



European Medicines Agency

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Information on benefit-risk of medicines: patients', consumers' and healthcare professionals' expectations

Executive Summary

Patients today are increasingly involved in discussing with healthcare professionals about their choice of treatment. It is crucial that there is a clear understanding of the benefits and risks of medicines to help them reach a decision on the most suitable treatment for the individual patient. Following a request from patients, consumers and healthcare professionals, the European Medicines Agency carried out a survey to find out ways to improve the information it provides on the benefits and risks of medicines.

Eleven patients' and consumers' organisations, twelve healthcare professionals' organisations in the European Union and representatives of the European Medicines Agency took part in this survey. They were asked to fill in a questionnaire on their understanding and expectations in terms of communicating the benefit and risks of medicines. This was followed by a workshop, where the participants had the opportunity to share their experiences and to make proposals for improvement.

The results of this joint project highlighted that patients and healthcare professionals focus their consideration on the benefits and risks for individual patients. However, because medicines are assessed at the population level, the results of these assessments may not always be reproduced at individual level. It is therefore important that information on medicines be transmitted as clearly as possible so that the information gathered at population level can be best applied to each individual. Patients and healthcare professionals recommended that benefits and risks must always be communicated together, clearly explaining the benefits on one hand and the risk on the other. Where possible, there should also be a clear description of the factors that could have an impact on the benefits or the risks for individual patients. The participants also recommended that concise easy-to-read summaries of benefits and risks of medicines should be presented alongside more comprehensive scientific data.

The European Medicines Agency together with the Patients' and Consumers' Working Party (PCWP), and the Healthcare Professionals' Working Group (HCP WG) have prepared a report on the outcome of this project and proposals for action. The Agency will continue to work with patients, consumers and healthcare professionals to improve the quality of information on medicines based on the recommendations made in this survey. In particular, the Agency will consider involving more stakeholders in preparing relevant information, making outcome of scientific assessments more accessible and using additional communication tools.

[Please follow the link to a presentation prepared by the Agency that summarises the main outcomes of this project](#)

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Table of Contents

Report

Introduction	3
Background.....	3
Design of the project.....	4
Results of the survey and workshop.....	5
Discussion and proposals for action	9
Action plan	11

Annexes

Annex I Organisations and Committees involved in the discussion	13
Annex II Compilation of answers received from patients' and consumers' organisations	14
Annex III Compilation of answers received from healthcare professionals' organisations.....	24
Annex IV Compilation of answers received from regulatory authorities	33

Information on benefit-risk of medicines: patients', consumers' and healthcare professionals' expectations

Report by the Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Group (HCP WG)

Introduction

The European Medicines Agency (EMA) Road Map¹ and the recommendations and proposals for action of the EMA/CHMP Working Group with Patients' Organisations² have emphasised the important challenge of providing adequate information on the benefits and risks of medicines.

The EMA's Committee for Medicinal Products for Human use (CHMP) has recently reviewed the way it conducts benefit-risk evaluation for the authorisation of medicinal products and issued a reflection paper on benefit-risk assessment methods³.

The present document addresses the communication aspect in the light of society's need for transparent information on the benefits and risks of medicines. It has been prepared in association with patients' and healthcare professionals' organisations and the EMA with the objective of making proposals to further fulfil patients' and healthcare professionals' expectations. It focuses on communication on benefits and risks of medicines provided in regulatory information, i.e. product information (summary of product characteristics, labelling and the package leaflet), public assessment report and product safety announcements.

Background

Nowadays, patients and consumers are increasingly involved in making decisions regarding their treatment. This trend has led to a partnership between patients and healthcare professionals in the choice of treatment and medicines, where exchange of information on benefits and risks is crucial.

With the increasing communication on medicine through various media channels, such as the internet, public access to reliable and good quality information is essential⁴. In this respect it is important to bear in mind that healthcare professionals and competent authorities remain primary sources of information on medicines⁵. This is illustrated in a recent study in the United Kingdom (UK)⁶ which showed that healthcare professionals are the most trusted source of information on benefits and risks of medicines to

¹ EMA Road Map to 2010 (<http://www.ema.europa.eu/htms/general/direct/roadmap/roadmapstatus.htm>).

² EMA/CHMP Working Group with Patients Organisations Outcome of Discussions: Recommendations and Proposals for Action (EMA/149479/2004 Final, 17 March 2005).

³ CHMP Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use (<http://www.ema.europa.eu/pdfs/human/brmethods/1540407enfin.pdf>).

⁴ Final Conclusions and Recommendations of the High Level Pharmaceutical Forum (2nd October 2008) (http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf).

⁵ Council Conclusions on the Communication from the Commission to the European Parliament and the Council concerning the report on current practices with regard to provisions of information to patients on medicinal products, in accordance with Article 88a of Directive 2001/83, as amended by Directive 2004/27/EC on the Community code relating to medicinal products for human use.

⁶ Risks and Benefits of Medicines and Medical Devices – Perceptions, Communication & Regulation - Overview of Ipsos MORI Research Conducted for The Medicines & Healthcare products Regulatory Agency (MHRA).

patients. Package leaflets represent the second source of information while it is younger people who are more inclined to refer to the internet to find additional information. Finally, this research showed that public awareness of regulatory agencies⁷ is very low.

Marketing authorisation of medicines in the European Union is supervised by regulatory agencies with national competent authorities and EMEA working together in the European regulatory system network. The EMEA is based in London and coordinates the best possible scientific resources of Member States to evaluate medicines⁸ for the benefit of public and animal health. The product information, consisting of the summary of product characteristics, the labelling and the package leaflet (information to be provided in the packaging of the medicine), is part of the marketing authorisation and is publicly available. In addition, regulatory agencies are increasingly transparent about their evaluation of medicines through the publication of assessment reports. For example, since its creation in 1995, the EMEA has published on its website (www.emea.europa.eu) a “European Public Assessment Report” for every medicinal product authorised through the Community procedure. Over the past few years, the EMEA has been reinforcing its interaction with all its stakeholders, in particular patients, consumers and healthcare professionals, in order to meet their expectations as much as possible.

In this context, both patients’ and consumers’ organisations and healthcare professionals’ organisations have recommended that the EMEA work with them to improve the provision and dissemination of good quality benefit-risk information on medicines to support the dialogue between patients and healthcare professionals.

Design of the project

To investigate how to improve communication on benefit-risk information on medicines, the EMEA organised a joint project with the three parties: European patients’ and consumers’ organisations, European healthcare professionals’ organisations and European regulatory authorities (see Annex I).

The project was led by three topic leaders: one representative of patients’ organisations, one representative of healthcare professionals and one EMEA representative.

Earlier discussions between EMEA, patients’ organisations and healthcare professionals’ organisations had shown that communication on the benefit-risk of medicines is a complex issue which encompasses different situations and depends on numerous factors. The project therefore had to clarify what is meant by “benefit-risk” before analysing the need in terms of communication and finally considering areas for improvement. To achieve these objectives, a survey was first carried out among representatives of the three parties which was followed by a meeting to share results and experiences and to discuss areas for improvement.

The survey was conducted from March to April 2008 and consisted of a single questionnaire to be completed by all participants. The questionnaire, developed by the topic leaders, included six simple questions (see table below) giving flexibility to each party to answer according to their expectations and needs as well as facilitating exchange of experience. All answers were compiled separately for each group (patients and consumers, healthcare professionals and regulatory authorities) and they are attached as an annex. The three compilations were discussed in the presence of the three parties during the annual joint

⁷ Lack of awareness of MHRA is apparent as only 1% report having used the agency to obtain information about medicines.

⁸ The EMEA is responsible for the scientific evaluation of medicines applying for “Community marketing authorisation” — i.e. medicines that will have a single 'marketing authorisation' (licence) for use in all countries of the European Union (EU). This procedure applies in particular to new medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, immune dysfunctions and viral diseases, as well as orphan medicines, and medicines derived from biotechnology and other advanced technologies.

meeting of the EMEA Patients' and Consumers' Working Party (PCWP) and the EMEA Healthcare Professionals' Working Group (HCP WG) at the Agency's offices in London on 5 June 2008.

Questions addressed to representatives:

- 1) What is the benefit-risk of a medicine for you?
- 2) Which information do you expect in terms of benefit, risk, and, benefit-risk balance of a medicine?
- 3) Do you communicate benefit-risk information? If yes, how?
- 4) What information on benefit risk, do you think is missing?
- 5) What would you propose to improve information on benefit-risk of medicine?
- 6) What is the minimum time necessary to address benefit-risk during a patient-healthcare professional consultation?

All representatives of patients and consumers' organisations, healthcare professionals' organisations and regulatory authorities participating in both EMEA working groups were invited to complete the questionnaire. The list of organisations that contributed in writing or participated in the discussion is given in Annex I.

The present report reflects the answers of the survey, the outcomes of the discussions and the proposals for action agreed by the three parties. It has been adopted by the EMEA working groups with patients and consumers and healthcare professionals.

Results of the survey and workshop

The rate of participation in the survey and/or the discussion was very good (higher than 75 % of consulted organisations and working groups) which supports the representativeness of the views expressed by the three parties. Rather than reporting each party's answers to each question, the results are presented in the form of a summary highlighting similarities and differences between the three parties.

One key outcome was that expectations of patients and consumers on one hand and healthcare professionals on the other hand are strikingly similar. Their expectations are therefore often described together.

The benefit-risk of a medicine for patients, consumers and healthcare professionals

Various ideas were expressed to answer the question "What is the benefit-risk of a medicine?" More than establishing a definition, all parties stressed a common driving principle for communicating benefit-risk which consists of communicating the essential information about the medicine to ensure safe and appropriate care of a patient to optimise his or her well-being. In practice, patients and healthcare professionals describe the benefit-risk of a medicine as the improvement that the patient can expect from taking the medicine compared to the constraints, including the undesirable effects that the patient may suffer from. Their considerations on benefit-risk are therefore focussed on the individual situation and expectations of each patient, rather than at the population as a whole.

The benefit-risk of a medicine for regulators

The European pharmaceutical legislation defines *risk-benefit balance*⁹ as an evaluation of the positive therapeutic effects of a medicinal product in relation to any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health. A marketing authorisation shall be refused if the risk-benefit balance is not considered to be favourable¹⁰. The legislation also foresees that a competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable to ensure that the risk-benefit balance may

⁹ Article 1 point 28 of Directive 2001/83/EC as amended

¹⁰ Article 26 of Directive 2001/83/EC

be continuously assessed¹¹. In practice, competent authorities judge the benefit-risk balance of a medicine by assessing the results of scientific tests and studies that pharmaceutical companies are legally required to perform according to internationally agreed scientific standards, to show the efficacy and safety of a medicine for obtaining a marketing authorisation.

