Fast and effective?

How will EMEA use its new powers of conditional marketing authorisation?

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EMEA's new system for fast-tracking drugs aims to offer quicker access to promising new therapies without jeopardising essential research. Draft Guidance on the use of the new conditional marketing approval procedure will shortly be published, and patients, professionals and the public are being invited to have their say.

In July, the European Medicines Agency (EMEA) threw a possible lifeline to two groups of patients who have reached the end of the road with conventional drug treatment. EMEA gave conditional approval for the use of sunitinib malate (Sutent) for patients with advanced and/or metastatic renal cell carcinoma (mRCC) where interferon alfa and interleukin-2 therapies have failed. It also granted conditional approval for its use in patients with unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) where imatinib mesylate treatment has failed due to resistance or intolerance.

For these patients, the early approval of sunitinib gives some new hope. For everyone with an interest in new therapeutics – as patients, public, health providers or drug developers – this represents the first chance to see how EMEA, which has responsibility for approving all new cancer medicines, intends to use its new powers to grant conditional marketing authorisation (CMA).

The concept of CMA was adopted by the EU in 2004 "in order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies." Pressure had been growing from European patients with cancer and other life-threatening diseases who could not understand why they should wait months or years longer than patients in the US for access to drugs that could save, prolong or improve their lives.

There was also a perceived need to update the regulatory procedure to take account of the way drug development has been transformed by progress in molecular imaging. The early stages of traditional drug development (pre-clinical, phase I and phase II) tested whether the drug was safe and effective enough to be worth trying in a large confirmatory (phase III) clinical trial. The regulatory procedure therefore focused on the outcome of the phase III trials.

Now researchers are able to see more about what is happening at molecular level, and the early stages have become a fount of information. Researchers can explore how the drug works, what targets it is hitting, which patients have the target and what dose and schedule should be most effective.

The new procedure, modelled in part on the US 'accelerated approval' procedure, gives EMEA two new powers. The first is to approve drugs for a one-year period, renewable annually, as soon as sponsors show data strong enough to demonstrate a positive benefit–risk balance. This has the potential to reduce the period between a drug going into development and the marketing application being handed to EMEA. (The time EMEA spends assessing the drug, is dealt with by a separate regulation on 'accelerated assessment'.) The second is the power to lay down conditions with some legal standing requiring the sponsors to carry out post-approval studies to clarify certain aspects of the drug – duration of effect, which patients it works best in, what is the optimum dosage, and so on.

The CMA procedure is expected to be widely used for new cancer drugs. In particular, it is likely to be used for drugs that would previously have been

The Agency. Decisions on which new drugs will make it to the EU market and which won't are made here at EMEA's headquarters in Canary Wharf, London

dealt with under 'exceptional circumstances' approvals procedure, for which the criteria are more restrictive.

The implementation regulation (507/2006), which came into force in April 2006, spells out the type of drugs that may be eligible for CMA (see box). It also spells out the basis on which conditional marketing approval can be renewed after the approval year is over.

However, the regulation is remarkably vague when it comes to criteria on which approval should be granted. The first criterion listed under Article 4 says simply that "The risk–benefit balance as defined in Article 1(28a) of Directive 2001/83/EC is positive," that is, any risk relating to the quality, safety or efficacy of the product as regards patients' health or public health. There is not the merest hint of direction about how risks or benefits should be measured.

It is equally vague about what EMEA can ask for in post-approval studies. The regulation mentions only that the holder of a CMA shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk–benefit balance is positive and providing the comprehensive clinical data referring to safety and efficacy that would normally be required for standard approval.

THE CMA REGULATION

Eligible therapies (article 2)

- Medicinal products aimed at treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases
- Medicinal products to be used in response to public health emergencies
- 'Orphan' medicinal products for rare diseases

Requirements (article 4)

- Positive risk–benefit balance
- Applicant 'likely' to be able to provide comprehensive data post-approval
- Meets unmet needs
- Early approval of benefit to public health on balance

Renewal (article 6)

- Annual renewal
- Risk–benefit balance to be confirmed, meeting CMA obligations

CMA versus Exceptional Circumstances

Approval under exceptional circumstance can only be applied to drugs where it is deemed impossible ever to collect comprehensive data due to rarity or because it is contrary to medical ethics, or the state of scientific knowledge does not allow such data to be collected. The CMA procedure can be used to give early approval to drugs that can show a positive benefit–risk before the comprehensive data set is available, leaving the supplementary clinical data to come later.

Collection of further pharmacovigilance data can also be required.

Quite how this will translate into practice, and the implications for cancer patients, drug developers, and health providers, depend heavily on how these broad-brush requirements are interpreted.

Will there have to be data from a randomised trial? Will the new therapy need to be compared against best care or a placebo? Could it be enough just to show the response in a single-arm trial? Will drug sponsors have to show which target is being hit, and identify the group of patients who are most likely to respond? How many patients will be required for data on efficacy or safety? Will the drug need to show clinical benefit on survival or symptoms? If 'surrogate endpoints' are used (see box), what level of certainty will be required to show that the surrogate is reasonably likely to predict clinical benefit?

