

## **FORUM TO CONSIDER EARLIER ACCESS TO MEDICINES**

### **SUMMARY OF DISCUSSIONS**

1. The second Forum set up under the Ministerial Industry Strategy Group (MISG) met on 24 September 2007 to debate whether making medicines available to patients at an earlier stage of their development was feasible and desirable.
2. The topic of earlier access to medicines was chosen by the Panel to provide a preliminary consideration of a recommendation made by Sir David Cooksey in his Review of UK Health Research Funding. This report recommends conditional licensing of new drugs at an earlier stage in the development process (eg at the end of Phase II). It also recommends allowing clinical use under strict controls, plus a systematic programme of pilot studies of conditional licensing for new drugs at an earlier stage, allowing initial use by specialists - but not GPs - in the context of a randomised control trial.
3. The aim of this Forum was to bring together representatives from all the stakeholder groups who might be expected to have an interest in earlier access to medicines, to explore the possible benefits and potential problems that might arise from such a scheme. The Forum comprised representatives from patient groups, academia, safety scientists, the pharmaceutical industry, medicines regulators and other Government officials concerned with medicines' pricing and reimbursement mechanisms and health technology assessments (NICE).
4. Specifically, the Forum discussed a number of possible scenarios for providing patients with earlier access to promising new treatments:
  - expansion of existing EU conditional licensing provisions (EU Reg 507/2006), which currently covers seriously debilitating or life-threatening illnesses, to include less serious diseases which nevertheless represent unmet medical and/or public health needs and where new treatments in development show exceptionally promising results;
  - a two-step "staged" approval process, which would give patients access to new products provisionally approved for the treatment of acute and chronic conditions which are not serious or life-threatening. Provisional approval would be given on the basis of initially limited clinical data derived from studies other than large-scale clinical trials, with subsequent close monitoring of patients in a "real world" setting. Once comprehensive data becomes available the provisional approval would be converted to a full approval;
  - Some sort of compassionate use provision allowing reimbursed managed access such as the French ATU system;

- Other possible models such as the Canadian Notice of Compliance with Conditions and FDA accelerated approval and treatment regimes.
5. Each of the stakeholder groups represented made a presentation setting out the issues to be considered from their perspective, should proposals for an earlier access scheme be taken forward. A discussion followed, focused by reference to the following questions:
- Is there a consensus that we want a system of earlier access to new medicines for UK patients than is currently available?
  - For which diseases and conditions should medicines be provided under this regime?
  - At what stage of development should new medicines be made available under this regime, and how exceptional do the results have to be?
  - What level of risk is acceptable, and will this be different for different medicines, different diseases, different stages of disease?
  - What information needs to be provided for patients, clinicians?
  - What controls/tools are needed (eg real-time safety monitoring, product withdrawal, etc)?
  - How would arrangements for NICE/Health Technology Assessment, reimbursement and supply need to be adapted? What are the liability, patient consent, patient information, advertising implications?

### **Discussion and conclusions**

6. There was a general view that earlier access could be of benefit to patients under certain circumstances. It was also noted that the consequences of this may be to expand the supply of new drugs. The Forum focused on the question: “under what conditions would there be a workable consensus to move forward?”

### **The conditions**

7. These fall into three categories:

*scientific and clinical* – where there needs to be established:

- significant unmet medical need – not just for cancer and HIV, but also chronic diseases such as MS and rheumatoid arthritis;
- clear evidence of efficacy;
- confidence about safety, as far as possible prior to the approval, with a good system for collecting evidence afterwards;
- regulatory tools able to deal with emerging problems with earlier access drugs (eg reduced efficacy, safety issues, failure to deliver on commitments etc);
- a regime that will not compromise the ability of the developer to complete the clinical trials programme, leading ultimately to the granting of a full marketing authorisation.

***access and reimbursement:***

- earlier dialogue between sponsors and health technology assessment agencies on cost/benefit measures to include in clinical trials will be needed to ensure medicines are most appropriately valued for early access, whilst avoiding a “rush to false precision”, reimbursement systems should assist, and not frustrate, the concept of earlier access;
- pricing arrangements for any medicine receiving a conditional approval will need to be based on discussions between manufacturers and the Department of Health.

***communication and liability:***

- what constitutes “informed consent” and how to ensure that patients are given all necessary information, including what is not yet known about the drug;
  - the need to address the problem of litigation faced by pharmaceutical companies and who could be considered liable if a product caused harm and had to be withdrawn.
8. The Forum agreed that the process was unlikely to be “one size fits all” and both clinicians and patients will need to be informed and agree about the benefits and risks of engaging in earlier access programmes.

