Relation between pharmaceuticals regulatory framework and timely access of medicines to patients: Reflection on difficulties and opportunities

Summary of comments from member states

Member States (MS) were asked at the 72nd Pharmaceutical Committee meeting in March 2014 to consider carefully the relation between pharmaceuticals regulatory framework and timely access of medicines to patients in light of current discussions on adaptive licensing pathways and in particular EMA's pilot project on adaptive licencing (AL). In particular the members of the Committee were asked to:

I. send comments, ideas and proposals, in particular with regard to the following points:

1. Analyse the perceived problem and the reasons for it and to what extent they are related to marketing authorisation procedures or other policy areas
2. Examine whether current approaches to marketing authorisation meet the objective to ensure timely access of patients to new medicines
3. Study if there are ways to improve the situation within the current legal framework
4. Analyse the perceived merits and weaknesses of an adaptive licensing approach from the regulatory/policy point of view, including the acceptable levels of uncertainty, possible change of paradigm and the consequences of shifting evidence gathering to the post-authorisation phase
5. Examine how AL fits within the current legal framework and principles of legislation
6. Consider whether any action would be useful or necessary

II. inform the Commission whether any studies have been carried out on this topic or whether actions are considered or taken at national level to ensure timely access of patients to medicines

The European Commission received responses from thirteen Member States. This document presents a factual summary of these responses which are compiled by theme of discussion. It does not present the views of the European Commission.

General comments to AL Pilot Project

In general Member States acknowledge the need for improvement of timely access to new medicines and support in general EMA's pilot project on adaptive licencing.
Most MS welcome the pilot as it is seen as a tool:

- to evaluate if the AL concept is feasible;
- to analyse currently available marketing authorisation procedures and their weaknesses and to correct them before proposing to add any other type of procedure;

- to obtain new knowledge on possible ways to improve the licencing system;
- to test the current licensing flexibilities to their maximum extent and show how the methodology of AL might work in practice;
- to be considered for providing better and faster access of medicines to patients.

A Member State highlighted the need to encourage companies with innovative medicines at the correct stage of development to apply for the pilot, as this will be the key to the success of the pilot and also emphasised the need for publishing clear timetable of the project to manage the expectations of industry, patients and health care professionals.

Some Member States considered that the pilot phase of AL should be carefully monitored and discussed by all MSs and that next action(s) should be based on the outcome of the pilot.

Scope of AL Pilot / AL

In general the responses indicated that the scope of AL is not well understood and needs to be further defined and clarified:

- One of the respondents considered that there is need to define the scope of AL in order to consider whether there is a need to change the EU legal framework or not. AL's current aim as defined in EMA's document on the pilot project ´to address serious conditions where there is an unmet medical need, especially when there are no satisfactory alternative therapies´ fits to existing legal framework, however the concept as described in the paper on Adaptive Licensing (*Clinical Pharmacology & Therapeutics* (2012); 91 3, 426–437) is envisaged to broaden the scope of the currently existing legal tools and would require changes in the current legislation.
- Several respondents though thought that the EMA adaptive licensing pilot project can be implemented without amending the current legal framework.
- One Member State stated that in AL, only a presumption of efficacy would prevail, which under the current legislation would not allow the granting of a MA, if efficacy is not sufficiently proven. In the current form AL would be just another exceptional authorisation with a vague concept.
- The scope of the pilot project on AL should be further clarified by EMA as to the nature of its scientific/technical objectives and relation to the legal framework, as well as the realistic possibilities and methods of cooperation with HTA and reimbursement bodies in MSs.
- Several Member States were of the opinion that ´One size does not fit all´ - AL will only be suitable for a restricted population with an unmet clinical need, e.g. conditional marketing authorisation (CMA) and MA under exceptional circumstances.

Problems with the existing regulatory system

Overall several Member States considered that the current EU regulatory framework does allow for timely access, hence the EU legislation does not need to be amended. Early access opportunities can be implemented at national level in situations of unmet needs for rare or serious diseases, in the absence of therapeutic alternatives, hence give the opportunity for early access to innovative medicines. However some bottlenecks in the current regulatory system were also highlighted in the individual responses below:

