EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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The European Medicines Agency Road Map to 2015: The Agency's Contribution to Science, Medicines, Health

Draft for Public Consultation

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1. Introduction

The European Medicines Agency (referred to in this document as "Agency") developed in 2005 a longer term strategy[1] as an important pillar of its proactive approach to the continuing evolution of the pharmaceutical arena in the European Union (EU). This strategy mainly focussed on contributing to better promotion and protection of public health[2], improving the regulatory environment for medicinal products, and helping to stimulate innovation, research and development in the EU.

The Agency's Road Map to 2015 is a continuation of this longer term strategy, building on current achievements, but also taking due account of the changing environment in which the Agency will have to operate over the next five years. In further developing its Road Map project the Agency will ensure that its vision is consistent with and complementary to strategic directions provided by the European Commission[3],[4],[5] and Heads of Medicines Agencies[6].

The Road Map to 2015 sets out the Agency's vision, elaborates on the main drivers for progress and change that will impact on it, and explores the main initiatives to be undertaken to successfully meet the challenges it will face. This vision encompasses the Agency's strategy for both medicines for human and veterinary use in line with the joint responsibility of the Agency[7]. Detailed information on the implementation of the Road Map to 2015 will be provided in a document "From Vision to Reality" once the public consultation on the Road Map has been concluded and a revised Road Map has been prepared.

Striving for as broad a consensus as possible on the best way forward, the Agency will discuss the Road Map to 2015 with its partners and stakeholders. Following a public consultation in 2010, including face-to-face discussions, and subsequent consideration of the comments received, the revised Road Map to 2015 will be published after adoption by the Agency's Management Board.

1 The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future (Doc. Ref. EMEA/H/34163/03/Final).
2 The term "public health" refers to both public and animal health, unless otherwise stated.
3 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions – Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector (COM(2008) 666 final).
4 European Commission Health & Consumer Protection Directorate General Future Challenges Paper: 2009-2014
5 Communication from the Commission to the European Parliament and the Council: European agencies – The way forward (COM(2008) 135 final).
6 The Heads of Medicines Agencies Strategy Paper: Developing the Heads of Medicines Agencies Strategy for the European Medicines Regulatory Network – A Discussion Document.
7 An explicit reference to either sector will only be made where necessary.

2. Setting the Scene: the Agency and its Environment

2.1. The European Medicines Agency as a Public Health Agency

The mission of the Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public health. This is fully in line with the Agency's legal role and responsibilities to provide the EU Institutions and the Member States with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products referred to it in accordance with the EU legal provisions governing medicinal products. The Agency's sphere of responsibilities has gradually expanded over time in line with new Community legislation, most recently in the fields of paediatric and advanced therapies medicinal products. Furthermore, new legislation is under way (e.g. in the fields of counterfeiting and pharmacovigilance) which will further increase the Agency's (coordinating) role in the pharmaceutical arena. As a result the Agency's involvement in public health has further increased and will continue to do so, hereby establishing the Agency as an important guardian of public health in the EU.

2.2. Collaboration with the Agency's Partners

A critical factor for the Agency's success has been the provision by the Member States of high-quality scientific resources for the evaluation and supervision of medicinal products. Such provision of resources, coordinated by the Agency, is one of the features of the EU Regulatory System Network, a concept which is unique in the world. Another feature of this Network is the platform provided by the Agency for the coordination of activities at EU level (e.g. in the fields of mutual recognition and decentralised medicines, and clinical trials). The Agency in its Road Map to 2010 emphasised the need to strengthen the partnership between all EU Regulatory Authorities, leading to the establishment of a network of excellence at EU level. Further reinforcing such partnership will continue to be pivotal for the Agency.

Other factors to be taken into account when considering the Agency's environment relate to its partnership with other EU Institutions as well as the Agency's positioning on the international scene. The Agency's interaction with other EU Agencies (such as the European Food and Safety Agency (EFSA) and the European Centre for Disease Prevention and Control (ECDC)) particularly has expanded over time in the area of public and animal health. Collaboration with the EU Institutions currently focuses on a deepening of the interaction in the fields of research related work and emerging diseases.

International cooperation nowadays builds on long established interaction in fields such as the International Conference on Harmonisation ((V)ICH), Codex Alimentarius and the World Organisation for Animal Health (OIE), as well as collaboration with the World Health Organisation (WHO). Other important international activities in the pharmaceutical sphere are the Mutual Recognition Agreements (MRAs) and similar agreements. Further progress in the international field has been made through Confidentiality Arrangements concluded with the United States, the Japanese, the Canadian and Australian Health Authorities, whilst new developments relate to the interaction with the Standards Development Organisations (SDOs) in the frame of the development of international standards for the definition of data structures, as well as the development of controlled and internationally agreed terminologies defining valid entries. The next years will see intensified efforts to further expand international cooperation in line with the Agency's International Strategy which is currently under development. Such Strategy will elaborate on the creation of synergies through collaboration, cooperation and communication with international regulatory partners with a view towards supporting in the long term a global approach to the authorisation and supervision of medicines.

2.3. Interaction with the Agency's Stakeholders

An element of growing importance is the involvement and participation of civil society representatives (patients/users of medicines and healthcare professionals) in the Agency's activities. Their membership of the Management Board and some Scientific Committees, as well as their involvement in other parts of the Agency's work has led to the development of specific frameworks of interaction. Recognising the added value of patients and consumers in benefit/risk considerations as they enrich regulatory outcomes by complementing them with the views of those directly affected by regulatory decisions, the debate currently focuses on how to achieve a more structured involvement of patients in the Agency's activities. Likewise, discussions are ongoing on how to better engage healthcare professionals in the Agency's activities. Another trend is the increasing contribution by academia and learned societies to the Agency's work, hereby supporting the development of regulatory science.

3. The Agency's Drivers for Progress and Change

The future tasks of the Agency and the environment in which it operates are shaped by the need to consider the following business drivers:

- **Efficient operation of the Agency's core business**

The main focus for the Agency over the next years will continue to be the operation of the core business in line with its tasks described in current and upcoming Community legislation. The Agency's roles and responsibilities have further expanded since the drafting of the first Road Map and cover nowadays a wide range of activities. The European Commission's impact assessments on the new legislative proposals in the areas of counterfeiting and pharmacovigilance have indicated that the consequences for the EU Regulatory System Network, and for the Agency in particular taking into account its coordinating role, will be very important.

Efficiency will, therefore, be even more key for a successful operation of the core business. An important consequence of the Agency's growing area of responsibilities is that its tasks have become much more complex. The Agency currently comprises 6 Scientific Committees and some 35 Working Parties and other (scientific) fora to which scientific support is being provided. A particular challenge in this field relates to the interactions and interdependencies which exist at various levels between these fora.

- **Addressing public health needs**

As highlighted in the European Commission's White Paper[8] there are several challenges to public health which require a new strategic approach. These include demographic changes, emerging public health threats, antimicrobial resistance, as well as the rapid development of new technologies including E-Health which will also heavily impact on existing healthcare systems. Another aspect which will remain high on the public health agenda relates to the availability of medicines for rare diseases and other current unmet medical needs such as medicines for the paediatric population. Rational and better targeted use of medicines has years ago been identified as an important factor in order to reduce morbidity and mortality and to contain medicine expenditure. An aspect which is closely linked relates to the need to investigate the impact on public health of decisions taken by Regulatory Authorities, and to subsequently introduce the necessary remedial actions.

Likewise, in the area of animal health, the Community Animal Health Policy[9] will have to be taken into account. In particular, priority will have to be given to reducing the risk of antimicrobial resistance arising from the use of medicines for veterinary use in view of the impact on human and animal health, and the availability of medicines to treat disease in animals. Another aspect to be considered relates to the Agency's role in promoting greater availability of medicines for veterinary use in general and specifically with respect to vaccines to protect against diseases such as Foot-and-mouth disease, Bluetongue and avian influenza, as well as medicines intended for minor markets (to reduce the need for off-label use).

- **New and emerging science**

Although new and emerging science (such as personalised medicine, nanotechnologies, regenerative medicine, synthetic biology[10] as well as advances to streamline non-clinical and clinical development) could possibly be considered as already part of the new wave of medicine development, representing new ways to address current unmet medical needs, they also bring along a number of aspects that

[8] White Paper – Together for Health: A Strategic Approach for the EU 2008 – 2013 (COM(2007) 630 final).
[9] Community Animal Health Policy 'Prevention is Better than Cure' (ISBN 978-92-79-06722-8).
[10] Synthetic biology refers to two main activities: the design and construction of new biologically-based parts, novel devices and systems; and the re-design of existing, natural biological systems for useful purposes.

require careful consideration. Among the challenges they all have in common is the appropriateness of the current legal/regulatory framework in particular with respect to the benefit/risk evaluation, and the development of tools for the anticipation of potential safety issues, hence necessitating a debate on how to best support and translate the new science into regulatory requirements. Further thought will also have to be given to aspects such as ethical and environmental considerations. Such important scientific progress will require Regulators to be attuned to the new technologies and to learn from research and experience in other industry sectors.

In addition, the Agency is likely to be confronted within the next few years with challenges stemming from a reappraisal of the device legislation in the EU, and in particular activities focussing on the interaction between medical devices/diagnostics and medicinal products.

- **The impact of increasing globalisation**

The importance of globalisation has further increased over time and will continue to do so. One of the main drivers is the global nature of medicine development and research. Manufacturing and clinical trial activities will continue to see an increased international focus over the next years. The movement of clinical research to lower cost countries presents particular challenges, such as safeguarding the integrity of the data and ensuring equivalent ethical standards are met, the threat of double standards, as well as the need to be confident in local regulatory and supervision arrangements. Another field of growing concern relates to the increasing manufacture of Active Pharmaceutical Ingredients (APIs) outside the EU, and in particular the potential for substandard material to enter the supply chain.

In the area of regulation of medicines for veterinary use the impact of globalisation will also become increasingly noticeable in terms of harmonisation of regulatory requirements through VICH. Also, closer cooperation will be required with international partners, particularly Codex Alimentarius, in setting acceptable limits for residues of veterinary medicines in animal foodstuffs, and in risk assessment methodologies. An increased focus on international cooperation recognises the fact that EU consumers are only really protected from risks related to products of animal origin when the same standards are applied irrespective of whether animals are reared in the EU or elsewhere.