The many facets of benefit-risk

The benefit-risk of medicines encompasses several aspects and depends on numerous factors such as: the patient, the disease to be treated, the therapeutic alternatives, and existing knowledge about the medicine.

There are numerous factors influencing the benefit-risk of a medicine which depend on the individual such as his or her medical history (e.g. concomitant disease, liver or renal impairment, concomitant treatment), age, ethnic origin, childbearing potential, or lifestyle (e.g. adherence to treatment, tobacco use, diet, alcohol intake). Therefore, the benefit-risk of a medicine may differ from one individual to another or between one individual and the general population, or may even change during the course of an individual's life.

The acceptable level of benefit-risk balance may differ depending on the natural course of the disease and the availability of treatment. For example, in the case of a life-threatening disease, a patient may be prepared to accept higher risks linked to a new treatment. However, when the medicine is not likely to give any essential benefits, the tolerated risks are expected to be much less.

In addition, it was acknowledged that some economic factors (such as availability, price, reimbursement and substitution aspects) may impact the possible therapeutic choice of an individual patient. However, economic factors go beyond the scope of this paper which focuses on scientific information on medicines.

Furthermore, progress in genetics can help to give an improved prediction on the extent an individual can benefit from a medicine. This encompasses the area of pharmacogenomics where the inter-individual variability in genes related to drug transporters, drug metabolism and drug targets is studied in relation to efficacy of drug treatment and adverse drug reactions. Patients and healthcare professionals expect further progress in this area. Meanwhile, one should consider all therapeutic options and asks questions about who will benefit most from a medicine and who will be particularly vulnerable to undesirable effects.

Benefit-risk of medicines: from population data to individual expectation

Observation of anecdotal evidence of benefits or risks in one or few individual(s) is usually not sufficient to demonstrate the efficacy and the safety of a new medicine. Therefore, to ensure a scientifically robust assessment before authorising a new medicine, regulatory authorities require well-performed clinical studies¹² in larger populations to be as representative as possible of the final users. Thus, regulatory authorities assess the benefit-risk balance of medicine at population level.

Because of the many facets of benefit-risk, the assessment performed at population level may not always predict the answer to each individual situation for patients and healthcare professionals, i.e.; “*is the medicine likely to give the required benefit with the least risk, given the particular circumstances of the individual patient?*” It is therefore important to distinguish the benefit-risk assessment at population level and at patient level.

In terms of communication, participants of the survey consensually agreed that there is no single method for communicating the benefit-risk of medicine. However, to reconcile individual needs with data at population level, it is necessary to communicate high quality information on medicines. Information on the benefit-risk of medicine should first of all consist of a neutral but balanced description of the benefits on one hand and the risks on the other hand. Any known factors which may influence a benefit or a risk should also be communicated.

¹¹ Article 23 of Directive 2001/83/EC

¹² E.g. ICH harmonised tripartite guideline on general considerations for clinical trials.

Information on benefit

Information concerning the benefit of a medicine comes from the results of clinical studies¹³. The general principles for conducting clinical studies have been agreed worldwide¹⁴ between the pharmaceutical industry, regulatory authorities and their medical experts. To obtain a marketing authorisation, a pharmaceutical company shall perform clinical trials to show that the efficacy findings of the medicine support the proposed dose and indications. Clinical trials shall compare a medicine with an established medicine of proven therapeutic value and/or placebo depending on ethical considerations and the therapeutic area. Efficacy of the medicine is tested by measuring its effect on a primary variable (also named “primary endpoint”) representing the most clinically relevant and convincing evidence related to the treatment of the concerned disease. This effect should be shown in an appropriate group of patients mirroring as closely as possible the real population to be treated with the medicine. Data from specific subsets of the population (e.g. women, children, elderly or patient with hepatic failure or another relevant concomitant disease) are also often required through appropriate additional study. However, it cannot be reasonably expected that all potential differences depending on individual patient characteristics or all comparisons with all existing alternatives are available at the time of marketing authorisation.

Healthcare professionals’, as well as patients’ and consumers’ organisations recognise the value of this source of information, and ask for access to more qualitative and quantitative information on benefit.

The qualitative information on benefit should provide a clear understanding on direct and indirect actions of the medicine on the disease and the quality of life. It should therefore explain the importance of treating the disease in view of the natural evolution of the disease. It should then make clear whether the medicine will cure the disease or alleviate symptoms. Effects should be described at short-term and long-term. The potential benefits should be described with the effect on the “primary endpoints” but also on other relevant measures (named “secondary endpoints”). Secondary endpoints are of interest both to patients and healthcare professionals because they may complete the information regarding the main expected benefit, or carry additional information of importance for the individual such as quality of life improvement. Any known success factors for benefit or possibilities to optimise the benefit by adjusting the dose or its timing should be clearly communicated. Information on the constancy, the time to onset of the effect and on the duration of the effect is also expected.

The quantitative description will inform on the degree of efficacy of a medicine. The quantitative data should both illustrate the proportion of patients who will benefit and the extent of the benefit on the different symptoms or other aspects of the condition. Results of clinical studies usually present the quantitative benefit of a medicine with the mean score in the “primary endpoint” in key clinical trials. It may for example consist of a mean benefit of the medicine on a particular measure (e.g. blood tension or pain scale) or the proportion of patients having benefited from the medicine (e.g. proportion of successful anti-infective treatment). The range of this response should be provided in order to give information on the variability of the effect. Information on secondary “endpoints” may give a broader idea of the effect of the medicine. It should however be known that their value is weaker than information on primary endpoints (because more false results are detected when measures are numerous¹⁵). In any case, results of clinical trials should be communicated to the patient together with an explanation of their meaning in daily practice.

¹³ The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the Declaration of Helsinki.

¹⁴ The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. (<http://www.ich.org/cache/compo/276-254-1.html>).

¹⁵ For further information see CHMP Points to consider on multiplicity issues in clinical trials (<http://www.emea.europa.eu/pdfs/human/ewp/090899en.pdf>).

Information on risk

There are two main sources of information on risks of medicines. The first source consists of data obtained by the pharmaceutical company during the development of the medicine and submitted to regulatory authorities when applying for a marketing authorisation. The second source consists of undesirable effects reported or published once the medicine is marketed. The two sources complement each other. The first source detects common undesirable effects but cannot detect all rare undesirable effects because of the restricted number of patient exposed. The second source from a larger population may help detect rarer undesirable effects. For some years now, European regulatory authorities have been asking for risk management plans to strengthen those sources of safety information. Risk management plans outline activities to minimise an identified risk (e.g. laboratory monitoring to avoid bleeding) or ask for a post-authorisation safety study to clarify a potential risk (e.g. epidemiological study to assess the risk of cardiac disease after long-term use of a medicine).

Patients and healthcare professionals want clear, unbiased and transparent information on undesirable effects but also practical information on risk factors and on how to deal with the risks (i.e. time of onset, early symptoms, action to be taken, expected time of recovery, reversibility). As for benefit, information should be given qualitatively and quantitatively.

Complete and transparent information must be ensured about any potential harm which could result from the intake of the medicine. This should encompass potential harm related to the occurrence of any undesirable effects related to the medicine, as well as any negative impact on the patients' quality of life (e.g. interference with daily activities, disturbance of personal and social life, stress related to the intake or the effect of the medicine). Information should also cover the risks of abusing or misusing the product and/or becoming dependent on the product. The effect to be considered may occur with an appropriate use of the medicine or not (e.g. in case of medication errors, overdose, misuse or abuse), after a short or long-term use, due to an interaction with another medicine, or may be related to the mode of administration or the storage conditions of the medicines. All undesirable effects should be described independently according to their severity, however, information on an undesirable effect should also detail the potential consequence for the patients. As far as possible, additional information should be given to facilitate the prevention, monitoring or management of undesirable effects. In this respect, it should be noted that the rarer the risk the more difficult it may be to characterise it. Patients and healthcare professionals also want to be informed where there is only limited knowledge about the safety of a medicine.

The quantitative description should provide information on the frequency and the degree of severity of a risk. The frequency should be given as proportion of patients experiencing the undesirable effect. To avoid misinterpretation, numerical frequency is preferred (e.g. 1 in 1000 patients). However, a semi-quantitative description (e.g. common, rare or very rare) is better than nothing when a quantitative measure cannot be given. The degree of severity should be given at least in a semi-quantitative way (e.g. mild, moderate, or severe).

Healthcare professionals would expect that the information on life-threatening or other potentially serious adverse effects are presented first followed by non-serious adverse effects according to their frequency.

Communication and risk perception

As described above, a great deal of information on the benefits and risks of medicines is expected; qualitative and quantitative descriptions of the benefits and risks, data in specific sub-populations, comparative data with alternative treatments, success factors and risk factors. To answer to patients', consumers' and healthcare professionals' expectations, it is necessary not only to obtain such detailed information but also to communicate it appropriately avoiding misinterpretation.

Patients and healthcare professionals acknowledged that all information which would allow individualising treatment for all situations cannot be reasonably expected but would like comprehensive and balanced information. Information on benefits and risks must always be communicated together since the perception on risk is proportional to the expected benefit of the medicine.

For example, the risks of HIV medicines are of higher concern today - when the long-term benefits are well-known - than in the past, when no established treatment was available.

To support this transparency objective, all participants supported the quality principles on information as defined by the Pharmaceutical Forum (i.e. objective and unbiased, patient-oriented, evidence-based, up to date, reliable, understandable, accessible, transparent, relevant and appropriate¹⁶).

Benefit-risk information is communicated in three main situations; when treating a patient, when preparing guidance on the treatment of a disease and when publishing medical information (on a medicine or a disease).

Communication between patients and healthcare professionals is of utmost importance and focuses on the specific needs of the individual patient, e.g. to optimise the therapeutic choice. The time necessary to address benefit-risk during a patient-healthcare professional consultation is highly dependent on the nature of the consultation and the individual patient as well as on the healthcare professional's role and availability. In practice, the average medical consultation across Europe is 11 minutes¹⁷, so focus is essential for the doctor and patient. At least, the patient should be informed of the benefits of taking the medicine and be aware of the risks in order to know what to do in case of an undesirable effect. Concise information with the key characteristics of each medicine would therefore facilitate discussion between patients and healthcare professionals. In more complex situations (e.g. chronic disease in a patient with co-morbidities), detailed data will be expected to adapt the therapeutic choice to each individual need. In these situations, additional time will be necessary for discussing the benefits and risks of the therapeutic options, and, a document with comprehensive information is expected.