- The current regulatory regime for MA is lacking flexibility, possibilities for innovation and has rising costs (notably Pharmacovigilance (PhV) requirements).
- The existing regulatory flexibilities are not used optimally and as proactively as they could.
- The lack of an integral vision from the evaluation of the marketing authorization to the use of the medicinal product and lack of consistent decisions by both regulators and payers has frustrated the conditional approval as a form of stepped access to new treatments for unmet medical needs.
- Currently, we are faced with a complex system of successive evaluations, usually of the same data, without an integrated vision of the evaluation of medicines. The existence of multiple, successive assessments have given different results with the consequent lack of confidence in the system.
- As regards Conditional Marketing Authorisation (CMA) the following problems were noted: after authorisation MAHs have presented their products as fully authorised and have demanded access as a full license; MAHs are not fulfilling post-authorisation commitments in timely manner in a way that data lose their value for regulatory purposes; reluctance of payers due to immaturity of development, lack of data and/or high prices; Low incidence or/and specific characteristics of some illness make on some occasions that clinical data are only obtained from sample estimates that might not represent the targeted population. Therefore, neither clinical nor cost-effectiveness data in real life settings are available, which give rise to clinical and short-term budget impact uncertainties delaying pricing and reimbursement decisions and access to market; patients consider that a new medicine fulfils the same requirements like other (full) authorised medicines and therefore claim for access to medicines independently of their real value and price; doctors feel that a fully prescribable medicine is on the market also for off-label use in other related conditions.
- Granting centralised authorisation does not guarantee the availability of a product on all EU markets as MAH is not obliged to place the product on every MS market (especially the ones which are small, but include high costs, especially related to PhV obligations).

Merits of AL

Respondents perceived the following as merits of AL:

- time for a developing medicine to reach the market can be shortened.
- decrease in the costs of development and the final cost of medicinal products and promote innovation.
- higher knowledge about medicines (more real life data) which could give more realistic approach to medicines authorization and positioning of the product in real life.
- early use is ensured by a license and not by the willingness of the sponsor to provide patients free with medicine e.g. in the framework of compassionate use programs.
- reduction in demand for unlicensed supply of medicines and increase of confidence in the licensing system, which has recently been perceived as too rigid.

Weaknesses of AL

On the other hand respondents noted the following as perceived weaknesses of the AL approach:

- The AL model does not appear suitable in the proposed format that introduces a vague notion of authorisation from a regulatory point of view.

Limited data on safety and efficacy

- The consequences of shifting evidence gathering to the post authorisation phase (e.g. Post Authorisation Safety Studies (PASS) and/or Post Authorisation Efficacy Studies (PAES)) should not compromise the benefit risk (B/R) assessment, which should remain positive in the indicated population.
- Patients will be exposed with fewer guarantees both in terms of efficacy and safety, and this will be only justified in very specific cases of serious conditions without available alternatives.
- There is a possible risk that an (too) early authorisation could lead to serious safety problems and can further raise important debate in the community.
- Unsatisfactory evidence to ensure that health systems as well as individuals can benefit from safe and effective medicines does not bring added value and it might be a loss of opportunity for patients and for the community in terms of therapies (incl. non-drug ones) whose effectiveness is well proven.
- Increased uncertainty of efficacy and safety of the new medicines due to lack of the results of confirmatory clinical trials may undermine the trust of patients and physicians.
- Orphan medicines, products with an orphan designation, may not be licensed as orphan medicinal products as the available data for AL showing a positive B/R

balance might be insufficient for COMP to substantiate the claim for significant benefit (over other existing orphan products) and might result in registration as non-orphan or no registration at all. This higher risk for products losing their orphan status at first stage of licensing may have negative consequences for the development of medicinal products for rare diseases in the long run.

- A case by case handling of development programs may undermine the trust of applicants in the consistent regulatory practice.

Lower quality of post-authorisation data

- Post authorisation data would be collected through cohorts with a lower standard of proof than in randomized double-blind clinical trials. The benefit/risk balance would never be properly identified.
- Performing randomised clinical trials (RCT) could become problematic in terms of ethics and feasibility (it can be difficult to recruit patients when there is a product registered already). The alternatives are registries, which due to lack of robustness of the data generated may make further regulatory approval more problematic than in the context of the current regulatory framework.

Reflection on other challenges / concerns

Pricing and reimbursement

- Problem of access to medicines is related to pricing and reimbursement issues and not only to cause by delayed MA; accelerated marketing authorisation only is not sufficient to solve the availability problem. The main problem is how to fit this early access with pricing and reimbursement decisions.
- Introduction of a two-step authorisation ("initial" and "full") would raise the questions concerning the price, reimbursement and liability between the two steps.
- The cooperation with the HTA bodies and pricing and reimbursement authorities would be useful, but there are no EU harmonized health-technology-assessment (HTA) rules and pricing and reimbursement is solely under national authorities' competence.
- In addition, there is an increasing difference between various EU member states with regard to the reimbursement agreements at the national level. This gap may become even bigger when registration is based on less mature data, resulting in unequal access for patients throughout the European Community as compared to the current situation.
- During the HTA process, the data acceptable for accelerated licensing from a regulatory point of view may not be acceptable from a technical assessment point of view, to justify the cost to the MS of having medicinal products made available on the basis of less data to compare to already available products that may be more cost-effective.