**Possible earlier access programmes**

9. The Forum noted other examples of earlier-access programmes currently in use around the world that might provide a basis for an earlier access regime including:
- France’s Autorisations Temporaires d’Utilisation (ATU) system, introduced in 1994 to cover genuine public health needs and products which are “unique”;
  - a similar scheme which is also in place in Sweden;
  - Canada’s Notice of Compliance with Conditions (NOC/c) policy, which is similar to the EU Conditional Approval regime and requires the sponsor to undertake additional studies to confirm the product’s clinical benefit; and
  - US accelerated approval (Subpart H) procedure, which is also similar to the EU conditional approval regulation and requires confirmatory studies.

**Expansion of the conditional licensing regime laid down in Regulation 507/2006 EC and the compassionate use regimes laid down in Regulation 726/2004 EC**

10. The provisions in the new conditional licensing Regulation could be expanded but the Forum agreed this would take considerable time and would be dependent on EU-wide agreement. It was felt that further experience of operating the regulation and a review of the existing regime would be necessary prior to any view being taken on whether to expand the existing regulation. Only 4 approvals have been granted at the time of writing, although a further 20-30 are expected in the coming 2-3 years.

11. The Forum discussed how many of these alternative systems could be introduced in the UK without requiring change in EU legislation, and concluded that this would apply to compassionate-use provisions; the others mechanisms would involve fundamental changes to the EU licensing system and would require EU negotiation.
12. It was also suggested that ideally a process of earlier access should be developed that would apply at least EU wide, and ultimately globally, and that this might best be achieved through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process.

### **Scope of any earlier-access programme**

13. It was agreed that such a regime would be most appropriate in respect of products to treat serious, chronic/debilitating or life-threatening illnesses. The Forum considered both the licensing of new drugs and extensions for already-approved drugs. For some new drugs, such as gene therapy products, the benefits can be remarkable, albeit in very small numbers of patients, and for these there is an extremely strong indication for very early access. In these circumstances the risk benefit needs to be carefully considered, taking account of patients' views and robust real world safety monitoring/ pharmacovigilance must ensure the ability to respond quickly should problems arise. However, for the majority of new treatments, the level of benefit is often unpredictable for individual patients. Demonstration of clinical benefits relies on statistical analysis and this in turn requires completion of significant clinical trials programme.
14. For existing drugs whose safety profiles have been established, some will work in new indications, some in new combinations and others in different stages of a disease. The Forum noted that this can radically change the risk benefit profile of the drug. In these circumstances robust surveillance to monitor extra risk would be required. The Forum noted that the expected development of "personalised" medicines could also impact on the way regulation developed.
15. The Forum also noted that the needs of children should not be excluded from early-access decisions, but recognized that drugs licensed for use in the adult population could have very different effects in children.

### **At what stage in the development of a drug, would earlier access be appropriate?**

16. The Forum concluded that early access should be available no earlier than when a favourable profile of benefits and risks is indicated. Only in rare cases will such data be available prior to confirmatory (ie Phase III trials) when robust efficacy data begins to emerge.

17. The Forum debated the current frequent policy of requiring each phase of clinical development to be concluded before finalizing the plans for, and initiating subsequent phases, however more recently a number of companies have been exploring conducting Phase II and III trials “seamlessly”, with inference based on the pooled dataset. The regulators pointed out that work is ongoing to develop “inferentially seamless” Phase II-III trials, although they expressed caution about trial integrity, statistical methodology and acknowledged, for example, that it would need considerable upfront planning as it could lead to a loss of “thinking time” between the different trial phases. The EU Committee for Medicinal Products for Human Use (CHMP) has published a draft reflection position paper on the issue.
18. The Forum noted that 30% of medicines fail to progress beyond Phase II - a percentage which has not changed in 10 years - so there should be caution about earlier access to products that may not ultimately have a favourable profile of benefits and risk and have later to be withdrawn.
19. It was also agreed that there was scope for the NICE Health Technology Assessment programme to be involved in providing advice at an earlier stage of a drug’s development to help inform manufacturers plans for the development programme, which in turn will provide the information that NICE will need to make judgments about clinical and cost effectiveness. The Cooksey report had suggested that, in such circumstances, NICE might make only interim judgments on new medicines, which would allow limited early adoption of those thought to be cost-effective. The Forum highlighted that health technology assessments needs robust evidence to provide useful certainty of the cost effectiveness of medicines, and premature use of HTA may be of limited value if performed before this evidence was collected. Further work would need to be done to establish how or whether an assessment could be performed with limited amount of information if the medicine is made available at an earlier time point, although another option was to accept that the NICE review would not take place until later in the overall development process. NICE might, however, need an entirely different set of criteria for assessing drugs for conditional approval. The Forum noted that earlier access has two dimensions: firstly the timing of any regulatory approval, and secondly the proportion of patients who might appropriately benefit from access to a new medicine, and it would be important to ensure that any arrangement for conditional licensing addresses both of these aspects if it is to achieve the outcomes outlined in the Cooksey report.