- **The model for regulation of medicines**

The model for regulation of medicines is a complex concept, encompassing elements such as the requirements for medicine development, the benefit/risk balance, the point of decision-making for granting a marketing authorisation, and post-authorisation follow-up. Over the past few years there have been several developments in each of these areas which *de facto* mean that the current model for medicines regulation is being reviewed. A recent development in the pharmaceutical arena is the growing importance of Health Technology Assessment (HTA) bodies on the access to market of novel medicines, due to a large extent to increased pressure on healthcare budgets.

More specific comments relate to the field of herbal medicinal products where it needs to be acknowledged that the innovative concept of list entries and monographs not really has been followed-up in terms of subsequent marketing authorisation applications based on such concept. Furthermore, aspects related to borderline issues with nutritional supplements still require resolution.

The last thirty years has seen a gradual convergence of the legislation governing medicines for human and veterinary use leading to an improvement in the quality of veterinary medicines but also an overall increase in the regulatory requirements and in their complexity. The European Commission has recognised the need for an impact assessment of the veterinary medicines legislation that will look at issues such as whether or not there is a need to reconsider the extent to which the legislation governing veterinary medicines should, in future, be tailored to the specific requirements of this market sector.

- **Ensuring patient safety**

For several years the focus within the EU has been directed towards a more proactive approach in ensuring patient safety, whilst continuing efforts to further improve the spontaneous reporting scheme. This resulted in a number of legislative changes in 2005 introducing new tools such as the novel concept of risk management plans. In addition, strategic initiatives were launched in the EU within the frame of the European Risk Management Strategy (medicines for human use) and the European Surveillance Strategy (medicines for veterinary use). In both cases the aim is to achieve high standards of public and animal health protection with respect to the use of medicines. Work is underway[11] to further progress the implementation of the various initiatives. It needs, however, to be recognised that public opinion over time has become much more risk averse, resulting in increased demands for more refined pharmacovigilance tools for medicines for human use.

- **Demands for more transparency and openness**

For any public body in the field of medicines regulation, transparency and openness are important factors in order to gain, maintain and strengthen trust by its stakeholders. The next years will see increasing requests for more information and openness on the various activities undertaken by the Agency, hence necessitating action both in terms of the tools applied (allowing for access to documents and access to information contained in its public databases) and the content of the information (such as information on the opinion/decision-making process for the evaluation and supervision of medicinal products, transparency of adverse drug reactions and clinical trial information). Providing for more transparency will entail specific challenges for the Agency, especially with respect to the need to find the right balance between earlier and greater availability of information vis-à-vis the protection of commercial confidentiality of proprietary information.

[11] Implementation of the Action Plan to further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (2008-2009) (Doc. Ref. EMEA/280089/2007).

4. Addressing the Drivers for Progress and Change

4.1. Current Achievements

The Road Map to 2010 clearly states that its ultimate objective is to ensure that the Agency adequately prepares the ground for further success in the future, building on the achievements of its first 10 years. At regular intervals[12,13] the Agency has reported on progress made with the implementation of its Road Map to 2010. Overall, the Agency largely succeeded in delivering the planned activities and initiatives and meeting its 2010 priority objectives of "top-quality scientific assessment, timely access to safe and effective innovative medicines, continuous monitoring of medicinal products, access to information and specific needs for veterinary medicines". Scientific excellence (as a result of EU wide pooling of expertise and data) has been a key strength. In this respect it should be stressed once again that such excellent progress has been highly dependent on the close collaboration between the Agency and the National Competent Authorities (NCAs) within the context of the EU Regulatory System Network and in particular the valuable input of high-quality specialist expertise provided by the Member States. Another important enabler has been the Agency's continuing efforts in conducting process improvements through an ongoing review of the operation of its core business to identify efficiency gains.

4.2. Objectives and Priorities for the Next Five Years

Although it can be concluded that the Agency has now successfully prepared the ground for the future, further progress on the 2010 Road Map objectives is still needed. Whilst the Agency's tasks have further expanded over the past years in the field of innovative medicines, the scope of the work to be undertaken in other areas (e.g. herbal medicinal products) remained quite stable. Since 2005 additional challenges had to be addressed either as a result of new legislation in the fields of paediatric and advanced therapies medicinal products, or through the Agency's involvement in the areas of biosimilar, generic and non-prescription medicines. This resulted in an important increase in workload.

To address the aforementioned business drivers the Agency's first priority over the next five years will still be on a successful delivery of its core business in line with current and upcoming Community legislation. Efforts to strengthen the Agency's efficiency will continue, hereby further reducing the administrative burden. More detailed information on the measures taken to further improve efficiency as regards the Agency's core business will be provided in the "From Vision to Reality" document. Acknowledging the Agency's achievements so far, the focus for the next period will now be more directed towards the quality of the outcome of the Agency's work and in particular how to increase such quality. In addition, it should be recognised that there will also be other developments and challenges in the fields of science, medicines and health which the Agency will have to face and to which it believes that it can provide an important contribution. Pivotal for achieving this aim will be to further strengthen the close collaboration and cooperation with the Agency's partners in the context of the EU Regulatory System Network, building on the excellent progress made over the past years.

To address the business drivers listed in Chapter 3, the Agency has identified three strategic areas for the future.