- Although AL could be a solution for the authorisation of medicines, cost and HTA considerations have to be measured and dealt with for the final outcome i.e. having the medicine available for all the patients in the EU.
- The unwillingness of companies to make their products available in small insular markets makes it difficult for the common EU market for medicines to function. This will be even more difficult for the products authorised through AL.

Acceptance of the higher level of uncertainty by the society

- Problem with lack of awareness and engagement of other stakeholders or sectors as already visible with CMA. Will reduced piece of data allow making consistent decisions by both regulators and payers?
- The payers might be reluctant to commit public funds to reimburse products with incomplete data and uncertain future.
- As medicines will be approved for a restricted population based on evidence only on this subpopulation, it remains unclear how to assess the benefit/risk ratio in so early stages with scientific and statistical approaches that enable regulators to put medicines on the market with confidence.
- Difficulties to communicate the uncertainties of evidence for efficacy and safety to the patients, general public, payers and doctors.
- Patients consider that a new medicine is available that fulfils the same requirements like other authorised medicines. AL implies the involvement of patients in the regulatory process, however what the patients' contribution can be at the different stages of the decision making is unknown yet.

Resources

- AL presents a series of major challenges for authorities, industry, healthcare professionals and patients – which need to be met by a new level of involvement of all stakeholders and will require a substantial investment in the form of human resources and financing.
- The AL will add complexity and extra burden to the existing regulatory system, especially regarding PhV.
- Additional work load and financial burden for national competent authorities (NCAs), especially for small MS who have limited human resources.

Post authorization measures (PAMs):

- Consequences on regulators/patients of failed follow-up studies (already an issue with the CMA).
- Difficulties to withdraw the product from the market in case positive B/R balance cannot be confirmed at a more mature stage, especially if a drug is hardly efficacious (e.g. experience with CMA).
- How to perform additional PhV measures in all MSs needs to be clarified – in some countries e-registries or pharmacy-epidemiological databases are not available.

- The risk of off-label use must be taken into account and discussed carefully.

Recommendations

- Already existing different types of MA procedures should be better defined and explored, before concluding that they are ineffective.
- EMA AL concept should also take into account demonstration of substantial improvement over existing therapies with a higher evidence level (e.g FDA "Breakthrough Therapies").
- To use the existing legal tools and national regulations even more frequently.
- A more flexible approach to ensure the future European position that innovative medicines will be registered in the EU is needed.
- Companies need to be made more aware of the current flexibilities in the EU regulatory framework.
- Best practices of the EU MSs should be collected and utilised.
- Change EU Regulation to oblige MAHs to market medicinal products in all MSs.

Conditional Marketing Authorisation (CMA)

- Explore how the existing system could already now be used, for example making better (and more frequent) use of CMA.
- CMA could be considered as an AL with an integration of all stakeholders.
- To make the procedure of currently available CMA more efficient:
  - create an additional committee for designating eligible products for expedited review/accelerated process; pre-authorisation review, fixed dates for the R&D plan, (e.g. FDA "rolling-review");
  - currently, CMA can be used as a bypass by industry in the case of incomplete development or insufficient quality. In addition, there is a growing number of "classical" MAs which are yet subject to conditions to clarify the benefit / risk after MA is granted. The CMA should be reserved for truly innovative products.
  - review the status of implementation of efficacy and / or post-authorization safety studies with binding measures
- It might be useful to consider if CMA should be made accessible on a case-by-case basis for other conditions than the ones which are life-threatening and without treatment alternatives.
- To introduce an even more step-wise approach of CMA than to today.

Involvement of relevant parties

- To develop necessary integration of all the system on medicines authorisation process and align the actions of EMA and NCAs before considering other national or supranational bodies.
- Early involvement of all relevant stakeholders to the discussions on AL and the

strengths and weaknesses of the process for each application can be explored.
Coordinated, streamlined procedure with the focus on key decision makers (industry - development, EMA & EC - authorisation, national bodies – reimbursement, doctors & patients – usage). Progress in pharmaceutical regulatory system can only occur with coordinated (inter)national effort by all relevant stakeholders.