There are also questions about post-approval study requirements. What sort of studies will be asked for, and what will happen if a drug sponsor does not fully comply? Will CMA be withdrawn if the post-approval obligations are not fulfilled?

Three main stakeholder groups will be affected by the way EMEA addresses these questions: patients who have run out of other options, drug developers, and the general public.

The patient – a lifeline

What matters to patients is access to effective drugs as quickly as possible, through 'conditional' approval or any other route, such as participation in clinical trials or compassionate use programmes. Safety is not the primary issue for many of them, who are facing the prospect of death or a very impaired quality of life anyway. They would probably set the risk–benefit hurdle fairly low. This translates into accepting less demanding trial designs, and allowing benefit to be measured in terms, for instance, of tumour shrinkage, which tends to be quicker to measure, but may not accurately reflect true or sustained benefit in terms of survival or quality of life.

Precise identification of the target group will not be a major priority. If the data indicate that the drug is effective in one in ten patients with a given indication, most patients would at least like the option of 'giving it a go', particularly if side-effects appear encouraging. Patients are likely to be very supportive of any studies that could throw further light on how and in whom the drug in question works best – but not at the cost of delaying access.

The industry – quicker returns

The second group of stakeholders are the sponsors of experimental drugs, principally pharmaceutical companies. Kapil Dhingra, vice president of the oncology division at Roche, speaking at the European Society for Medical Oncology (ESMO) last October, welcomed the new approval, and said the approval of sunitinib was "a good start". He characterised the main advantages for the industry as early certainty about a drug's launch, and early return on investment.

The July 2005 issue of *Regulatory Rapporteur* said that early approval may be particularly important for biotech companies, which play a key role in developing molecularly targeted therapies but don't always have the resources to conduct long and expensive phase III trials.

Financially, then, this would be a good deal for the industry, good for shareholders, and good for the rest of us if lower costs stimulate innovative research or result in lower prices and more thorough research into new drugs.

From the developer's point of view, the guiding principle on approval is 'the earlier the better'. In general, they will be looking for the number of patients and the length of time required to prove efficacy and safety to be set somewhere at the lower end of the scale, and they will want EMEA to adopt less rigorous measures of efficacy. Rather than having to show survival data, which can take a long time to collect, the industry would prefer CMA to be granted on data about response rate (tumour shrinkage), time

SURROGATE ENDPOINTS

Surrogate endpoints are measurable variables deemed likely to predict clinically meaningful endpoints such as longer survival or reduced symptoms. They can be quicker to evaluate than clinical endpoints, but their predictive powers are not very accurate. CMA is likely to rely heavily on data from surrogate endpoints, with the option of requesting post-approval studies to see how this translates to clinical endpoints.

Traditionally, a limited group of surrogate markers have been accepted on a case-by-case basis, including response rate (tumour shrinkage) and time to progression or progression-free survival. These may, in the future, be extended to include functional imaging, such as measures of apoptosis/antiproliferative effects, and also pharmocodynamic biomarkers such as PSA as a marker for prostate cancer or CA 125 for ovarian cancer. However, statistical validation of these sorts of surrogate biomarkers is proving very difficult.

Response rate was the basis for 30 out of 48 approvals, but this translated very poorly into survival benefit

to progression (how long the drug keeps the disease at bay), functional imaging (imaging levels of cell death or cell proliferation) or biological markers of efficacy.

The industry also has a view on post-approval studies. Once a new drug as been approved, pharmaceutical companies will want to move on. They have little interest in tying up resources in research that may offer little financial benefit and may even diminish the market as research identifies which subgroups of patients respond best.

There are also ethical and logistical problems to conducting such studies after a drug has reached the market. Patients often join a trial of an experimental drug in the hope of being randomised to receive the new treatment. Once the drug is on the market, joining a randomised trial actually decreases their chances of getting the drug which they could otherwise have on prescription.

At the ESMO meeting, Dhingra stressed the need to have a very clear definition of the clinical objectives, scope and timelines for post-approval studies, and said that EMEA needed to take account of what was feasible.

The public – effective treatment

As a third stakeholder, what the general public wants amounts to efficacy and efficiency. As potential patients, they want a system that encourages drug developers to find effective therapies targeted precisely at the specific malignant phenotype driving the cancer. They want the treatments that can be delivered in the most effective schedule, dose, combination, and method of administration, and they don't want to take therapies that might be of no benefit for their particular disease, but might have nasty side-effects.

As tax, medical insurance or treatment payers, the public does not want to foot the bill for prescribing an increasing number of highly expensive drugs to broad populations of patients if only a minority are likely to benefit, and if clinicians do not have the information to use them to greatest effect.

A group of researchers at the Mario Negri Pharmacology Research Institute, in Milan, argue that EMEA and its US counterpart, the FDA, have "a major role in improving public health, as they fall between clinical trials and (public) health care" and that "drugs must be rapidly released for patients who need them, but not at the expense of adequate knowledge about the benefit of the drugs."

