



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2013
EMA/607864/2013
Stakeholders and Communication Division

The patient's voice in the evaluation of medicines

How patients can contribute to assessment of benefit and risk

Introduction

The ultimate *raison d'être* of any medicine is to benefit patients. However, older and more paternalistic models of medicine often treated patients as a passive group who were to be given instructions but who should not be confused or worried by too much information. Although the best healthcare professionals have always recognised the importance of listening carefully to their patients, the idea that patients' knowledge, views and preferences were as significant as those of any other stakeholder in the healthcare process was not a standard part of this model. Over the past decades this has changed, as it has become increasingly clear that such a model is neither appropriate nor useful in a better connected and less deferential world.

Regulators and manufacturers, too, have learned the importance of consulting and involving patients. Since patients will be the ones taking these medicines it makes absolute sense to incorporate their values and their knowledge at different stages throughout the long process of developing, assessing, licensing and monitoring medicines. The European Medicines Agency (EMA), with a remit to help ensure that over 500 million European citizens, from very varied environments and cultures, are provided with safe and effective medicines, has been at the forefront of efforts to involve patients as critical stakeholders in the regulatory process and works extensively with patient and consumer representatives.

As part of its on-going commitment to this idea, the Agency held a workshop on 26 September 2013, at its headquarters in London, bringing together representatives of patients, consumers, healthcare professionals and the pharmaceutical industry with members of the EMA's scientific committees and staff, in order to get a better understanding of the current and possible future role of the patient during the development of medicines, and particularly what patients can contribute to the assessment of benefit and risk that lies at the heart of the regulatory process. Because patient views of risk and benefit can differ from those of other stakeholders, and may vary between patients and at different stages of disease, this is an important and complex area that may require innovative methodologies.



What we can learn from a pioneering model – ECAB and the HIV community

One of the seminal events that led to greater patient involvement in drug development and regulation was the crisis posed by the HIV virus from the 1980s onwards. An intense outburst of patient activism, highly motivated and well informed, forced both the pharmaceutical industry and regulators to reconsider the way they interacted with patients. The European Community Advisory Board (ECAB) is a working group of the European AIDS Treatment Group, a patient organisation for people living with HIV and AIDS. ECAB was set up in 1997 as a forum for interactions with the pharmaceutical industry and regulators, to allow a more constructive dialogue and encourage the timely availability of safe and effective therapies.

As this relationship has expanded and matured, an enormous amount of knowledge has been accumulated by the ECAB membership, not only within the specific therapeutic area of HIV and AIDS, but also in terms of developing models for the interaction of different stakeholder groups while maintaining the proper independence of each, and understandings about the role of the 'expert patient' and the importance of achieving consensus within a group representing patients with diverse backgrounds and viewpoints. In addition, means to address the concerns of industry (such as release of commercially sensitive information in public reports, and the need to work within industry's Code of Conduct) have been explored, and a recognition has developed that academia and the wider scientific community are important stakeholders with whom interactions to date have been under-developed.

Much of this knowledge is valuable and transferrable, and ways of sharing this knowledge (not only externally but in terms of training new patient representatives within the group) are currently being considered, including the development of a 'school of excellence'.

Assembling patient data in a pan-European context

One of the most important ways patients can contribute to both pre- and post-licensing development of medicines is by contributing data derived from their use of medicines. This is particularly important post-authorisation, where sharing data over long periods and in a more varied population helps to understand benefit-risk in a real-world context. However, the difficulties of pooling patient data derived from many different countries should not be underestimated. The workshop looked at the lessons that could be learned from development of the EUREMS register, a multinational multi-sponsor partnership between clinical centres and patient organisations to harmonise the many national and regional registers and databases for multiple sclerosis patients that exist across the EU.

Agreeing a common dataset had proved difficult, since it had potentially to meet the needs of many different groups, including clinicians, the pharmaceutical industry, patient advocates and government health technology assessors (HTAs). However, now such a dataset has been agreed, it has already begun to demonstrate its real-world value in clinical studies, and will hopefully help in addressing the enormous variations in access to specialist care and treatment that still exist within Europe for multiple sclerosis. In particular, the incorporation of patient-reported outcomes allows a unique patient perspective to be derived from the data.