- To enhance collaboration between different authorities and to adopt an integrative vision – single assessment of medicines evaluation combining different methodologies to avoid successive, parallel assessments of the same data of the medicine from different bodies, with the goal of more agile regulatory decision-making process.
- "Early dialogue" should be more elaborated - regulatory authorities to provide more support to the companies who are at certain stages of product development so that they meet regulatory standards (good example - FDA's breakthrough designation.
- To implement more stepwise approach and involving/including scientific advise by the NCA.
- HTA bodies involvement in an early phase
  – the development of more comparable HTA methods and quantitative instruments;
  – because it can turn out that only big MSs will have an advantage of getting medicinal products in an earlier stage; for the others they will not be available because of the high cost of post marketing safety and efficacy surveillance.
  The criteria used by licensing authorities such as EMA differ from the institutions responsible for reimbursement (positive risk/benefit vs. added benefit). To address this problem, EMA in cooperation with HTA institutions has been offering scientific advice to applicants to assist with developing new medicinal products, the German NCA pursues the same approach, inviting the IQWIG to scientific consultations, if the applicant wishes so.
- A novel aspect of AL is that patients and the representatives of patient organisations are also to be involved in the consultation process. Issues relating to data protection and conflict of interest should be discussed in a larger context.
  The role/value of involvement of patients at the different stages of the regulatory process should be explored.
- The concept should be clearly explained to the society in order to achieve a high level of understanding of what it means. Therefore, the key role of NCAs in the process should be recognized.
- Patients should be well informed.

Data

- Comprehensive clear criteria for the use of AL should be developed; AL scope to be well defined.
- Clear rules for the absolutely necessary data for the benefit/risk appropriate level of evidence and acceptable level of uncertainty to be established.
- To clarify the beginning of the data protection/exclusivity period for AL products.

- Questions relating to the approval of medicines for "niche indications" (such as orphan drugs) and the further development regarding wider indications must be discussed carefully under the aspect that the first patients treated must be registered and off-label uses avoided, mainly in view of the fact that clinical trials are conducted worldwide (also in third countries).
- Patients treated with AL medicines should be included in patient registries.
- More links between the marketing authorisation dossier data and the use of medicines in real life should be established.

Post authorization measures (PAMs)

- For increased number of safety and efficacy commitments, it is necessary to ensure that the current regulatory system is able to cope with increased post- authorisation monitoring (PhV and effectiveness evaluation).
- The establishment of clear post marketing commitments from the very beginning - protocols, study outcomes to be expected and regulatory consequences of the deviation from expectations are needed.
- The possibilities of PAES to be more explored. Better control of implementation of PAES & PASS with binding measures is needed.
- Further investigation of the post licensing data to be outlined in RMPs.
- Structured data gathering after marketing authorization need to be in place.
- To make completely sure/clear that (regulatory) actions can be adopted during all phases of AL.

Pricing and reimbursement

- The change of regulatory status in the AL concept of a given medicine over time could have implications for pricing and reimbursement decisions.
- To link reimbursement amount with level of development/proof of new evidence could provide an incentive for companies to complete developments, and take away hesitations on the part of licensing authorities to grant a conditional approval.
- Accelerated marketing authorisation itself as a tool for patients' timely access to new medicines is not sufficient. It will be necessary to speed up the process of reimbursement setting or make changes in the methodology so it allows making (reimbursement) decisions based on incomplete evidence.
- Change in the national legislation regarding reimbursement would be needed in order to put 'AL concept' medicinal product on the positive list (reimbursed list) and involve the national HTA assessment for this kind of medicines.
- Full attention should be given to the outcome and recommendations of the recent ´corporate responsibility in the area of pharmaceuticals project facilitating supply to small markets´. Further work and collaboration on the network of pricing and reimbursement is needed.

NATIONAL INITIATIVES (studies, actions) to ensure timely access of patients to medicines

Spain: In collaboration with payers and regional health authorities, the Spanish CA has developed a system for positioning medicines once approved (therapeutic utility) taking advantage of the work done in the authorisation system and maintaining the leadership of health authorities and the consistency, continuity and integration of the different assessments to avoid conflicting results.

NL: Study ´Minds Open – Sustainability of the European regulatory system for medicinal products´ by the Netherlands National Institute for Public Health and the Environment has been published in June 2014.

RIVM report Minds Open_Sustainability c

UK: Report of the Expert Group (industry, patient and health professionals) on innovation in the regulation of healthcare, 25 September 2013 has been published: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con336728.pdf
MHRA Innovation Office for scientific support for industry has been established: http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm
Early Access to Medicines scheme has been launched on 7th of April 2014: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm