institut, 9 February 2010

After completing the visits to the five National Competent Authorities, a visit to the Paul-Ehrlich-Institut (PEI) in Germany with respect to the specialized areas of vaccines and biomedicines was considered of value.

PEI, in contrast to the other agencies, is divided by product related divisions. In total, 13 assessors from the different divisions of PEI were interviewed, following the same method of group interviews as in the Spanish agency. These interviews confirmed the key findings previously mentioned in this report, namely that there are varying views on what is a risk and a benefit, with risks being generally harder to define. Interestingly, perhaps because of the mission and nature of PEI, the interviewees mentioned more often than in other agencies a concern for 'quality'. In line with the fluid distinction between risks and benefits, some interviewees described quality as a benefit, others as a risk.

At PEI, like in the other agencies, there is no structured approach for the benefit-risk balance; the weighing and balancing of benefits and risks is an implicit process based on expert judgment that varies according to the category of pharmaceutical product (e.g. allergens differ from vaccines). When asked to describe the process, assessors at PEI confirmed the implicit process of benefit-risk balance that was described in this report: First start from the benefits ("Is there a clinically significant benefit?"), next turn to the "risks" side ("look at adverse events"). It was interesting to note that, as in the other agencies, the evaluation of risks is acknowledged as being influenced by the initial evaluation of benefits. "If so (i.e. if there is a clinically significant benefit), look at adverse events. Are they acceptable for the patient?" While this is understandable, this suggests the possibility that a certain 'risk factor' might be assessed as posing higher risks if evaluated after evidence of low benefit than after evidence of high benefit. In other words, this suggests that the benefit-risk balance could be systematically affected by the order with which information is seen.

The benefit-risk assessment is generally achieved via group discussion and an established peer review system. The fields of advanced therapies and monoclonal antibodies were considered as the most challenging in terms of benefit-risk assessment due to multidimensional aspects of benefits and risks. Other type of products have harmonised criteria/definitions for assessing benefits and risks, thus facilitating the benefit-risk assessment.

Suggestions made by the assessors for the improvement of the benefit-risk assessment were aligned with those expressed in this report, and included:

- A well structured presentation of the relevant data on benefits and risks

- A common unit for comparing benefits and risks

- A thinking tool/model that could add transparency

- A tool to help them deal with uncertainty and with complicated sets of data

Annex 5: Overview of the EMA centralised procedure

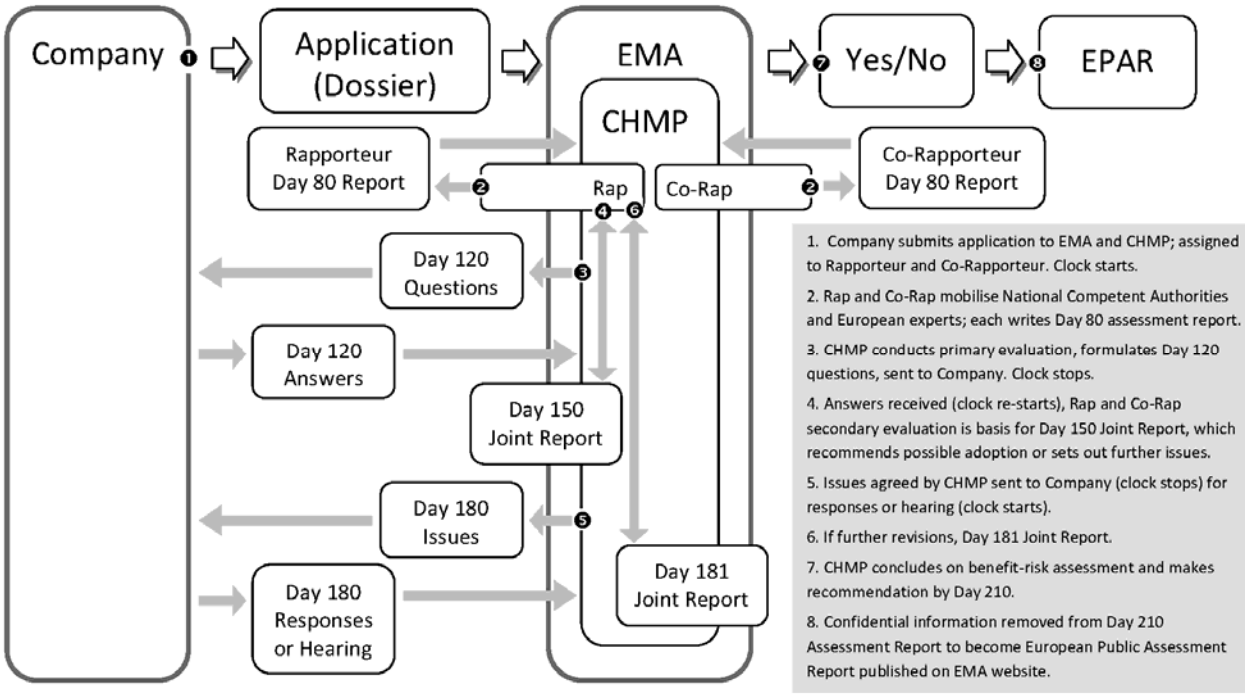

Figure: The centralised procedure for approving medicinal products in the European Community. Grey arrows indicate information flows.

Table: Timeline for the centralised procedure

Day	Action
1	Start of the procedure
80	Receipt of the Day 80 Assessment Reports with draft list of questions from Rapporteur and Co-Rapporteur by CHMP members and EMA. EMA sends reports to the applicant.
100	Rapporteur, Co-Rapporteur, other CHMP members and EMA receive comments from Members of the CHMP (incl. peer reviewers).
115	Receipt of draft list of questions from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMA.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA. Clock stop
121	Submission of the responses and restart of the clock.
150	Joint Assessment Report from Rapporteur and Co-Rapporteur received by CHMP members and EMA. EMA sends joint Assessment Report to the applicant.
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-Rapporteur, EMA and other CHMP Members.

Day	Action
180	CHMP discussion and decision on the need for adoption of a list of outstanding issues and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped.
181	Clock restart and oral explanation (if needed)
210	Adoption of CHMP Opinion + CHMP Assessment Report