Patients in drug development – an industry perspective

The value of patient input in drug development is also recognised by the pharmaceutical industry, which has come to see the information that surrounds a medical product as being as much a part of its output as the products themselves. Patient-reported outcomes have been increasingly important in this over the last two decades, but the techniques for obtaining them are still developing, whether these be

form-based, interviews, or through online communities. In addition, the industry has explored ways to convey the patient experience of their illness to researchers. However, legal and regulatory restrictions may constrain the ways in which companies can communicate with patients.

Perhaps the most important role of patients in initial development is as subjects in clinical trials and one area of much interest is the way in which trial results (including negative trial results, which can be potentially devastating in areas of unmet clinical need) are conveyed to patients. Although there is considerable pressure on the industry to release full clinical trial data, it has been argued that there may also be a need for lay language summaries of trial results for participants, in order to give them an understanding of the outcomes, as well as direct briefings where outcomes are sensitive or troubling. The same level of transparency should also be assured for academic and non-industry trials.

Summaries of trial outcomes might be useful for other stakeholders, including the media as a way of limiting inappropriate reporting of results. There may also be a role for a less legalistic 'lay summary' of the informed consent documentation, as a way of encouraging patients to enter clinical trials in the first place.

Patient input in the Scientific Advice process

One way in which patients, and more broadly, consumers of medicines, are currently involved in the development process of medicines at the European level is as experts within a Scientific Advice Working Party (SAWP). Companies can request scientific advice on the appropriate tests and studies in the development of a medicine at any stage during that development. This increases the likelihood of a positive and speedy outcome to licensing applications and is thus an important tool to facilitate the availability of safe and effective medicines. Scientific advice is supplied by a working party convened of experts chosen for their knowledge of the appropriate area, and may involve a face-to-face meeting with the company if necessary. An analogous procedure, protocol assistance, is offered to developers of orphan medicines.

Increasingly, the EMA has been including patient representatives among the members of SAWPs. Although advice on the most technical areas may not be suited to patient involvement, the Agency has tried to include them in the procedure wherever feasible. These representatives can add a unique patient perspective on areas such as the feasibility of study proposals, the patient population, the duration and design of the study and the relevant outcomes and safety concerns from a patient point of view (which may not be the same as that of the other stakeholders). Patient involvement has proved particularly valuable when participants can attend in person rather than giving advice in writing.

EURORDIS (the European Organisation for Rare Diseases), which is one of many patient organisations working as partners with the Agency, surveyed a number of patient representatives who had been involved in this process and found that overwhelmingly they considered the experience interesting and beneficial, and in around 50% of cases had made an important contribution to the final outcome, although there was a clear desire for more support and training in this time-pressured role and it was regretted that the confidentiality agreement which all experts in the SAWP must sign prevented the patient representative from discussing the issues with fellow patients who might have had valuable input to offer. The importance of a good rapport between the meeting chair and the patient representative was also highlighted. In the light of the largely positive contribution that patient representatives were making at a European level a similar contribution should be encouraged for those medicines that were developed and evaluated at a national level.

New ways to capture patient preference and represent benefit-risk

For a medicine to be licensed in the European Union (EU), its benefits must be shown to be greater than its risks. This balance lies at the heart of the regulatory process. But capturing and quantifying these values in a way that allows one to be offset against the other is one of the most difficult areas of the process, even for professional regulators. If patients are to be encouraged to contribute further in this area, ways to assist all participants in the process are urgently needed. This is particularly true because patients are not a homogeneous group, and individual values can be influenced by many cultural and other factors such as age and stage of disease.

The EMA is actively engaging in and supporting research in this area. The VALUE study, which benefited from collaboration with the UK Multiple Sclerosis Society, used novel software (MACBETH) to elicit patient preferences for different outcomes in the treatment of multiple sclerosis, and assign weightings that could be used to quantify the relative attractiveness of those outcomes. The study was able to identify factors that influenced patient preferences and willingness to risk adverse effects (notably severity of disease and ability to walk) and this input could be used to build decision models for actual treatments. In addition, the software approach was considered highly configurable, and if suitably validated could potentially be used much more widely to help patients, healthcare professionals, regulators and health technology assessors identify the relative importance of the criteria that affect their decisions. Another research example is the on-going PROTECT project. This large collaborative European project has a number of workstreams, one of which is looking at ways of representing benefit and risk and at how these different methods, both textual and graphical, affect the perception of benefit-risk, and the consequent decisions made by patients, healthcare professionals, and regulators.