[12] Status Report on the Implementation of the Road Map (Doc. Ref. EMEA/171321/2006).
[13] Second Status Report on the Implementation of the Road Map (Doc. Ref. EMEA/359050/2007).

Strategic Area 1: Addressing Public Health Needs

Objectives[14]	Impact/Result Indicators[14]
Stimulate medicine development in areas of unmet medical needs/neglected and rare diseases, and for all types of medicines for veterinary use.	Increase in the number of scientific advice requests for medicines for unmet medical needs/neglected and rare diseases, and for all types of medicines for veterinary use. Increase in the use of specific procedures such as Article 58 procedures (under Regulation (EC) N° 726/2004).
Facilitate new approaches to medicine development.	Existing model for medicines regulation is adapted to enable integration of new and emerging science.
Apply a more proactive approach to public health threats where medicines are implicated.	Effective preparedness mechanisms which take due account of learnings from previous public health threats/crisis situations are available.

Gaps in Medicine Development

An important public health challenge currently faced relates to the lack of medicines for unmet medical needs/neglected diseases (including rare diseases). One of the most critical areas concerns the limited availability of novel antibiotics, often caused by unfavourable conditions for developing new effective antibiotic agents as well as strategies to limit the development of antimicrobial resistance. In addition to infectious diseases, other fields of concern are rare and neglected diseases, leading in particular to challenges for developing countries.

The Agency envisages undertaking the following:

- Analyse the reasons for discontinuation of the development of medicines for human use starting with selected designated orphan medicines and propose remedial action. This could include the provision of incentives such as the establishment of an accelerated assessment scheme for medicines intended for unmet medical needs (e.g. novel antibiotics), rare and neglected diseases in the EU and beyond.

- Assume a more proactive role in advising the European Institutions on any gaps in medicine development, taking into account the Agency's knowledge base on medicines under development, and on better incentives to stimulate medicine development. This approach could also be undertaken for neglected diseases in developing countries, hence complementing existing initiatives such as Article 58 Opinions (under Regulation (EC) N° 726/2004).

- Launch initiatives to address the lack of development of antibiotics and the potential threat of antimicrobial resistance arising from the (mis)use of antimicrobials in human and veterinary medicine. Reference is in this respect made to the work jointly undertaken by the Agency and other EU Agencies such as ECDC and EFSA[15, 16].

[14] Each time only the longer term objective(s), with corresponding impact or result indicator(s) is (are) described in this document. Further information will be provided in the document "From Vision to Reality" and the Agency's yearly Work Programmes.

[15] ECDC/EMEA Joint Technical Report: The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and development of new antibacterial agents.

[16] ECDC/EFSA/EMEA/SCENHIR Joint Report on Antimicrobial Resistance (AMR) Focused on Zoonotic Infections.

- Explore how to best contribute to challenges stemming from demographic changes, in particular as regards population ageing. Taking into account current achievements in this field, the Agency will undertake additional efforts to ensure that the needs of elderly people are taken into account in the development and evaluation of new medicines.

New and Emerging Science

Scientific progress over the next five years will be an important driver for change. Building on current experience with advanced therapies (cell therapy, gene therapy and tissue engineering) the Agency will have to address new challenges on the horizon relating to nanotechnologies, synthetic biology, regenerative and personalised medicine. The concept of personalised medicine is rapidly moving from a theoretical concept to everyday reality. The Agency has already been confronted with this concept, primarily in the oncology field. Some centrally authorised products already have personalised (pharmacogenomics) indications in the approved product information. Many diverse applications of novel nanotechnologies to medicine development are also a reality, but experience is still very limited. In addition, the field of nanotechnology is very diverse. Likewise, only a small number of applications may be seen over the next years for regenerative medicine. For these novel scientific approaches the scientific/technical and regulatory challenges will be very significant.

In order to address these challenges, the Agency proposes:

- To advise, through pooling of specialist expertise, on the necessary adaptation of the regulatory framework to the new technologies. This will complement existing initiatives such as the setting-up of a dedicated biomarker qualification procedure and the provision of regulatory and scientific support to the Innovative Medicines Initiative (IMI).
- To explore within the forthcoming review of the legislation governing veterinary medicines to what extent the requirements of evolving science (stem cell technology, growth factors, tissue engineering) can be met within the existing legal framework and to what extent new legislation would be required. Whilst recognising that it is impractical to develop a framework as comprehensive as in the field of advanced therapies for human use, a lack of legislation should not be allowed to be an impediment to the development of novel veterinary medicines, particularly as there is currently great interest in adapting advanced therapies for human use to veterinary applications.

Public Health Threats

The current pandemic H1N1 influenza outbreak underlines the importance of prompt action in response to emerging public health threats. Putting in place the necessary preparedness mechanisms has shown to be a very complex exercise since it is a multifaceted undertaking covering aspects ranging from the availability of a dedicated legal/regulatory framework for the authorisation and supervision of medicines, rapid scientific assessment processes up to a targeted and coordinated communication strategy. In addition, it required the Agency to expand its interaction beyond the EU Regulatory System Network in which it operates. Excellent collaboration between all parties in the wider EU public health environment has been and will continue to be pivotal in addressing this challenge. Whilst experience in this field is now building up, whereby lessons learnt from previous pandemic like situations and bioterrorism strategies are being taken into account, there is also a need to prepare for new communicable disease patterns caused by climate change and increased, unrestricted travel.

Recent experience with the pandemic H1N1 influenza outbreak, the emergence of Bluetongue, the contamination of medicinal products containing or derived from heparin, the shortage of radiopharmaceuticals, have demonstrated the need for preparedness for Regulatory Authorities to adequately cope with public health threats/crisis situations through the availability of dedicated processes and systems, as well as efficient coordination across the EU Regulatory System Network. Although each of these emerging situations has its own characteristics, they often have three elements in common: the complexity of the problem, the global dimension and the need to find a quick solution to the issue.

Another area of major concern relates to the use of substandard active substances and counterfeiting. Whilst specific Community legislation is under way in these fields the issue will remain high on the political agenda until implementation of the new legislative proposals.

The following is envisaged:

- Acknowledging that it will never be possible to have a “one size fits all” response, the Agency will investigate on the basis of accumulated experience, in close collaboration with its partners and stakeholders, if its preparedness mechanisms should be revised.
- The Agency will conduct a “Lessons Learnt” exercise after each major event in order to further improve existing preparedness mechanisms.

Strategic Area 2: Facilitating Access to Medicines

Objectives	Impact/Result Indicators
Address the high attrition rate during the medicine development process.	Increase in the number of successful marketing authorisation applications for which scientific advice has been sought and adhered to. Scientific information on failed medicine development processes is made available to the scientific community.
Reinforce the benefit/risk balance assessment model.	Increased inclusion of quantitative elements, alongside an improved elaboration of the rationale for the decision/opinion in the benefit/risk considerations, for subsequent publication in the European Public Assessment Reports (EPARs) (medicines for human use). Systematic reference in all EPARs to the concept of benefit/risk assessment applied during the scientific review (medicines for veterinary use).
Continue to improve the quality and the regulatory and scientific consistency of the outcome of the scientific review.	Structured external surveys performed by the Agency's stakeholders on the outcome of the scientific reviews demonstrate an increase in the quality and the consistency.

Medicine Development Process, Early Assessment and Continuing Dialogue

Despite the increase in research efforts in previous years the pharmaceutical sector is confronted with the widely recognised phenomenon of the medicine development productivity gap. Feedback has indicated that both the suboptimal management of the medicine development process by sponsors as well as new requirements for medicine development have been identified as important contributing factors. In order to address the high attrition rate during the medicine development process and the increasing productivity gap, the Agency is of the view that a number of initiatives could be undertaken to improve the situation:

- Acknowledging that the scientific advice provided by the Agency if adhered to by the sponsor increases the rate of successful marketing authorisation applications, the Agency will continue its efforts to optimise the scientific advice process.
- Although the concept for guideline preparation on medicine development in the field of medicines for human use has been in place for several years, it would seem timely to strengthen the involvement of stakeholders (and in particular academia/learned societies and patients' organisations) in this process, for instance by organising workshops at a very early stage of guideline development where these stakeholders can actively contribute.

- Experience with the EU Paediatric legislation has shown that the mandatory engagement of Regulatory Authorities in early phase development plans of pharmaceutical industry has the advantage to establish early dialogue with sponsors and to provide Regulators with considerable knowledge of the data at an early stage which in turn facilitates the scientific review process. It could be explored if the concept of early dialogue could also be introduced in the frame of the development of medicines for the adult population.

- It needs to be recognised that even a failed medicine development process will generate useful information and scientific knowledge that in most instances currently is lost because of either proprietary information related aspects or the lack of access to these data by Regulators. Taking into account the added value of such data (in terms of avoidance of repetitive and redundant animal or clinical studies, avoidance of the use of inappropriate parameters, etc.) the Agency is of the view that it would seem appropriate to explore what incentives could be offered to make this otherwise lost information available to the scientific community.

- Furthermore, although the Agency is already collaborating with the European Commission, and in particular Directorate General Research, on research related aspects, such involvement so far has been rather fragmented. The Agency, therefore, would like to create a platform for dialogue with the European Commission in order to improve its input into the EU research agenda for medicines. This would complement current initiatives on fostering innovation in the context of IMI and the European Technology Platform for Global Animal Health to which the Agency already provides an important contribution, and where efforts over the next years will have to continue.

- With respect to the veterinary sector, uptake by the animal health industry of the potential of the scientific advice resource has been disappointing. Measures will be explored to increase both the uptake and the perceived usefulness of the scientific advice procedure through discussions with pharmaceutical industry taking into account experience gained in the field of medicines for human use.

- Another aspect which needs careful consideration relates to the area of clinical trials and two major initiatives need to be highlighted: The Conference on the Operation of the Clinical Trials Directive, held on 3 October 2007, provided a number of recommendations for further improvement, and further work is still needed, especially as regards the current disconnection between EU scientific advice and clinical trials. In addition, the European Commission has performed an impact assessment in view of the introduction of legislative changes in the field of clinical trials legislation. An aspect which will require particular attention is the regulatory oversight of medicine development which should be further improved. An overarching regulatory process should be established covering all stages of medicine development up to licensing (inception, initial scientific advice, first in human trials, ongoing interactions on scientific advice, up to the application for marketing authorisation). Although these concepts are more developed in the field of medicines for human use, a similar approach should be explored for veterinary medicines.

- The aforementioned proposals will need to be complemented by the introduction of a continuing dialogue between Regulators and sponsors during medicine development. Therefore, the concept of scientific advice should be expanded to provide continuous scientific support during medicine development, combined with an integration of earlier appointed (Co)-Rapporteurs which would augment the interaction between Regulators and sponsors during medicine development, in addition to formal face-to-face meetings at the critical stages of the medicine development process. This will require clear roles and responsibilities of all involved parties.

The impact of the increasing globalisation of clinical research and manufacturing and its movement to low to middle income countries (who may be confronted with limited experience and resource, and a less developed regulatory framework) needs careful consideration. In order to address this challenge the Agency will undertake a number of initiatives, including:

- In the area of clinical research, further developing and subsequently implementing the Agency's Strategy[17] for acceptance of clinical trials conducted in third countries including the development of advice and guidance on ethical standards and data quality requirements for clinical trials submitted in the EU. Furthermore, the Agency, in close collaboration with the Member State Competent Authorities and its international partners, will invest in supporting capacity building and local awareness with the Regulatory Authorities, research communities and pharmaceutical industry of these countries.
- In the field of the manufacture of APIs and of finished products, working with its international regulatory partners to improve the framework for the implementation of Good Manufacturing Practices (GMP) standards through capacity building, and to ensure inspection coverage based on sharing of inspection planning and outcomes.

[17] EMEA Strategy Paper: Acceptance of Clinical Trials conducted in Third Countries, for Evaluation in Marketing Authorisation Applications (Doc. Ref. General-EMEA/228067/2008).

Benefit/Risk Assessment and Communication

To address the Regulators' dilemma of balancing access to market vis-à-vis the need for an as complete data package as possible prior to licensing, several factors need to be considered. Pivotal in this respect is the benefit/risk assessment and communication. Work on improving the benefit/risk balance model concentrates on three major aspects: ensuring a consistent approach, providing a better rationale for the outcome of the benefit/risk review and improving the communication with the various stakeholders. This work goes hand-in-hand with the Agency's objective to focus on further improving the quality of the outcome of the scientific review.

- Building on current achievements work in the field of medicines for human use should now focus in terms of the methodology used on the introduction of more quantitative elements, as well as the inclusion of patients' utilities and values. Any opinion on whether or not to grant a marketing authorisation should bear in mind the availability of other therapeutic options taking into account the degree of unmet medical need. Further work is also needed on improving transparency of the outcome of the scientific review, including the justification for the opinion/decision taken. This is even more important in situations where the Agency's views would not be in line with the outcome of the review by non-EU Regulatory Authorities.

- Optimising the benefit/risk assessment process as regards medicines for human use can be undertaken through a variety of initiatives. First of all the Agency would like to explore the introduction of a more continuous dialogue during the assessment of a marketing authorisation application. In addition, the robustness of the scientific review should be further strengthened through the use of more statistical expertise. Furthermore, patient empowerment as well as patient participation in healthcare decisions will further stimulate the ongoing debate on the level of patient involvement in the scientific review process. As mentioned before, this should optimally lead to patients' values being taken into account for the benefit/risk assessment. Likewise, it would seem an opportunity to debate the level of involvement of prescribing physicians, academia/learned societies in the scientific assessment process throughout a product's lifecycle.

- As regards the veterinary sector it needs to be acknowledged that the state of art in terms of the benefit/risk methodology is not as advanced as in the field of medicines for human use. Current emphasis is on the development and documentation of a systematic methodology for benefit/risk assessment, as well as on the provision of training within the EU Regulatory System Network. Therefore, work over the next years will focus first on more clearly embedding the benefit/risk methodology in the assessment procedure and better communicating to the Agency's stakeholders on the methodology used. Other challenges will be to demonstrate within the EU Regulatory System Network that a consistent approach to benefit/risk assessment is applied irrespective of the licensing route and that the methodology can bring benefits in terms of availability when applied to medicines for emergency diseases and limited markets.

- Further improving the quality and the regulatory and scientific consistency of the outcome of the scientific review processes will be a key objective for the Agency. Activities will concentrate on improving the benefit/risk balance model as outlined above. In addition, efforts will be directed to regular external surveys to monitor the outcome of the scientific review processes for medicines for human use. For medicines for veterinary use, consultation will continue with stakeholders to identify the key parameters to measure performance and to put in place systems to monitor them.

- An in-depth reflection is also needed on how to further improve the use of the legal tools for the granting of a marketing authorisation. A key issue for Regulators will be if a more "staggered" approval should be envisaged, characterised by a better defined/ more restricted population of good responders, followed by a broadening of the population post-authorisation when more "real

life" data are available. In parallel the Agency will explore how to refine the conditional marketing authorisation concept for medicines for human use since it needs to be recognised that this concept has not really been applied as initially foreseen. In addition, maximising the value of information generated in the post-authorisation phase should be developed through the use of cohorts and other prospectively collected use data, especially in the case of conditional marketing authorisations. Likewise, consideration should be given to if, and in what form, the concept of conditional marketing authorisation might be introduced for veterinary medicines.

- Strategies on the best way to increase the knowledge of a medicine in the post-authorisation phase need to be set-up at the moment of licensing and subsequently to be reviewed when new information emerges. Although the risk management plans in the human medicines field meet this aim and have been a real step forward, it would merit to broaden this concept to systematically include information on the benefits of a medicinal product as well, hence supporting a continuous benefit/risk assessment throughout a medicine's lifecycle. Therefore, the current risk management plan for medicines for human use should be converted into a benefit/risk management plan. Furthermore, work also needs to be undertaken to improve the formulation, implementation and monitoring of post-authorisation commitments for marketing authorisations not benefiting from the conditional marketing authorisation concept. Subsequently including a revised concept of post-authorisation commitments in the aforementioned benefit/risk management plan should increase the efficiency of the system.

Facilitation of the Relative Effectiveness Assessment

A number of differences have been pointed out when comparing the licensing process with the relative effectiveness and the cost/benefit assessment process, in terms of the choice of clinical endpoints, efficacy versus effectiveness, and relative efficacy versus placebo controlled studies. This leads to a situation whereby Regulators and HTA bodies, although both aiming for the availability of medicines which make a contribution to public health, are currently applying different approaches. Calls have been made for a closer interaction and collaboration between both parties of the healthcare system, whilst fully respecting their distinct roles and responsibilities. The High Level Pharmaceutical Forum agreed in October 2008[18] on a set of recommendations including that Member States with the involvement of the Agency should continue their efforts to consider how EPARs can further contribute to relative effectiveness assessments. The Agency, therefore, envisages to make progress in this field, albeit in a stepwise manner, while continuing to ensure that cost/benefit assessment remains distinct and separate to the licensing process.

Two major initiatives are envisaged:

- First of all, the Agency will improve as an information provider. HTA bodies rely heavily on the EPARs and the Agency will increase its level of transparency on the outcome of the scientific review process as summarised in the EPARs, including the rationale for the decision/opinion, whereby more emphasis should also be put on the quantitative aspects of the benefit/risk assessment.

- Secondly, the Agency will explore how to engage with HTA bodies from early medicine development (to avoid as much as possible the appearance of two different medicine development programmes) throughout the medicinal product's lifecycle. Maintaining the dialogue with HTA bodies especially in the post-authorisation phase is very important in view of the vast amount of data which are obtained through post-authorisation collection.

[18] High Level Pharmaceutical Forum 2005 – 2008 – Final conclusions and Recommendations of the High Level Pharmaceutical Forum.

Strategic Area 3: Optimising the Safe Use of Medicines

Objectives	Impact/Result Indicators
Strengthen the evidence base in the post-authorisation phase to enable better regulatory decision-making.	A regulatory model which facilitates the post-authorisation collection of data on benefits and risks of medicinal products is put at the disposal of the Regulatory System.
Enhance patient safety by avoiding unnecessary risks to patients as a result of the use of medicines.	A revised risk management concept, which targets both novel pharmacovigilance methodologies as well as a risk minimisation toolbox better adapted to reduce harm, is available.
Become a reference point on information for medicines evaluated by the Agency.	A high-quality, informative and targeted set of information on medicines, falling within the sphere of the Agency's responsibilities, is proactively put at the disposal of the EU Regulatory System Network at the moment of licensing/updating of the marketing authorisation.
Improve the decision-making process by taking due account of patient experience, hence contributing to the rational use of medicines.	Conclusions from outcome research projects analysing the impact of the regulatory decisions on public health are used to provide input in future regulatory policy decision-making.

Patient Safety

Pharmacovigilance and safety of medicines will continue to be a priority for the Agency, with a strong focus on ensuring that both risks and benefits are monitored throughout a medicinal product's lifecycle. Avoiding unnecessary risks to patients is becoming an increasingly important factor in strategies developed on the protection of public health, and efforts are undertaken at EU level and internationally to enhance patient safety. In the EU the focus is both on a strengthening of research in this field, alongside the launch of new legislative proposals aiming at rationalising and strengthening the EU framework on safety monitoring of medicines for human use. In addition, international collaboration on medicine safety as a result of globalisation and the need for best use of resources will result in finding synergies between the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (led by the Agency) and Sentinel (led by the Food and Drug Administration (FDA)) initiatives.

The Agency's initiatives in this field for medicines for human use will include:

- A revision of the risk minimisation measures/tool box in the frame of the current Review and Learning project on risk management plans for human use, the aim being to further reduce harm caused by the use of medicines. Taking into account the impact of certain risk minimisation measures on the EU Health Workforce (doctors, pharmacists, nurses) and the pivotal role of healthcare professionals versus patients as regards the use of medicines, particular attention will be given on how the risk minimisation measures impact on the work of healthcare professionals throughout the EU.
- Progressing the European Risk Management Strategy with focus on a more proactive approach in ensuring patient safety, targeting aspects such as new data sources for the monitoring of medicines in the EU, capacity building for post-authorisation monitoring, addressing the impact of

the introduction of international standards and controlled and internationally agreed terminologies in the pre- and post-authorisation phase.

- Involvement in research related activities on pharmacovigilance methodologies, in particular within the context of the IMI project.

Post-authorisation Follow-up

In order to optimise the safe use of medicines more information has to be obtained in "real life" situations:

- As a starting point, the focus should be on the Marketing Authorisation Holder's post-authorisation development plan whereby it should be explored what kind of incentives to pharmaceutical companies can be provided to facilitate inclusion of the post-authorisation medicine development in the current Agency's scientific advice framework. Secondly, developments in the field of human medicines such as an increasing use of the conditional marketing authorisation concept, the need for additional data within the frame of the benefit/risk evaluation for advanced therapy medicinal products leading to efficacy follow-up plans, as well as the introduction of new biomarkers will result in more reliance on post-authorisation collection of data to augment the knowledge on a medicinal product's benefits and risks at the moment of licensing. This should ultimately lead to an integrated assessment of benefits and risks under real life conditions. ENCePP which is currently being set-up will be an important tool for such post-authorisation data collection.

- Taking into account the possible important consequences on the environment resulting from the use of medicines for human and veterinary use, initiatives should be taken to look into the longer term impact on the environment.

- In the field of veterinary medicines, the European Commission's impact assessment of the veterinary legislation will provide an opportunity to explore the possibility of developing a post-authorisation framework that is particularly suited to the needs and resources of the animal health sector. The Agency will consult with all involved stakeholders on how best to develop an appropriate risk management framework and to what extent it is possible to licence medicines for veterinary use at an earlier stage of development based on the requirement to provide the necessary post-authorisation data.

Authoritative Source of Information

The Agency has met the demands for more transparency and openness by developing a draft Transparency Policy[19]. In addition, the Agency is of the view that:

- Irrespective of the currently ongoing political debate on the best way forward for providing information on medicines to patients, the Agency should strive to become the authoritative source of information for all medicines evaluated by it, for syndication to the EU Regulatory System Network. This should also facilitate recognition by the general public of the Agency as a leading authority in the field of evaluation and supervision of medicinal products. Initiatives should be directed towards the preparation by the Agency of timely, targeted and high-quality information for patients/users of medicines and healthcare professionals for the medicines it evaluates. In this way the Agency can concentrate on the quality and consistency of the information provided and other parties can focus on ensuring maximum penetration of this information to the target audiences, and in particular patients and healthcare professionals, hereby fully respecting the characteristics of the EU Regulatory System Network model in this field. Strengthening the interaction with the

[19] The EMEA Transparency Policy – Draft for Public Consultation (Doc. Ref. EMEA/232037/2009 – rev*).

NCAs and with patients and healthcare professionals' organisations to build up a network of excellence at EU level will be an important target. Furthermore, a joint reflection with the Member States and other interested parties is also needed on how to best address further developments in the field of provision of information, in particular the link with E-Health.

- Work should be undertaken to put more emphasis on balanced benefit/risk communication, hence contributing to the implementation of the empowered patient concept. Aspects such as how to best address the complexity of the data requiring careful interpretation, and determining the most appropriate timepoint for communication on benefits and risks when new information emerges, will require particular consideration. It will be equally important to clearly communicate to prescribers the reason why the medicinal product is not indicated for use outside the approved indication so that prescribers can make an informed choice.

Outcome Research

Analysing the impact of the regulatory decisions on public health has been identified by the Agency as an important activity for the next years. Outcome research in this field has been started in line with the Agency's Standards for Internal Control requiring it to perform an evaluation of its activities, and efforts in this field will continue over the next years:

- Building on current initiatives (the emphasis in a first phase being on the benefit/risk assessment and communication model), the Agency will further engage in monitoring the use of medicines, in close collaboration with academia. To gain maximum understanding of the implications of regulatory decisions the focus for the next years should be on studies looking into how medicines are being used versus the intended use, studies looking at the effectiveness of risk minimisation measures, including aspects of feasibility in healthcare, as well as studies investigating if the current regulatory model contributes to better therapy outcomes. The outcome of these studies should also be used to provide input in future regulatory policy decision-making.

5. Implementing the Agency's Road Map

The Agency will implement its vision in line with the document "From Vision to Reality" which will be drafted following the outcome of the public consultation on the Road Map to 2015. This document will provide information on the prerequisites to be fulfilled and the enablers (including managerial and operational aspects) needed to allow the Agency to successfully contribute over the next five years in the fields of science, medicines and health.

In addition, following the finalisation of the Road Map to 2015 and the document "From Vision to Reality" the Agency will complement its planning process by applying a multi-annual programming approach which will equally cover a five year timeframe. This multi-annual programming concept, which will address aspects such as workload and (human) resources forecasts, budget planning, accommodation needs, etc., should provide benefits to the Agency by assisting decision-making in a more effective and predictable way and achieving a gradual implementation of the Agency's vision over the next five years. Following endorsement by the Management Board the multi-annual planning will feed into the Agency's annual Work Programmes.

6. Conclusion

It is the Agency's view that its vision outlined in the Road Map to 2015, as well as the proposed solutions to address the identified challenges, will allow the Agency to increase its contribution to science, medicines and health, and thereby to the promotion and protection of public health. An important prerequisite for a successful delivery of the Road Map to 2015 will be the further development and reinforcement of the EU Regulatory System Network which has already shown to be a pivotal cornerstone of the EU pharmaceutical landscape.

The Agency is looking forward to its partners and stakeholders engaging in a constructive dialogue on the proposed way forward.