### **Determining acceptable levels of risk**

20. Novel medicines such as biotechnology products, new antibodies and gene therapy may offer the best hope of a cure or significant relief of suffering from a previously unmet need, but they may also be accompanied by novel and completely unpredictable risks. Earlier access may significantly increase the possibility that serious side effects go undetected before the drug is made widely

available, and therefore the level of risk which is acceptable depends on both the therapeutic context and how well the known and unknown risks can be managed. The Forum also noted that the fear of litigation can lead to withdrawal of drugs which, taken overall, could be argued to be more advantageous than not. For example the withdrawal of a drug because of a perceived unacceptable level of risk in the developed world had meant that it was no longer available in the 3<sup>rd</sup> world where it had been a highly effective treatment for children.

21. Recently, the emphasis on managing risk has moved from passive to proactive collection of safety data, and the risk management plans which are now mandatory under EU regulations require sponsors to set out not only what is known about the product's safety profile but also what is not known about it, with proposals to fill these knowledge gaps with continued research and apply risk-minimisation measures. If there is a move to earlier access, risk management plans will assume much greater significance, so there is a need to ensure that they are clearly enforceable, that MA holders have the commitment and resources to deliver them and that regulators have the resources to be able to get at the safety data quickly, and act on it quickly. At present, effective monitoring of "real time", "real world" safety still presents many challenges. It was also suggested that risk management plans could be published.

### **Involving patients in making benefit/risk judgements**

22. The Forum noted that patients suffering from many diseases can be less risk averse than regulators and industry – especially in circumstances when their options seem limited and also in relation to their judgement about accepting the possibility of rare, but potentially serious adverse events associated with a treatment. Patient representatives told the Forum that patients are often prepared to take risks within a well-regulated context, for example a clinical trial, in which the results will be examined and followed up, not only for their own benefits but for those of others. However, the Forum agreed that risk must always be viewed in the context of benefit, including consideration of the risk in not taking the medicine. Disease subgroup populations differ in what they consider to be an acceptable level of risk, and this must be dealt with case-by-case.
23. Medical professionals - including nurses and pharmacists – would need to be fully educated about the earlier access process including pharmacovigilance to ensure they have the skills and tools needed to communicate fully with their patients and report safety findings appropriately. Developments such as Connecting For Health could provide access to enhanced data for safety monitoring in the future.
24. It was also agreed that patients not only approach the issue of risk differently but can also change their minds at different stages of their illness about what level of risk is acceptable. Moreover, the patient's view of "informed consent" may be different to that of the industry and the legal profession. In such circumstances an

understanding of the meaning of informed consent is uncertain, particularly if patients are desperate and do not have alternative options.

25. It was also suggested that patients receiving medicines on an early-access basis could provide informed consent through a “patient partnership agreement”, under which information on the medicine is made available to them but they also accept responsibilities, for example in documenting adverse reactions, so that they become part of making this drug available at an earlier stage and undertake not to sue the sponsor in return for having been given all the information. However, the Forum speculated as to what would constitute a satisfactory and legally acceptable amount of information in such partnerships, and suggested that this could provide the basis for a lawsuit.
26. High-profile cases such as Vioxx have, to some extent, undermined public confidence as to how drugs are tested and assessed, and further public concerns could arise from the earlier-access proposals, speakers warned. The process of how a new medicine is assessed needs to be available to the public and qualified, with more openness and transparency in the system, in order to restore public confidence, the Forum concluded.

### **Summary of outcomes from the Forum**

27. A programme of work should be commissioned to explore the possibility of developing a regime that would provide earlier access to medicines under certain circumstances in the UK. This work will need to take account of thinking on this issue in other countries – such as in France, Sweden, Canada and the future FDA system.
28. In developing a possible scheme, the work programme will need further to explore the following issues:
  - Ensuring patient safety and availability of a robust system for data capture for pharmacovigilance and possible efficacy and availability of appropriate tools for the regulator;
  - Legal issues (liability, advertising);
  - Communication, patient consent and patient information;
  - Arrangements for reimbursement and timing of health technology assessment;
  - Nature of acceptable evidence of efficacy and ensuring ongoing and subsequent clinical trials are not compromised;
  - Ensuring a UK initiative remained compatible with EU provisions.
29. Greater experience of the EU conditional licensing provisions in operation needs to be assessed prior to any view as to the adequacy of the current regulation, particularly as more of these types of products are expected in the coming years.

## **Next steps**

30. A recommendation to progress this work was made to the MISG on 1<sup>st</sup> November 2007, including the proposal to put in place a process to work on the issues raised at the forum with the key stakeholders. MISG endorsed the proposal and agreed that the work should be taken forward within the MISG regulatory workstream of the Long Term Leadership Strategy (LTLS).