Patients in drug licensing – an industry perspective

Just as in drug development, the pharmaceutical industry recognises the vital importance of the patient voice in the regulatory/licensing process. However, it also recognises that there are a number of practical challenges that need to be overcome, and questions to be asked, to enable current developments to evolve still further and to enable regulation and licensing to keep pace with scientific development. This will require continuing dialogue with all stakeholders, which may include groups such as those responsible for health-technology assessment and delivery and financing within the healthcare system as well as those currently engaged in the process.

One important vehicle for engaging patient interaction with other stakeholders is via the Innovative Medicines Initiative (IMI), a public-private partnership involving multiple stakeholders which is managed by a neutral governing body to regulate conflicts of interest. Because of the latter, and because IMI projects cover the entire lifecycle of medicines development, it provides a good environment for testing new tools and methodologies such as those referred to above. Patient groups have been involved in many aspects of IMI-related research, not just as participants and advisors but as active collaborators helping to shape protocols and priorities, generate ideas, and develop the clinical questions that are to be asked. Reciprocally, projects such as EUPATI (the European Patients Academy on Therapeutic Innovation, which aims to provide reliable information on the research and development process) are helping to inform and empower patients.

The current setting of priorities for IMI2 represents a unique window of opportunity to involve patient representatives (and also healthcare professionals) at an early stage of planning. The environment in which these priorities are being developed is very much influenced by the WHO's updated report on health priorities and the priorities being set by European authorities, and given the influence these

factors will have on the industry's research priorities it is vital that patients have a voice and are able to hold other stakeholders to account.

Patient involvement in Scientific Advisory Groups

At present there is no patient representative sitting as a member of the Committee for Human Medicinal Products (CHMP), the EMA scientific committee with the responsibility of evaluating licensing applications for human medicines. However, as part of the evaluation process, the CHMP commonly convenes Scientific Advisory Groups (SAGs), to allow it to benefit from specialist advice where the Rapporteur and Co-Rapporteur, the two members charged with leading the evaluation, have come to different conclusions, or where there are other difficult or controversial issues to be addressed. Patient representatives are commonly involved as members of SAGs (over 80% in 2013), and an EMA survey found that patients were able to follow the discussion and contribute to it in most cases, although this did vary somewhat with the type of question being addressed and between representatives. Effective patient involvement can strengthen the validity of the SAG's conclusions. Because it can be a challenging environment, requiring some background knowledge and the review of extensive paperwork, it has been suggested that there may be a role for the development of a more permanent 'expert patient' representative role, and supplementing this with additional 'naïve patient' representatives to counteract the risk of coming to adopt an overly regulatory viewpoint. Although the patient representatives in such a group cannot be expected to represent their entire patient community, let alone the broader interests of medicines consumers and civil society as a whole, they supply a unique perspective and their presence in the SAGs is an important tool for bringing patient values and preferences into the system.

Patient involvement in the scientific committees – the lessons of PRAC and the potential for CHMP

In 2012 the EMA's newest scientific committee, the Pharmacovigilance Risk Assessment Committee (PRAC) came into being, embodying new European legislation designed to improve the reporting and assessment of medicines safety before and after licensing. Although the EMA had previously begun to involve patients in the process of safety assessment, the formation of the PRAC allowed the patient role to be formalised, with a patient representative and alternate sitting as full members of the Committee. As a result, patients are now fully involved with the difficult assessments of benefit-risk that sit at the heart of the regulatory process.

Experience to date has shown that the patient representative plays an invaluable role in ensuring that regulators remember for whom they are working, and in contributing to decisions about the wording and timing of risk communications which play a fundamental role in ensuring medicines safety. Furthermore, as channels of communication between the Committee and patients' organisations and wider civil society, they can play an invaluable part in explaining the concepts of benefit-risk and the way medicines are licensed and regulated. The role is challenging, and patient representatives may sometimes need individualised support in particular areas, but as in other regulatory roles, the presence of a unique patient viewpoint strengthens and enriches the Committee's conclusions. However, it was noted that input could be improved if both the patient representative and the alternate could attend meetings, which would permit mutual support and maintain continuity of knowledge.