Apart from the face to face discussion between a patient and a healthcare professional, the wider discussion on benefit-risk focuses on the disease as a whole. For example, when assessing a medicine, regulatory authorities consider the state of the art on the disease (including the availability of treatments) to determine what the medical need in terms of benefits is and what the acceptable risks are. Then they assess information on benefits and risks of the new medicine at population level, considering the need for data in appropriate sub-population. When giving an opinion on the authorisation or not of a new medicine, regulatory authorities have to balance the need for rapid access to innovative medicines and the expectations for extensive data on their benefits and risks¹⁸. Public assessment reports should consider all these aspects when communicating on the benefit-risk of the medicine. Similarly, health technology bodies, learned societies or local authorities prepare therapeutic guidelines which are disease specific and which will have to be followed according to each individual patient's needs. Comprehensive information on all therapeutic options is necessary for preparing these guidelines.

To facilitate communication on benefit-risk in the different situations, regulatory authorities should therefore provide both concise and detailed documents. The documents should cross-refer between each other to facilitate their consultations.

Discussion and proposals for action

Medicines are authorised based on a benefit-risk assessment at population level. Information should clearly describe the benefits of the medicine on one hand and the risks of the medicine on the other hand. Patients and healthcare professionals should also be informed on any known factors which may influence a benefit or a risk, and, on important missing information (e.g. in pregnant women). This would contribute towards personalised use of medicine.

¹⁶ Pharmaceutical Forum - Second Progress Report, 26 June 2007.

¹⁷ Brink-Muinen A, van den; Verhaak, PFM; Bensing, JM. An International Comparative study in Six European Countries on Doctor-Patient Communication in General Practice. Utrecht: NIVEL; 1999. The EUROCommunication Study.

¹⁸ Eichler H-G et al., balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma, *Nature Reviews Drug Discovery* 7, 818-826 (October 2008).

To improve communication on benefits and risks of medicines, patients, healthcare professionals and regulatory authorities recommended having continuous interaction and made proposals for action to foster preparation and dissemination of high quality information on medicines and to optimise safety communication.

Fostering the regulatory information on medicines

Regulatory authorities should increase their role as a reliable source of information for healthcare professionals and patients. Existing regulatory information on medicines (product information, public assessment reports and post-marketing information) should be supported, developed further and brought to the attention of the general public. In all documents, the benefits and the risks should be clearly presented together with the identification of specific patient groups for whom risks or benefits may differ. Information should be qualitative and quantitative (see also earlier sections on information on benefit and on information on risk).

For example, the package leaflet could progress from a document on the use of the medicine (which may create fear in patients when reading the warnings and list of undesirable effects) toward an “*information tool*”. It should provide more information on benefits in understandable terms. Undesirable effects should be presented in a more readable way allowing patients to have a clearer estimation of the risk of experiencing undesirable effects. Patterns which may modify the benefits or risks should be made clearer. Further effort should be made to prevent medication errors through improved package design and labelling.

The content and presentation of the summary of product characteristics and of the public assessment report should be further discussed with healthcare professionals to facilitate both an easy daily use and access to complete information (e.g. for preparation of guideline on the management of diseases by learned societies or healthcare body). For example, it should be discussed how clinical trials studies should be presented in each document.

Dissemination of information

The EMEA and national competent authorities should simplify and harmonise public access to regulatory information on medicines, independently of the route of authorisation (centralised procedure, national authorisation, mutual recognition or decentralised procedures). This information could be presented in a public “book” about all medicines available in Europe where information addressed to patients should be in lay language and in all European languages. Preferably, there should be a central web portal provided by EMEA and national competent authorities. The possibility of open source health portals with quality assurance provided with a “Trust mark” was also proposed. Specialised journals and organisations’ websites could be used to disseminate regulatory information. To foster the role of regulatory authorities as a reliable source of medicine information for health professionals and for patients, it is very important to intensify networking and coordination between EMEA and national competent authorities. As a practical example, it was requested to speed up the process of the inclusion in the Eudrapharm database of information on all the medicines authorised via the different authorization procedures.

Descriptions of benefit and risks

Patients and healthcare professionals are willing to participate in any regulatory project aiming to better communicate benefits and risks, especially with regard to quantitative aspect and area of uncertainties.

Different methods were given for consideration; a graphic mode (e.g. benefits would be presented with an ‘at a glance’ system [e.g. 1-5 stars rating] and undesirable effects could be presented in a colour table first sorted by severity and then in each severity class, sorted by their frequency), illustration of the benefits and risks using the number needed to treat or to harm, or proportion of (non-)responders, frequencies.

Safety communication

How to provide information in areas of uncertainty needs to be further investigated. At least, lack of information should be made clear, especially for preventive treatment or medicines for which long-term safety is missing. In this respect, some proposed to extend the UK system identifying medicines with limited safety knowledge with a black triangle on the box of the medicine.

Timely update on post-marketing safety data should be ensured. Organisations offered regulatory authorities their support for the preparation of public statements in case of post-marketing safety issue and to facilitate rapid dissemination of information through their members if necessary. In addition, organisations asked regulatory authorities to have a closer contact with media, to facilitate timely public communication of valid information on important medicine issues, thereby preventing dissemination of less documented information which may create undue fears or expectations to patients.

Other communication tools

Education should further facilitate the discussion between the various parties. Patients and healthcare professionals should be better informed about the role of the regulatory authorities in order to be aware of where the data come from, where to find information on benefits and risks and how to interpret the information. Organisations should contribute to the dissemination of the information as well as to the specific education of their members. For example, patients' organisations should contribute to informing patients on how to become more involved in their treatment, and healthcare professionals would benefit from more training on 'how to communicate' to patients to individualise the treatment according to his or her individual needs.

Action plan

EMA and its working groups with patients and consumers and healthcare professionals agreed to develop their proposals as part of their work programmes for the coming years:

- Further explore how to optimise regulatory information (in particular the product information and public assessment reports) to facilitate their use and fulfil patients and healthcare professionals' expectations e.g.:
 - by providing information on benefits and risks in the package leaflet;
 - by clarifying the extent of information expected in the summary of product characteristics and the public assessment report;
 - by facilitating access to and consultation of the public assessment report (e.g. in improving its format);
 - by involving patients, consumers and healthcare professionals in the preparation of relevant information;
 - by considering additional communication tools.
- Foster dissemination of information through:
 - the EU regulatory network;
 - stakeholders;
 - public database of medicines;
 - considerations of other dissemination tools.
- Prepare recommendations on the quantitative descriptions of benefits and risks;
- Prepare recommendations on risk communication in areas of uncertainty;
- Further explore how best to communicate on safety issues;
- To investigate other action facilitating communication between the three parties.

Annexes

Annex I: Organisations and committees involved in the discussion

European AIDS Treatment Group (EATG)
European Cancer Patient Coalition (ECPC)
European Federation of Neurological Associations (EFNA)
European Patients Forum (EPF)
European Public Health Alliance (EPHA)
European Organisation for Rare Diseases (EURORDIS)
Health Action International (HAI)
International Alliance of Patients' Organisations (IAPO)
International Diabetes Federation (IDF)
International Patient Organisation for Patients with Primary Immunodeficiencies (IPOPI)
The European Consumers Organisation (BEUC)

European Academy of Paediatrics (CESP-EAP)
European Association for Clinical Pharmacology and Therapeutics (EACPT)
European Association for the Study of Diabetes (EASD)
European Association of Hospital Pharmacists (EAHP)
European Federation of Nurses Associations (EFN)
European Society for Medical Oncology (ESMO)
European Society of Cardiology (ESC)
European Union Geriatric Medicine Society (EUGMS)
European Union of General Practitioners (UEMO)
Pharmaceutical Group of the European Union (PGEU)
Standing Committee of European Doctors (CPME)
The European Specialists Nurses Organisations (ESNO)

Committee for Medicinal Products for Human Use (CHMP)
Committee for Orphan Medicinal Products (COMP)
Committee for Herbal Medicinal Products (HMPC)
Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMD(h))

Annex II: Compilation of answers received from patients' and consumers' organisations

All answers for each question were compiled together and classified in order to put together answers addressing similar topics. They are therefore presented in subsections to facilitate review of the answers. Subsections have been harmonised between the compilations of answers from patients' organisations, healthcare professionals' organisations and regulatory authorities to facilitate discussions.

1) What is the benefit-risk of a medicine for you?

Definition

- It represents the improvement I can expect from taking the medicine compared to constraints attached to taking it, in comparison with the adverse reactions I can suffer from.
- The benefit-risk of a medicine is perceived as the degree to which a particular patient can expect his/her condition to improve by taking a specific medication (rather than another or alternative medicine/treatment or no treatment), and in what time frame, set against possible severe and mild side effects and the reasonable assessment of the risk of these happening (based on known facts linked to the medicine and the history and circumstances of the patient).
- It is the balance between the benefits (the intended purpose-positive effects) and the risks (adverse effects) of a medicine.
- A ratio between the potential beneficial effects of a given medicine and the eventual harm it might cause.
- A delicate balance which is to be presented in an intelligible manner to the patient/consumer by the healthcare professional prescribing/dispensing the medicine.
- The relative benefit of the medicine compared with the potential risks.

Objectives

- To know in a given situation that the potential benefits outweigh the risks.
- A patient has the right to know the benefits and the risks of any medication prescribed – however this should be done in a factual, non-alarmist way.
- Knowing the benefit-risk ratio is essential for patients/consumers to make an informed decision and to actively participate in their health care.
- The purpose of this is to enable patients to make their own risk-benefit assessment as accurately and as confidently as possible in partnership with the healthcare provider.
- An essential tool to make an informed choice when deciding to start (or not) a therapy.
- An essential tool when contemplating different treatment options.
- To have been able to hold discussion with the Consultant or GP and to understand what is being said about benefit-risk (or harm).
- a solid background needed to empower people to take more responsibility for their own health and engage more widely in self-care.
- To promote that symptoms of the relevant disease are disappearing.
- To promote that complications of the relevant disease are being prevented or postponed.
- To promote that relevant blood and/or urine parameters are getting normal values.
- To promote that people with the relevant disease can function as normal members of their society.

Method (including timing)

- This balance should be based on complete and unbiased information provided by the manufacturer, i.e. the pharmaceutical industry.
- When a new product is granted marketing authorization, little is known about its safety as it has

been tested only on a limited number of selected people which is not representative in absolute terms. Therefore throughout the life cycle of a medicine there should be a continuous process of risk identification and assessment, as well as a regular evaluation of the benefit-risk balance.

- The risk-benefit ratio is often re-assessed when a safety signal occurs is then confirmed, or when new efficacy data show reduced efficacy. The situation where new studies showing an increased benefit are analysed to re-assess the ratio is rarer.

2) Which information do you expect in terms of benefit, risk, and, benefit-risk balance of a medicine? What information is the most important?

2.1 Expected information on benefit

Qualitative characteristics

- The benefit relates mainly to the capacity of curing the disease or improving the symptoms.
- Other important aspects to mention:
 - Why is it important to treat the disease?
 - What if it is left untreated?
- The potential benefits of the medicine, according to the current medical knowledge.
- Identify expected benefits—degree of clinical effectiveness on important outcomes, convenience.
- Therapeutic effect—how long does it take to feel the effect of the medicine? How fast does it go away?
- Description of the positive effects.
- The value of the benefit—does it cure or just lessen my symptoms.
- Sometimes, the information on what the medicine does not do is also important: a product aiming at treating a metabolic disease with both renal and cerebral impairment may improve the renal function and prevents from dialysis or kidney transplant, but may have no impact on already existing brain damages. Often, the most positive aspect is overemphasized, and patients and carers may expect from the medicine more than what it can actually do.
- Posology. Any dose adjustment involved?
- Onset of the medicine.
- Duration of the medicine.
- The nature and purpose of the medicine.
- Will effects continue after the medication is stopped?
- Information on secondary endpoints is also of importance in many cases: a quality-of-life benefit can translate in an enormous added value from the patients' perspective. An example is the effect of growth hormone in children, adolescents and young adults with Prader Willi syndrome: a clinical outcome is weight loss, which is more pronounced in children than in adults. But in adolescents and adults, even if the primary endpoint (weight loss) is not reached, a quality of life issue such as improved sexual function due to the normalisation of sexual hormones is a real benefit. In addition, very important benefits such as improved muscle mass, better breathing and sleep, which results in more activity and energy, better intellectual performances, less premature ageing were not evaluated in the first trials, and were reported after the marketing authorisation was granted.

Quantitative characteristics

- What are the benefits I can expect when using the drugs-What is the chance that I do not achieve these results.
- Degree of efficacy.
- The proportion of patients who reach the primary endpoint.
- Together with the meaningful explanation of what it means to reach the primary endpoint.
- Expressed in terms of numbers needed to treat to benefit (NNTB), rounded to the closest integer.

- Number needed to treat.
- There should be a very simple ‘at a glance’ system of analysing benefits—for example with symbols—e.g. 1-5 stars, together with a quantification that is as precise as possible for patients who want more detailed information.
- I may be interesting to also express the range of the response, not only the average. For example, a product indicated for primary pulmonary hypertension (PAH) can increase the average walking distance after 6 minutes exercise by x meters compared to placebo. Not only the threshold that can be recognised clinically significant could be mentioned, but also the percentiles of respondents: % of patient who did not respond, % of patients who improved the walking distance by 20 meters, % of patients who improved by 40 meters...

Comparison with other therapies

- Natural progression of disease with and without the medication.
- What is the difference with not using the drug.
- The possible alternatives.

Other

- The information provided should conform to quality criteria (as agreed by the Pharmaceutical Forum).

2.2 Expected information on risk

Qualitative characteristics

- Knowledge about the harm resulting from the intake of the medicine.
- Kind of risks. How often does this occur.
- Identifying potential side-effects, as well as frequency and gravity.
- Side-effects:
 - Explanation of the side-effects;
 - Classification according to degree of seriousness;
 - Or new medicines, information that there is only limited knowledge about the risks.
- Risk of and effects of inappropriate use of a medicine.
- Consequences of long term use.
- Risk of dependency.
- Safety track record.
- Ability to interfere with daily routine/activities, disturbance of personal and social life.
- What to do when I am afraid of, or have an adverse reaction.
- Even though risk usually relates to the occurrence of an adverse reaction imputable to the product, other risks exist that can affect my perception of benefit-risk:
 - Risk of decreased life quality if centring all day life activities on the action of taking the medicine: this is the (extreme) case for patients using electronic devices (DTO) to verify they swallow the pills every 4 or 6 or 12 hours as prescribed;
 - Risk of additional stress: “Am I going to respond to the medicine, or am I one of the unlucky where the medicine does not work”?
 - Risk of social disturbances: Do I want people to see me in public taking the medicine? If not, how can I take it as discretely as possible? Where can I stock them to avoid questions? Do I need to repack them in a completely different, neutral and non stigmatising package such as aspirin?
- Another risk is the consequence of a first line regimen failure on the chances of success for a second line regimen depending on options left: to hit hard and early, with the risk of no more options afterwards, or to hit smoothly and lately to secure a second line regimen? This is the case for many diseases, high blood pressure, antiretroviral therapy etc... It is more a treatment

strategy issue, but a key question when deciding to start the treatment.

- How to avoid those risks.
- What are the signs I have to be aware of and/or to monitor.
- Knowing what to do if experiencing a side-effect, how to report it.
- Is there a safety advisory on this product?

Quantitative characteristics

- Frequency of the side-effects expressed in numbers.
- Side effects–how likely are they. Would prefer numbers e.g. 1 in 1000, not vague words such as ‘rare’.
- Both the frequency and the severity of the risk considered should be mentioned.
- As for benefit, risk could be expressed in terms of numbers needed to harm NNTH, rounded to the closest integer.

Population concerned

- Use in pregnancy/elderly/ children.
- Interactions with other medicines and treatments or with food and other medication.

Other

- Is it the medicine being prescribed to one of the indications for which it has been approved? Implications of off label use.
- Clarify of information–written in understandable language.
- Direct information by the producer of the medicine.
- Information not filtered by any health care provider.

2.3 Expected information on benefit-risk balance

Qualitative characteristics

- Transparent as to the source, evidence-based, unbiased, up-to-date.
- Unbiased information about the ratio between potential benefits and eventual harm caused by the medicine.
- Short-term and long-term benefit-harm balances should be provided. What is the medicine doing? Is it slowing down of illness progress? Is it tackling only the symptoms of my illness? Long-term effects.
- A clear difference should be made with regard to medicines with potentially fatal side effects and in which circumstances, and those where the side effects could be unpleasant but bearable.
- The chance of a benefit (and what kind of benefit) against the chance of an adverse reaction.
- Open and honest information by an accepted authority in that country.
- This should be obvious, from the above information, however this will become more complex with imminently life threatening diseases/conditions when patients are generally willing to take a larger degree of risk to access a medicine that may be potentially life-saving, but with a larger array of known and possibly unknown side effects.

Comparison with other therapies

- Information on non drug treatments, i.e. for instance suggesting lifestyle changes in diet and physical exercise for diabetes type II rather than immediate medical therapy; social support, physiotherapy, psychotherapy-the risks and benefits of all the alternatives, including non-treatments.
- The consequences of not using the medicine.
- Better explanation of the risk for the patient by not using the medicine.
- Where possible the same data/info on comparable medicines which could be used instead.

- The information may include:
 - 1) What can be treated;
 - 2) State of the art of the treatment options [Class names and names of active ingredient, (brand names if possible under the national/EU legislation), Treatment goal and medicine mechanisms (how they act), Indications, Contraindications, Effectiveness, Evidence based comparison of medications];
 - 3) Future treatment prospects [Other treatments, What non-pharmaceutical treatments options exist].

3) Do you communicate benefit-risk information? If yes, how?

Direct communication to patient

- Ordinarily, however it should be outside the remit and responsibility of the patient organisation to communicate benefit-risk information. Their direct role could be to provide general advice to the competent authorities with regarding to improving benefit-risk information for patients but not to be the information bearers.
- Not in my daily work, but I do find that using absolute risk measures results in a better understanding of the ratio, rather than reverting to relative risk.
- Training people living with PD to be ambassadors to others.
- Yes—providing ‘decision making tools’ to help with the understanding of patient’s choice.
- As part of our work as a representative of a patient organisation.
- As a person with a chronic illness.
- Verbally in both situations-face to face and on the phone.
- Sure. By stressing the fundamental right on information to patients, even if the medicine is not (yet) available in that country.

Communication received passively by patient (e.g. package leaflet)

- Occasionally in writing on behalf of the patient organisation.
- Indirectly, many patient organisations through training, peer support etc—provide tools to enable patients to be able engage in shared decision-making with the healthcare provider regarding benefit-risk analysis and the importance of this.
- As an umbrella organisation, we do not communicate benefit-risk information however some member organisations would play an emergency role in relation to pharmacovigilance where an adverse drug event should be communicated rapidly to patient groups at risk.

Information requiring active search by patients (e.g. publication in scientific literature or on internet)

- Organisations communicate to consumers through their magazines and their websites. When informing about diseases and other health problems, they list and compare all available treatments or other solutions. Among these, also the available drugs. They present what is known about their risks and benefits, helping people making an informed choice.

Other

- Our members also disseminate the EMEA and the National Medicines Agencies messages on pharmacovigilance often including an explanation of the most technical terms.
- To involve patients & carers in the provision of literature available to patients so that it is patient and family focus.

4) What information on benefit-risk, do you think is missing?

For each type of missing information, what would be the best source in order to provide this information? (Regulatory authorities, healthcare professionals' or patients' organisations, doctor, pharmacist, nurses, package leaflet or labelling, others?)

General principles

- Patients need to know all the options available to treat their disease/condition.
- There is no “best source”. All stakeholders must play their own role, which role varies very much in the different countries. And is dependent on the law in that country.

Unavailable data (which do not exist)

- Companies tend to prefer comparisons against placebo or non-inferiority trials or equivalence trials against another drug, while the correct comparison should be with the one ‘most likely to be replaced’ by the new drug and the set-up of the trial should be one of superiority.
- The information provided in the EPAR summary on product efficacy or safety is not sufficient to allow a thorough appraisal of treatment options by patients.
- Comparison between drugs regarding benefits and risks are important for patients but this needs to be done in the framework of one single, universally recognised and respected centrally managed system like EMEA, where relevant experts (including medical and patient experts) are included in benefit-risk assessment.
- This could be communicated effectively through EUDRAPARM in the future.

Information difficult to obtain

- Unpublished data (healthcare professionals or patients cannot have access to them easily, e.g. pharmacovigilance).
- The percentage of people that does not benefit from the medicine.
- Onset and duration of the medicine.
- Information on how to assess the benefits in coping daily with a chronic condition(s).
- Companies tend to publish only the positive results, not the negative ones.

Poorly disseminated information

- Practical information on how to deal with the risks.
- Poorly disseminated information (healthcare professionals or patients cannot access it easily), e.g. result of PK study in patient with liver impairment as described in EPAR.
- Healthcare professionals often lack easy access to certain information–data on medicines’ side effects.
- Transparency. An example is provided above with growth hormone for Prader Willi syndrome, when interesting efficacy data with new endpoints were obtained after the generalisation of the marketing authorisation in Member States. This information is not reflected in the regulatory documents.
- Post marketing evaluation data: treatment strategy trials sometimes publish interesting results on the respective efficacy of different regimens or medicines. Or new data using endpoints that were not used during pivotal trials can also be published after the marketing authorisation. These new information are not always reflected in the EPAR. They may be analysed by health technology assessment agencies to revise the reimbursement level. Regulatory authorities usually analyse them in case the risk-benefit ratio could become problematic, rarely when it becomes even more positive.
- Also interpret the benefit: the criteria used are well described in the EPAR. However, the relation between the criteria used for the efficacy assessment and the clinical benefit is less clearly described. In some cases, the evaluation criteria are difficult to translate. The case of the 6 minutes walking distance for PAH is an example: who knows how long you can walk over a 6 minutes period, with or without PAH? Evaluation criteria are sometimes abstractions for the

patients, sometimes also for health care professionals. Still, they are based on scientific discussions. Another example was the approval by the former CPMP of photographs of the retina to assess the efficacy of ganciclovir to treat cytomegalovirus related retinopathy rather than the evolution of the visual field. Discussions on the correlation between blindness, visual field and photographs of the retina are key to understand why the photographs only can be used. This is important information for those who need to explain the efficacy to patients, health care professionals, patients' representatives, nurses... more than for the patients themselves, but this information is rarely easily available.

- Ensuring that the information above is current and that it is updated from monitoring usage.

Other

- Most clinical trials are industry-sponsored research which is likely to be favourable to the company's product.
- The information pushed by the industry tends to overstate the benefits and minimize the potential adverse effects, and does almost never indicate that in some cases a drug treatment may not be necessary.
- Pharmaceutical companies can invest a lot in their information policy while independent and truly reliable alternative information sources, having less financial means, have difficulties reaching the public and healthcare professionals.
- Pharmaceutical companies can be guilty of withholding "key information", such as evidence of health risks associated with their products or evidence of inadequate efficiency. Adverse events are often minimized and evidence of lack of benefit or of harm is sometimes even concealed by pharmaceutical companies.

5) What would you propose to improve information on benefit risk of medicine? How EMEA or other regulatory agency could contribute to this improvement?

Recommendation on the quality and extent of existing information

- Independent medicine information comprises both data and analyses of the highest possible degree of objectivity and is provided by bodies having no commercial or other interest in the promotion of particular patterns of medicine treatment. The already existing sources of truly independent and reliable information about medicines should be supported, developed further and brought under the attention of the general public. They should be made more accessible to the general public. In countries where they do not exist yet, such information sources should be created.
- Improving package information leaflet content and relevance as an information tool. (Patients organisations strongly support the EMEA initiative on the readability of the package information leaflets and EPAR summaries).
- Work more closely with patient groups when preparing statements.
- Pharmaceutical companies should fulfil their obligations concerning packaging. The European regulatory framework requires good quality labelling of drugs, including for partially sighted or blind citizens, and consultation on patients' leaflets with targeted groups of patients to ensure all leaflets are legible, clear and easy to use.
- When mentioning the proportion of responders, also mentioning the proportion of patients who did not respond to the medicine.
- To systematically comment on the proportion of patients who reach the primary endpoint together with the meaningful explanation of what it means to reach the primary endpoint. Consultation with patients at EMEA should systematically address this specific question. Not only ask patients' representatives to comment on the documents (EPAR summaries, package leaflets), but addressing a list of questions such as: "In this document, is the proportion of patients who respond and the meaning of the response explained in understandable terms?"

- To generalise the description of benefit and risks using NNTB and NNTH.
- To mention what should not be expected from the medicine, when applicable.
- To promote much more the significance of multi-morbidity and the use of medicines.

Recommendations on the disseminations of existing information

- All statutory information should be readily available in all Member States. A centralized web portal with access to all patient information leaflets and European Public Assessment reports should be provided. Additional information such as pre-market drug reviews forming the basis for regulatory decisions, post-market regulatory documents such as the PSUR, safety advisories should also be available.
- Making statutory information, i.e. the package leaflet, equally available and accessible in all member states.
- Speeding up the process of the inclusion in the Eudrapharm database of information on all the medicines authorised via the different authorization procedures.
- Drug regulatory authorities should foster their role as reliable source of medicine information for health professionals and for patients (e.g. access to EPAR and PIL on their websites).
- The EMEA and the regulatory agency should simplify and harmonize the communication of data to the general public.
- To recommend national competent authorities to do the same exercise for medicines that are approved nationally or via the decentralised procedure.

Recommendation for new tool for information, including increasing publication

- Improve media relations which will inform society.
- Press events to facilitate a dialogue between treatments & society.
- To use the colour scale above for frequency and severity of adverse reactions.
- A graphic mode could help, an example is shown below: for each product, adverse reactions are first sorted by severity (from green for the less severe, red for the most severe) and in each severity class, sorted by their frequency. This could be used to indicate some adverse reactions that can be both infrequently severe and commonly mild.
- This presentation could help the reader, as the listing of adverse reactions by frequency or severity in text mode only is often counterproductive (users do not read all the text, or miss information of first importance when diluted in a long list of information of less importance).
- Similar to information on benefits; there should be a very simple 'at a glance' system of analysing risks using symbols and also quantification for patients who want more detailed information.
- Health care providers and consumers should be informed about the relatively limited knowledge about the side-effects of new medicines. The black triangle system used in the UK should be extended to the public, by mean of the presence of a black triangle on the box of the medicine.
- Open source health portals with quality assurance (Trust mark) in lay language and in other languages of the EU following health literacy guidelines (on info already available from EMEA).
- To promote the development from evidence-based medicine into mechanism-based medicine and individualized medicine.
- To prevent the use of guidelines which are based on research and trials with pre-selected, not representative people, done several years ago and outdated.

Recommendation for further transparency

- Health professionals, patients and the public have a fundamental right to the complete body of scientific evidence on the health effects of medicines. Without access to this information, all medicine use is by definition uninformed.
- All information on drug safety and effectiveness that is submitted to regulatory authorities should be publicly available, including all pre-market laboratory and clinical data and post-marketing studies.

- To promote much more full openness by everybody.
- Measures to tackle the bias of information with regard to research and development of medicines are needed, as for instance:
 - 4) a reliable worldwide register of clinical trials;
 - 5) disclosure of all data (positive and negative);
 - 6) fostering existing sources of independent information.

Recommendation related to education

- Provide patients, public and healthcare professionals with the skills to distinguish between promotional material (direct advertising), promotional material that masquerades as information (disguised advertising) and unbiased information.
- Undertake media training before staff are interviewed on radio or TV.
- Health professionals as well as patients should be better informed about the role of the authorities in the provision of medicine information.
- The ability to communicate clearly Training courses for healthcare professionals on the topic of 'how to communicate'.

Other

- Pharmaco-economic guidelines aimed to increase the methodological quality.
- Transparency and uniformity of the pharmaco-economic submissions.
- Readily accessible sources of good quality health information exist in different regional or national contexts, allowing patients and consumers to make informed choices. They should be supported. Examples: independent drug bulletins which publish specific information for patients and consumers, independent patient organisations, consumer groups, healthcare professionals organisations, etc.

6) What is the minimum time necessary to address benefit-risk during a patient-healthcare professional consultation?

- At the moment a consultation across Europe is 12 minutes, so focus is essential by doctor and the patient.
- 1 consultation to address the main aspects of benefit and risks: minimum 15 min.
- 1 consultation to debrief and to address other aspects (secondary endpoints, how to identify early symptoms of some adverse reactions, and what to do), and how to take the medicine: 20 min.
- 1 consultation with another person to recap and to re-explain how the product efficacy will be monitored and assessed at the next visits: 15 min.
- It depends on:
 - patient and consumer's health literacy level;
 - the disease/condition: progress, gravity, type;
 - patient status, polymedicated or not?
 - the setting: GP practice, pharmacy visit, nurse visit;
 - the key message being delivered.
- Information providers should be aware of ethnic, cultural, sex, and age differences in the information needs of patients, and in their culturally determined interpretation of data. Patients' preferences should be explored when the prescription is introduced, and checked again in subsequent consultations.
- For many conditions, more than one consultation will be necessary.
- That varies from a few seconds to many, many hours (regarding a euthanasia medicine). I really do hope that this question will not try to make a new nonsense.
- In principle at least half of the time of the consultation should address the communication of the benefit-harm ratio.

- It is important to ensure that whenever healthcare professionals communicate with and inform patients, they do so in a patient-centred manner, free of bias, undue influence or paternalistic values and attitudes. Yet, healthcare professionals often do not take or do not have the resources to meet the needs of “expert patients”.
- Need to educate patients to make better use of their time by asking highly relevant questions e.g. checklist of questions to ask, diaries of symptoms.
- Health professionals make variable efforts to discuss medicines with patients and in all consultations an adequate amount of time should be devoted to the communication of the benefit-risk. It is difficult to quantify as it varies from individual to individual.
- The amount and complexity of information must be tailored to the perceived needs of a patient, Access to further information should be facilitated, and patients helped in interpreting the data.
- This is highly dependent on the nature of the consultation and the individual patient. The minimum time would be the time required to ensure that the patient understands the benefits of taking the prescribed medicine(s) (adherence), is also aware of risks, both general and linked to his her specific situation and environment and what to do in case of an adverse event.
- EMEA with the national competent authorities could run the info portal.
- Ensure patient/representative involvement in provision of information.

Annex III: Compilation of answers received from healthcare professionals' organisations

All answers for each question were compiled together and classified in order to put together answers addressing similar topics. They are therefore presented in subsections to facilitate review of the answers. Subsections have been harmonised between the compilations of answers from patients' organisations, healthcare professionals' organisations and regulatory authorities to facilitate discussions.

1) What is the benefit-risk of a medicine for you?

Definition

- Customarily considered as 'risk-benefit' because a prime concern is 'first do no harm'.
- The benefit-risk is the comparison of the risk of a medicine to its related benefits.
- A balanced summary of the evidence-based indications with the, common side-effects.
- Side effects unlikely in patients while the dosage selected remains effective.
- High therapeutic value.

Objective

- Tool for explaining to the patient the pros and cons of the therapeutic decision and giving him a better understanding of the treatment and its consequences, and by the way obtaining his agreement and participation in the decision.
- Essential information for clinical staff for delivering safe, comprehensive and appropriate care.
- Rationale in which is based the decision either to apply a medicine to a certain situation.
- Gives the profile of a medicine and allows to compare between different medicines.
- The question about benefit versus risk is of great importance when choosing to treat with one drug or another, or without drugs at all.

Method (including timing)

- Risk-benefit of a medicine is estimated, predicted or calculated (depending on the stage of development or overall level of knowledge or experience) on the basis of events in a particular type of population over a period of time. Applying such information to a single individual, therefore inevitably carries a degree of uncertainty. Is this medicine likely to give the required benefit with the least risk, given the particular circumstances of the individual?
- Evaluating if the appropriate treatment is provided to the patient, taking in consideration that potential side effects and/or adverse effects of the medicine will be less important than the expected beneficial action.
- Depends on the type of medication. When the medicine is possibly lifesaving, more risks are tolerated. When the medicine is not likely to give any essential benefits, the tolerated risks should be much less.
- Benefit-risk of a medicine is established taking into account new evaluation criteria, besides quality and safety: comparative efficacy, therapeutic value.
- Benefit-risk information results from the all development process of a new drug—from the first findings and researches, to the development of the new drug through clinical research, until the post marketing and clinical experience obtained from the medicines' therapeutic use—his all process is managed by only one party—pharmaceutical industry.

Others

- New and innovative medicines are clearly a health need, but it is only worth the investments if the benefits undoubtedly exceed risks, for that it is important to demonstrate that therapeutic value is added.
- A medicine is considered a therapeutic innovation when it covers a therapeutic indication for

each there are no other choices available, and when it demonstrates to generate the best results with absolute clinical relevance.

- The benefit-risk of a medicine could also indicate the possible availability of the medicine. A higher risk may indicate that the medicine could be restricted to certain healthcare settings (e.g. hospitals). This on the other hand may impact on patients' access to it.
- Benefit-risk profile should be based not only on safety and quality evaluation criteria, but a third vector of economic evaluation should be added. So that the benefit-risk of a new medicine is established, it is important to compare with other drugs already in the market – this in order to assure the best therapeutic choice.
- The benefit-risk of a medicine is also a ratio between the price of the medicine and the rapidity of treating the patient's condition. This is also applicable to the several products with one and the same formula but with different isomeric structure. This is also applicable to one and the same formula but with different pharmaceutical forms.

2) Which information do you expect in terms of benefit, risk, and, benefit-risk balance of a medicine? What information is the most important?

2.1 Expected information on benefit

Qualitative characteristics

- Improvement in health status/clinical outcomes.
- Improvement of the quality of life and rehabilitation.
- Efficacy for particular disease.
- Effectiveness for symptoms of disease.
- How does the medicine work, how well documented are the benefits?
- In order to evaluate the best benefits, it is important to know the impact of time exposition to the new medicine in the natural history of the disease or therapeutic condition.
- Well-defined and clinically significant end-points and outcomes, and not only statistically significant end-points.
- Parameters on efficacy established in clinical trials.
- Dosage range for duration of action.
- Whether 1st time treatment on adjunctive.
- Clear understanding of direct and indirect actions of the medicine for alleviating symptoms pertaining to illness.
- Quantitative characteristics.
- Percentage of patients that improve different aspects of their condition or that are cured.
- Information to be as quantitative as practicable.
- Evidence-based indications, number needed to treat.
- Population concerned.
- Efficacy as licensed, including use in particular populations.
- What benefits the drug will most probably have to a certain patient.
- What group of patients/diagnosis will benefit most/less?

Comparison with other therapies

- Comparative benefit of using a certain medicine pharmaceutical form instead of another.
- In order to establish the best benefit profile, it is important to have access to relative efficacy data. It is important to compare efficacy data between different medicines, in relation to robust evaluations but also to accelerate evaluation processes, sharing experiences between different countries.

2.2 Expected information on risk

Qualitative characteristics

- NOT to treat is part of the risk.
- What are the most important side effects, will they disappear when medication is stopped? How often do side effects occur? Severity of adverse effects.
- Information on side effects occurring with an appropriate use of the medicinal product.
- Separation of safety issues from tolerability issues.
- Severe outcomes such as those likely to lead to increased chances of mortality, disability.
- Reminder to consider rare but potentially serious adverse events.
- Mostly in what concerns to new medicines, with no market experience, it is important to have a complete and clear knowledge of what went wrong in clinical development phases.
- Toxicological pattern of the medicine established in clinical trials.
- Whether side effects are dose related or ingredients.
- Cause of adverse effects (is it a drug adverse reaction or is it due to a medication error).
- The risk information concerns not only the pharmacological/toxicological effect of the medicine but also other aspects that may alter the medicine or induce a wrong usage, therefore increasing the risk associated with the medicine.
- Advice to minimise occurrence or reduce severity of recognised risks.
- Information on administration precautions.
- Lists of contraindications, cautions and monitoring requirements and recommendations.
- Unambiguous guidance on when to stop treatment.
- Expected time of recovery from temporary side effects,
- Interactions with other drugs?
- Risks associated with administration with other medications. List of drug interactions.
- Information on interactions with other medicinal products occurring with an appropriate use of the medicinal product.

Quantitative characteristics

- Common side-effects + average incidence.
- Frequency of side effects.
- Frequency of the most common adverse events?
- Frequency and percentage of patients with adverse effects. Is the adverse effect frequent (for instance 10%), or has there been in the past one or two case-reports?
- Life-threatening, then other potentially serious adverse events and then non-serious adverse effects as a proportion of the number of patients treated per period of time.
- Number needed to harm.
- If levels of risk cannot be given quantitatively, then a semi-quantitative indication of severity may be appropriate (e.g., mild, moderate, severe).

Population concerned population

- What patients groups are most vulnerable to adverse events?
- Potential of certain side effects occurring within a given known population.

2.3 Expected information on benefit-risk balance

Qualitative characteristics

- Neutral and balanced information on what is mentioned above links to alternative treatment where the balance is not favourable.
- Risks and benefits are equally important to know/consider.
- How well documented are the benefits and risks?
- The periodicity of benefit-risk balance reassessment should be clearly stated.
- The global value of that benefit-risk balance, and what are the conditions that may vary the ratio.
- Information that allows both healthcare professionals and patients to assure that there is a systematic and proactive monitoring of the effects of the new medicine and clinical outcomes in real situations of clinical utilization.
- Under what situation the benefits may outweigh potential known harms occurring.
- Advice on measures to reduce risk or optimise efficacy that may not be addressed in the licence SmPC e.g. relating to dosage form or time of day.
- Expected time of treatment vs. outcome of the treatment.
- The benefit-risk of a medicine can also be related with the stability of the pharmaceutical form (aspects relating to storage, transport, preparation, and administration are important).

Quantitative characteristics

- Benefit-risk is preferably expressed as quantitatively as possible to illustrate for a given situation (disease stage, patient circumstance) the proportion of treated individuals expected to achieve benefit (extent and duration) compared with the proportion of treated individuals expected to experience adverse events (extent and duration) or tolerability issues.
- Because risk-benefit is so difficult to quantify for an individual (as opposed to a population), the most useful information is likely to be an absolute measure that takes account of the cumulative risk of the disease plus the medicine versus the likely benefit.
- Where possible communicate expected events in a standard quantitative format e.g. Events per 100 or 1,000 patient years of treatment, or per number of individuals treated for any time period.
- NNT/NNH ratio for each major benefit-risk instance.

Population concerned

- Which patients (diagnosis) will benefit most or less? Who will be particularly vulnerable to adverse events? What are the interactions with other drugs?
- The benefit-risk of a medicine is also function of the patient's age (e.g. use in children can represent higher risks).
- Groups of patients at risk e.g. infants.
- Effects of particular diseases on drug action.
- Information in relation to a comparable population in which drug is administered – ratio proportions of known adverse events occurring.

Comparison with other therapies

- Information regarding safety and efficacy, compared with other available medicines approved for the same therapeutic indications (e.g. combined active substances vs. different active substances separately; sustained or prolonged release vs. non-prolonged release).
- Guidelines for certain diseases.

3) Do you communicate benefit-risk information? If yes, how?

Direct communication to patients or healthcare professionals

Yes, to patients

- Directly to the patient when prescribing and always giving the patient the possibility to get in contact if symptoms suspected to be side effects, occur. Sometimes with written information.
- Answering to questions raised by the patient concerning the treatment.
- Explaining to the patient the reason of side effects.
- Comment on range of potential alternative medication options if available.
- On request, the pharmacists communicate the information about benefit-risk to the patient.
- Physicians but more often nurses are the one explaining to the patient the benefit risk of a treatment, mainly for having the patient better supporting the side effects.
- Side effects are not every time explained to the patient.

How

- You have approximately a one in whatever chance that this medicine will help you to achieve whatever treatment objective, and a one in whatever chance that it will cause whatever unwanted or dangerous side effect (assuming no treatment is not an option).
- Try to explain implications of severity or imposition to be expected by a medicine without creating undue concern or alarm.
- Advise on practical ways to reduce personal risk.
- Advise on symptoms to be wary of, and remedial actions.
- Verbally (to individuals) and writing.
- Re-check other medications taken by patient and comment if appropriate.

Communication received passively by patients or healthcare professionals (e.g. leaflet)

Yes, from healthcare professionals to patients

- Not as consistently as we should—so in a limited way mainly through the use of patient decisional support tools such as one to one, videos, leaflets.

Yes, from healthcare professionals to healthcare professionals

- Yes, the General Council of Pharmacists communicates benefit-risk information from the Health Ministry to the Pharmaceutical Associations, and then, they send this information to the pharmacists.
- Yes. We communicate the information benefit-risk from the Health Ministry to pharmacists.
- Yes, to our member pharmacies by phone, email or fax, based on guidelines from official organisations (EMA, FDA, federal government ...) or other data that we seek in the scientific literature.

Yes, from healthcare professionals to regulatory authorities

- Yes. When a drug related problem is identified, the pharmacist makes a report to the vigilance unit.

Information requiring active search by patients or healthcare professionals (e.g. publication in scientific literature or internet)

- Discussion of risk-benefit or 'balance of risk'.
- As a Drug Information Service when we are asked about benefit-risk profile, sometimes of different medicines in order to compare, described in literature (tertiary sources and summary of product characteristics).
- As a Drug Information Service when we are asked about some medicines main therapeutic indications and risks (adverse reactions, contraindications, interactions...). Re-check other medications taken by patient and comment if appropriate.

4) What information on benefit-risk, do you think is missing?

For each type of missing information, what would be the best source in order to provide this information? (Regulatory authorities, healthcare professionals' or patients' organisations, doctor, pharmacist, nurses, package leaflet or labeling, others?)

Unavailable information (data which do not exist)

- Comparative information, but this is often impossible to assess accurately as different trials are conducted in different ways [as an example look at the subtle different ways in which pivotal registration trials have been conducted for weight-loss medicines].
- Information concerning the possibility to accelerate the process of cure/treatment of the patient by using the medicinal product in specific ways could be enlarged (summary of product characteristics).

Information difficult to obtain

- Comparative efficacy & side effects (regulatory authorities, healthcare professionals).
- Information is often insufficiently quantitative [accepting the vagaries of reporting of adverse events].
- Long term utilisation of high dosages and its implication to the biochemistry of the patient (summary of product characteristics; package leaflet).
- Effects on age.
- Sufficient information on NNT & NNH.

Information poorly disseminated

- Information, especially about risks, is there, but often quite rare side effects are described in terms or symptoms that are extremely common in the population regardless of any drug taken, and it is difficult for non-healthcare professionals to evaluate how likely these symptoms are to be related to the drug taken. The benefits are often not easy to understand patients, especially when drugs are efficient treatment to very serious diseases. This information should be in a book about all drugs available (the book should be available to all the above mentioned persons/groups, and all the important effects/side effect on a leaflet within the package).
- Efficacy related to mode of adm. (package leaflet, doctor, nurse).
- Data on the frequency of adverse effects (package leaflet).
- The package leaflet could also include interactions with some specific foods.

Other

- Patient organizations, especially for chronic diseases can be a good source of information.
- The economic vector is missing—how much did the research and development process cost, what is the turnover expected (pharmaceutical industry and/or regulatory authorities)—this is important so that healthcare professionals may be critical towards benefit-risk data available.
- How much does a certain medicine cost compared to other similar medicines already available in the market (regulatory authorities)—this is important to assure the best therapeutic decision, both by healthcare providers and patients.
- How long did it take for the new medicine to be launched into the market (pharmaceutical industry)—this gives an idea of the extent of clinical research, which certainly influences the knowledge about risk profile.

5) What would you propose to improve information on benefit-risk of medicine? How EMEA or other regulatory agency could contribute to this improvement?

Recommendations on quality and extent of information

- Neutral and balanced information available for both healthcare professionals and patients to discuss.
- Having a complete updated information provided by the medicine manufacturer about all effects and side effects, including clinical tests results, available for healthcare professionals.
- Availability of information in patients groups at risk of adverse effects.
- Involve patient/carer groups & associations much more in the development, testing & evaluations of information provided.
- Ensure information on efficacy is comparable between individual drugs.
- Be very clear on how current patient information/decisional support tools actually.
- Inform patients/clients of the potential risks and benefits of treatments since many on the health care market are poorly designed.
- The information benefit-risk of medicinal product is large but not enough. In some cases there is no sufficient information for new medicines. Larger clinical investigation for new medicines could be considered. The time for assessing the documents for receiving Marketing Authorization for new medicines in some specific diseases has to be prolonged in order to allow more time to the assessors for precise estimation. For generic products and "well established" this time could be reduced.
- Post marketing vigilance and data collection should be made mandatory until a more solid benefit-risk profile is established-not only adverse drug events should be considered, but also all relevant data concerning medicine's therapeutic utilisation in a broader range of patients, including prescription patterns-large scale prescription of new medicines is partially responsible for public health problems that resulted in medicines withdrawn from the market-large scale prescriptions in a phase when only the top of the iceberg is known.
- The information leaflet included with the medicine must be modified by the EMEA in order to explain in an easy language all the facts related to its patterns of efficacy and toxicity and the issues that modifies that benefit-risk balance.
- Be more quantitative where practicable.
- Include practical advice on reducing risks.
- Provide up-to-date NNT, NNH information on major therapeutic targets and risks of commonly prescribed medicines.
- If possible, a system of quantification for the benefit-risk factor.

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- Provide up-to-date NNT, NNH information on major therapeutic targets and risks of commonly prescribed medicines.
- If possible, a system of quantification for the benefit-risk factor.

Recommendations on the dissemination of existing information

- The most important communication tool lies in the face to face meeting of healthcare professionals and patients.
- Very important for the EMEA is to quickly distribute neutral and balanced information to healthcare professionals and patients about drugs either new on the market or when there are serious doubts concerning a specific drug. These situations create respectively expectations or fear to patients when mass media publishes more or less documented information on drugs.
- Adverse drug events that occur during clinical trials and all clinical development phases should be communicated to healthcare professionals responsible for post marketing therapeutic utilization of the new medicine.
- Reports to health professionals as soon as possible on new actions and/or side effects of treatments and medicines.
- The time period that a new drug takes to be launched into the market should be regulated, so that, and taking always into account the disease in stake and the urgency needed, there are enough guarantees that all information about benefit-risk profile possible at this phase of development is obtained before the new medicine is made available in a larger scale.

Recommendations for new tool for information, including increasing publication

- The general population may not understand the real significance of benefit-risk information. Doctors, pharmacists, and nurses should be given the necessary tools to explain, in an easy language, that item.
- The information could be expanded through specialized journals and the Agencies' websites. Participation in patient's organizations.
- To exchange official information between agencies concerning their experience in clinical trials control.

Recommendation for further transparency

- There shouldn't exist the concept of "confidential information", mostly with regards to critical situations.
- Clinical trials results should be completely published.
- It is important to assure that all information available is as complete and clear as possible. And it should be given access to all information to healthcare professionals, so that the best therapeutic decision is taken and patients are as best informed as possible.
- A more detailed and clear information about clinical research and post marketing vigilance data

is needed (pharmaceutical industry and regulatory authorities)–mostly so that healthcare professionals may help patients making the best therapeutic choice.

Recommendation related to education

- It is important, that all the parts mentioned make an effort to minimize the fear that patients show when they read the labelling of medicines. They must explain that not all of the adverse events must appear in one patient.
- The patient must know, by all means, that it is very important to follow the dosage instructions in order to gain the major benefit of that medicine.

Others

- A higher level of regulation over clinical research and clinical trials should be applied. Clinical trials are the main source of benefit-risk information, mostly in what concerns to new and innovative medicines, so it is important to assure that there is enough investment in this clinical exploratory phase (time and money invested) so that they may assure the best benefit-risk information that is possible to obtain at this stage of development–clinical trials should be drawn so that may allow to establish the medicine’s real therapeutic value using measures relevant to patients, clinical trials should allow to predict the new medicine’s behaviour in a real clinical practice scenario.
- Pharmaceutical industry retains responsibility over the first findings and initial investigation process of a new medicine, is also responsible for the development phases and clinical trials, for promoting this new medicine near healthcare professionals and patients, influencing prescriptions and therapeutic guidelines – these are all stages retained by a single entity, so there must be a higher concern of applying regulation by other parties.
- Regulatory entities should be very critical in what concerns to data presented by pharmaceutical industry.

6) What is the minimum time necessary to address benefit-risk during a patient-healthcare professional consultation?

- As long as it takes to feel comfortable that the patient is adequately informed.
- It is difficult to give a precise time as this depends of numerous factors, such as: complexity of the disease or health condition, the medication in stake (if it is a new medicine or part of a new therapeutic, might take longer), the patient himself (degree of instruction and understanding), the interest of both the healthcare professional and patient about the benefits and risks of the therapeutic to be implemented, if the medicine is going to be administered in association with other medicines, the amount of information available and published, both for the healthcare professional and patient... The minimum time could therefore range from 5-10 minutes to 30-40 minutes.
- It depends on the emergency of the treatment.
- It depends on how far in details the patient can understand.
- It depends on the time allocated for the decision if the patient has the choice for alternative treatments.
- Varies according to patients and diagnosis, drugs and even healthcare professional. 2-4 minutes is minimum, and must be followed by an opportunity for patients to discuss again with the healthcare professional after digesting the initial information.
- 1-10 minutes.
- ~ 5 min.

Annex IV: Compilation of answers received from regulatory authorities

All answers for each question were compiled together and classified in order to put together answers addressing similar topics. They are therefore presented in subsections to facilitate review of the answers. Subsections have been harmonised between the compilations of answers from patients' organisations, healthcare professionals' organisations and regulatory authorities to facilitate discussions.

1) What is the benefit-risk of a medicine for you?

Definition

- The European pharmaceutical legislation defines *risk-benefit balance* ¹⁹ as follows: An evaluation of the positive therapeutic effects of a medicinal product in relation to any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health (and to any risk of undesirable effects on the environment).
- The benefit-risk balance of a medicine is an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health; or any risk of undesirable effects on the environment).
- There are two types of benefit-risk balance—(1) at population level; (2) at patient level (= therapeutic benefit-risk). (2) is relevant to patients and healthcare professionals, while regulatory authorities base their decisions on (1). Nevertheless, regulatory authorities should issue information which helps patients and HPs to take decisions for (2).

Objectives

- A marketing authorisation shall be refused if the risk-benefit balance is not considered to be favourable.²⁰ The legislation also foresees that competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable in order that the risk-benefit balance may be continuously assessed.²¹

Method (including timing)

- To allow competent authorities to assess the risk-benefit balance of a medicine, pharmaceutical companies are legally required to submit the results of tests-internationally agreed-to show the efficacy and safety of a medicine.
- A benefit-risk assessment is based on comparing data for efficacy, based on well performed clinical studies and data on adverse effects taking into account frequency and seriousness.
- In a benefit-risk assessment the expected benefit for the patient should outweigh the adverse effects and potential risk. This is dependent on seriousness of the disease and available other treatments.

Other

- Benefit is different from efficacy. While efficacy relates to pre-defined endpoints in CTs, benefit includes but is not restricted to effectiveness, which describes an effect under real life conditions. Benefit goes further and describes of desirable short-term and long-term preventive, therapeutic and/or curative effects and their positive influence on the otherwise natural course of disease and quality of life. We have to note that we should use the term benefit in the context of benefit-risk in the sense of probability of benefit.

¹⁹ Article 1 point 28 of Directive 2001/83/EC as amended

²⁰ Article 26 of Directive 2001/83/EC

²¹ Article 23 of Directive 2001/83/EC

- Please note that EU regulation chose to call benefit-risk risk-benefit balance to underline the importance of safety surveillance.

2) Which information do you expect in terms of benefit, risk, and, benefit-risk balance of a medicine? What information is the most important?

2.1 Expected information on benefit

Qualitative characteristics

- Will the medicine cure the disease or treat the symptoms (*most important*).
- Impact on course of disease, also in terms of probability. Probability of short-term and long-term effects.
- Specific quality (manufacture-related), non-clinical and clinical data have to be produced by pharmaceutical company to establish the efficacy of a new medicine. They are assessed by competent authority prior to marketing authorisation.
- Information able to demonstrate respective medicinal product significant contribution to treatment, diagnosis, or prevention of a disease (data on effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting adverse reaction, as resulting from pre-clinical studies and clinical trials conducted in medicinal product development and post-authorisation data on medicinal product safety).
- Success factors for benefit.

Quantitative characteristics

- Which percentage of patients will benefit from the medicine (This can vary from 100-20% or lower) - (*most important*).

Population concerned

- Is it for all age groups (children, adults, elderly, very elderly).
- Benefit of a medicine is best demonstrated by clinical trial designed to show a specific effect(s) in patients. Clinical trials shall represent as much as possible the population to be treated and the expected benefit.
- There are requirements for obtaining data in specific population (e.g. women, elderly, children...) or in patients with specific conditions (other concomitant disease or use of other medicine). However, clinical trials cannot reasonably cover all specificities of individual patients nor give an exact picture of the benefits experience by each patient.

Comparison with other therapies

- Benefit shall be shown in “controlled clinical trials” versus placebo or established medicinal product, depending on ethical considerations and therapeutic area. Thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.²²
- The benefit should also be assessed in view of the natural evolution of the disease and its potential consequences.

²² Annex I of Directive 2001/83/EC as amended

2.2 Expected information on risk

Qualitative characteristics

- Are there serious adverse effects and can these be avoided?
- Warnings in which situation medicine should not be used.
- Adverse effects in terms of frequency and seriousness.
- Quality and probability of adverse reactions and their outcomes. Risk periods of adverse reactions. Warning signs of adverse reactions and instructions on what to do. Reversibility of adverse reactions.
- Submission of as comprehensive as possible Adverse Drug Reaction Reports from both healthcare professionals and pharmaceutical companies, at both medicinal product development time and the post-authorisation period.
- Specific quality (manufacture-related), non-clinical and clinical data have to be obtained by pharmaceutical company to establish the safety profile of a medicine. They are assessed by competent authority prior to marketing authorisation.
- Risk is probability of harm which may be experienced by the patient and includes adverse effects due to any root cause and discomfort as well as risks to become dependent or otherwise abuse the product and experience. At population level, risks for off-label use, medication errors, abuse, misuse as well as accidental or intentional (e.g. suicidal or criminal) use have additionally to be taken into account.
- Risks which occur frequently and rapidly may usually be easily identified and quantified. However, it is not always possible to identify or quantify rare risk or risk occurring at long-term. Some non-clinical tests may help to suspect them. In other case, a risk management plan should be put in place at the time of the marketing in order to ensure prompt identification and management of risk which could not be confirmed earlier.

Quantitative characteristics

- Identified risk should be characterised; severity, frequency, timing, duration, risk factors, management. However, the rarer the risk is the more difficult it is to characterise.
- Specification of causality, ADR seriousness, frequency, presence of risk factors and possible mitigating preventive measure.

Population concerned

- Important interactions with food, alcohol, other medicines.

Comparison with other therapies

- Characterisation of a risk may have to be performed in comparisons of alternative treatment.

2.3 Expected information on benefit-risk balance

Qualitative characteristics

- Marketing authorisation holder shall show that the efficacy and safety findings support the proposed dose and target indications and that the product information will optimise the benefits and manage the risks is required.²³
- Expert judgement is the cornerstone of benefit-risk evaluation for the authorisation of medicinal products.
- A description of expected benefits in relation to known risks.
- Information on risks for the patient when the medicine will not be used.

Quantitative characteristics

²³ Annex I of Directive 2001/83/EC as amended

- N.A.

Population concerned

- It is in most cases based on the use of medicine in well controlled situation.
- Benefit-risk balance can be different for individual patients, but this is in most cases not predictable.
- Efficacy and safety findings are demonstrated for a group of patient and may not be predictive for each individual patient.
- Information provided should allow interpretation of the benefit-risk balance in the context of a specific pathology.

Comparison with other therapies

- Even if the assessment of risk-benefit balance of a new medicine has to be performed in view of an established existing therapy, it differs from the concepts of “placing the product in the therapeutic strategy” or “relative effectiveness”.

3) Do you communicate benefit-risk information? If yes, how?

Direct communication to patients or healthcare professionals

- No.
- By answering to public or media queries.

Communication received passively by Patients or healthcare professionals (e.g. leaflet)

- Yes.
- Competent authorities communicate benefit-risk information in various way:
 - by reviewing pharmaceutical company’s summary of product characteristics which will be the basis of information for healthcare professionals on how to use the medicine safely and effectively;
 - by reviewing pharmaceutical company’s package leaflet which represents the primary source of information for the patients (apart from discussion with Healthcare professionals).
- Benefit-risk information is communicated through posting on competent authorities’ website the Summary of Product Characteristics of medicinal products authorised for marketing.

Information requiring active search by patients or healthcare professionals (e.g. publication in scientific literature or on internet)

- Yes.
- Competent authorities communicate benefit-risk information in various way:
 - by publishing public assessment report;
 - by publishing press-release on specific topic (e.g. safety issue, information on a class of medicine, new indication...);
 - by answering to public or media queries.
- Benefit-risk information is communicated through posting on competent authorities’ website the Summary of Product Characteristics of medicinal products authorised for marketing:
 - translations of EMEA press releases on medicinal safety;
 - Health Professionals Direct Communications.
- Other medicine safety related information specific (e.g. list of on-prescription medicinal products and list of OTCs).

4) What information on benefit-risk, do you think is missing?

For each type of missing information, what would be the best source in order to provide this information? (Regulatory authorities, healthcare professionals' or patients' organisations, doctor, pharmacist, nurses, package leaflet or labelling, others?)

Unavailable data (data which do not exist)

- A marketing authorisation cannot be granted if the risk-benefit balance of the product is not assumed. This assumption has to be considered with the risk of delaying the marketing of a medicine which could help patients.
- In most of the case, the necessary amount of efficacy and safety information is available to confirm the positive risk-benefit ratio for a marketing authorisation for the general population concerned. However, some information may be missing to facilitate tailoring of its use in a special population or to characterise a particular risk. Waiting for this information would inappropriately delay the use of the medicine by the general population. Risk management plan will help to obtain information on missing data.
- In exceptional cases, an authorisation may be granted despite of missing data because of the scientific or ethical difficulty to obtain them or because of a medical need, provided that the risk-benefit balance is judged positive according to current knowledge.

Information difficult to obtain

- Impact on course of disease, also in terms of probability. Probability of short-term and long-term effects in terms of benefit. Success factors for benefit. Risk periods of adverse reactions. Warning signs of adverse reactions and instructions on what to do. Reversibility of adverse reactions. Maximum daily doses in mass or volume unit. Areas of uncertainty. This information (apart from areas of uncertainty) should be included in the package leaflets. If the information is unknown, this should be stated. How to provide information on areas of uncertainty, needs to be further investigated, but this information is very important e.g. when deciding to take a preventive treatment in the light of not yet investigated potential risks - this may even be the case of well-established medicines for which adverse reactions after long-term use may not be detected as causally related while on the other hand the scientific community is aware of the fact that information is actually missing. For the well-informed individual, research articles or literature reviews are currently a source for information on such missing risk and long-term benefit effect.
- When used in medical practice new information will become available and this should be included in official documents: summary of product characteristics, package leaflet. However, this is often dependent on initiative of companies.
- Stronger input from professionals', patients' and consumers' associations on their experience in use of medicinal products authorised for marketing.
- Better healthcare professionals' involvement and commitment in spontaneous AD reporting.

Poorly disseminated information

- Package leaflet provide information on the use of the medicine, however, information on the benefit is rare and information on the benefit may not be sufficient.
- Summary of product characteristics and public assessment report provide all available data on benefit and risk supporting the marketing authorisation. The accessibility, extent presentation and relation could be improved to facilitate consultation of information on benefit-risk.

5) What would you propose to improve information on benefit-risk of medicine? How EMEA or other regulatory agency could contribute to this improvement?

Recommendation on the quality and extent of existing information

- Expert judgement is the cornerstone of benefit-risk evaluation for the authorisation of medicinal products. In this respect, it is of utmost importance that competent authorities obtain appropriate healthcare professional experts opinion when necessary. Support from patients' representative may also be necessary, e.g. to better measure the impact on patients' quality of life.
- The content and presentation of the summary of product characteristics and of the public assessment report should be further discussed with healthcare professionals to facilitate both an easy daily use and a detailed consultation e.g. for tailored prescription or preparation of therapeutic guideline. For example, it should be discussed how clinical trials studies should be presented in each document.
- The package leaflet misses information on the benefit of the product. Risk should be presented in a more friendly way. Risk and benefit should be presented in close place to facilitate assessment of risk-benefit balance.
- A system for preventing medication errors through improved package design and labelling should be put in place.
- It is important to explain in lay terms that all medicines have adverse effects.
- The need of information on risk-benefit of a medicine may differ depending on the situation. It is therefore important that information on risk and information on benefit are clearly presented individually, both in detail and factually, and, in summary and lay language.
- Regulatory authorities should provide information on benefit-risk at population level as rationale for their decisions. Regulatory authorities cannot provide information on benefit-risk at patient level but should provide information on benefit and risks in a way enabling therapeutic decisions for the individual patient.

Recommendation on the dissemination of existing information

- Improved communication with MAH, associations of medicinal product manufacturers, healthcare professionals, patients and consumers.

Recommendation for new tool for information, including increasing publication

- Intensified networking among competent authorities, in the coordination of which EMEA and HMA have to play an increasingly important role.

Recommendation for further transparency

- Transparency should only be limited by personal data protection and commercially confidential information.

Recommendation related to education

- Patients and healthcare professionals should be aware of which benefit-risk information is prepared by competent authorities and where to find it.
- They should also be more involved in reporting of post-marketing information to regulatory authorities.
- Patients and healthcare professionals should be aware that all information on a medicine may not be available. In particular:
 - Regulatory authorities assess risk-benefit balance of a medicine based on pooled data obtained from a group of patients. Additional data are requested to foresee any potential difference in special population. However, a marketing authorisation cannot predict the risk-benefit for each patient;
 - Similarly, a new medicine will obtained a marketing authorisation only if its risk-benefit is at least equal to existing therapy in the targeted population. However, data required for

marketing authorisation may not be sufficient to place the new product within the therapeutic arsenal of a disease for the concerned population.

6) What is the minimum time necessary to address benefit-risk during a patient-healthcare professional consultation?

- Hugely depends on the disease, the possible treatments and the patient; from 1 minute to days.
- It is dependent on first visit or repeated consults.
- I would expect 10-15 minutes.
- This cannot be answered from a regulatory perspective.
- The time needed will depend on the severity of disease and risks of the proposed treatment(s), quantity of available information and its impact on the patient as well as his/her personal information needs, pre-knowledge and perceptions.
- There may be additional time needed to speak to family members, in particular where cultural and religious principles are touched.