In contrast to the PRAC, as has been previously noted there is no current patient representative on the CHMP. However, patient organisations are often consulted by the CHMP for advice on matters of benefit-risk, and their input has sometimes resulted in significant changes to the CHMP's views. Because the questions asked by CHMP can be complex and involve considerable research on the part

of the patient organisations it is important that they should be involved in the process from the early stages, and that the expectations of their role are clearly defined. Since the CHMP is fully aware of the value of patient input in other aspects of the regulatory process, including Scientific Advice, ad-hoc meetings, guideline preparation and its own SAGs, its 2013 work programme is looking at a role for patient representatives in the evaluation of benefit-risk. Since patient representatives are already engaging in this process via the PRAC, the time may be ripe for a more formal involvement in CHMP. However, allowing patient representatives to sit as voting members would require changes in legislation.

The EMA is drawing up a proposed framework with a view to further formalising and systematising the present situation. This will involve codifying the situations in which direct input should be sought, defining what outcomes are expected from patient or consumer involvement, defining ways to select and support patient representatives, and subsequently capturing and monitoring the results of this more systematic and consistent engagement to demonstrate the added value it brings.

Conclusions

Giving patients a voice in the development and evaluation of medicines is acknowledged as being of fundamental importance by the major stakeholders in the process. Patient involvement in areas such as HIV research, understanding of patient perceptions of risk related to adverse effects of multiple sclerosis treatments, and the safety of hormone replacement therapy has affected the treatment of many fellow patients and citizens for the better. Much has already been done, and the challenge is now to build on the extensive work to date, broadening patient understanding of medicines development and regulation, and the concept of benefit-risk that lies at the heart of it, so that patients can contribute their insights and understanding in the most effective way.

This will involve challenges to all the stakeholders. Patients or their representatives will need to be prepared to accept additional responsibilities, regulatory processes and procedures will need to be adapted to maximise the benefits of patient involvement, researchers and the industry will need to continue to examine the ways they communicate with and involve patients, and evidence of the value of these changes will need to be gathered and disseminated.

Building on the current extensive involvement of patients in the work of the EMA, formalising areas that are currently dealt with ad-hoc and extending contacts with other stakeholders, may require a forum in which the practical challenges can be explored and solutions can be developed. Among the issues that the workshop identified, it will be necessary to:

- continue to identify current best practice and learn from it;
- identify where quantitative versus qualitative input are needed, and develop and validate new tools for eliciting values and preferences and representing benefit and risk;
- take account of the way values vary between patients and change over the patient journey;
- develop means to identify and manage differences of view between patients and between patients and other stakeholders;
- look at what training and support is needed to maximise patient involvement at all stages of the process, for the full range of disease states, and who should be supplying it;
- continue to develop the role and timing of patient involvement in later post-launch stages of the product lifecycle (e.g. in signals assessment);
- identify, and work to minimise, legal, regulatory, financial and procedural barriers to patient involvement;

- consider the broader constituency of medicines users or consumers whose views will not necessarily be the same as those of 'patients'.

The work currently in progress at EMA to review the framework of patient interactions has already considered many of these issues and should provide an ideal platform to take such issues forward.

Further information

- Current framework of interaction between patient groups and the EMA:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018013.pdf
- Criteria and rules for involvement of patient groups in EMA processes:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/12/WC500018099.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074644.pdf
- Role of patients in EMA Scientific Advice Groups:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/12/WC500119201.pdf
- Role of patients in EMA reviews of product information:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004975.pdf
- Role of patients in the EMA Scientific Committees:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/12/WC500119614.pdf
- Patient and consumer organisations currently involved with EMA:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/q_and_a/q_and_a_detail_000082.jsp&mid=WC0b01ac0580035bf2
- Innovative Medicines Initiative (IMI): <http://www.imi.europa.eu/>
- EUPATI: <http://www.patientsacademy.eu/index.php/en/>
- The PROTECT Project: <http://www.imi-protect.eu/>