Their paper, published in the *British Journal of Cancer* (vol 93, pp504–509), analyses the basis on which EMEA has approved drugs for solid cancers over the 10 years since centralised marketing was introduced in 1995, and argues for raising the standard of proof, particularly for clinical benefit.

Looking only at applications for new drugs or for extended indications for therapies for solid tumours, they point out that response rate (usually given as the percentage of patients whose tumours shrunk by at least 50%) was used as the primary basis for granting 30 out of 48 approvals, but that, in cases where data were available, this translated very poorly into survival benefit. In 13 cases for which survival data were also given, the benefit ranged from 0 to 3.7 months, with mean and median benefit of 1.5 and 1.2 months.

The authors also point out that 30% of approvals were given on the basis of single-arm trials, despite the advice in EMEA's own Note for Guidance 'Evaluation of anticancer medicinal products in man' (2002). This says that randomised comparative trials are normally always required, with no comparative trials being considered acceptable only in the case of pretreated patients when no established regimens exist.

In the US, more than 90% of post-approval study commitments remained unfulfilled according to a 2005 FDA report. The Mario Negri researchers conclude that the public interest is best served by keeping the efficacy hurdle higher, rather than relying on post-approval studies to come up with more robust data.

They argue that EMEA should insist on seeing overall survival data in combination with formal assessments of symptom control or quality of life. These assume greater significance given the rather small median survival benefit of 1.2 months offered by drugs for solid tumours approved over the past 10 years.

On the question of trial design, they make the case that there should be a requirement for phase II randomised trials, with patients randomised to the new drug or to best available care. They also argue that phase III comparative trials should be the norm for the approval of new anticancer drugs, with phase II studies only accepted in exceptional cases, when there is really outstanding, unprecedented or unexpected activity.

EMEA is moving away from the 'gatekeeper' model towards more constructive communication

To ensure that the regulatory process takes into account the needs of patients for whom experimental drugs may be their only hope, the researchers suggest greater patient involvement in the EMEA evaluation process to help identify which drugs really need fast-track designation. They also emphasise the importance of effective information to spell out to patients the risks of a partially proven therapy.

Selective approval

Current understanding about the complexity of cancer and of mechanisms of action and of resistance to drugs suggests that the disappointing clinical benefit shown by many drugs in the above study may indicate not that the drugs are ineffective, but that they are effective in only a small part of the population they were tested in. The worry is that the great promise of the era of individually targeted treatments may never be realised if therapies are marketed early, with insufficient information about selection of the target group, especially if nobody takes responsibility for the necessary post-approval work.

The experience with gefitinib (Iressa) for non-small-cell cancer is often cited to illustrate the problems. Rejected by EMEA because of lack of survival impact in an unselected population, the drug has since been found to be effective in a certain very specific subgroup. Makers AstraZeneca claim it would have been almost impossible to identify this target group had the drug not been on the market, and thus widely used, in the US and Japan. Many voices from the national regulatory agencies, however, believe that companies seeking approval for a targeted drug should not expect to get approval for its use in an unselected population.

A key paper published in the *New England Journal of Medicine* two years ago (Roberts and Chabner, vol 351, pp501–505) argued that it may be unrealistic to expect pharmaceutical companies to carry out these studies, as they can be very complex, time-consuming and are likely, at least in the short term, to diminish the market for their drugs.

For the US, they proposed a mechanism for 'selective approval' whereby early approval could be granted, "only if the sponsor has initiated studies to identify subgroups of patients who are likely to have responses." The regulators and drug sponsors would reach agreement over how the studies could be concluded, with an option of forming a partnership with a public body such as the US National Cancer Institute or an academic centre, with a certain percentage of profits from the early marketing of the drug set aside to fund this research.

Sadly, Europe has no equivalent of the NCI. However, there are many international cooperative groups, as well as the European Organisation for Research and Treatment of Cancer or the French National Cancer Institute, INCa, which recently launched a post-approval trial (PHARE) to find out more about the best way to use adjuvant trastuzumab (Herceptin).

The view from EMEA

Faced with these potentially conflicting pressures from patients with unmet need, from the industry and from the public interest, how is EMEA going to implement the CMA regulation? So far, the approval of sunitinib is all that anyone has to go on, because EMEA is still in the process of drawing up draft Notes for Guidance. However, Francesco Pignatti, Scientific Administrator at EMEA, agreed to share his personal views with *CancerWorld*.

Pignatti stresses that CMA requires proof of a positive risk–benefit balance. "Some people understand CMA as putting drugs on the market without knowing their efficacy, and that is not what is meant by conditional approval. I think that even for CMA it is crucial that a drug is only ever put on the market when EMEA's scientific committee has judged that, based on the evidence available, the benefit–risk balance is positive The draft of the regulation started off saying the benefit–risk is 'presumed positive'. Now that word has gone from the final legislation."

He accepts, however, that, despite being as objective as possible, assessing the risk–benefit balance is not an exact science. "One needs to express value judgements on multidimensional concepts – benefits, risks – each estimated with variable degrees of uncertainty. Without comprehensive clinical data, as for CMA, the real challenge is to identify situations where it is still possible to conclude on a positive benefit–risk balance."

Given the subjective nature of the judgement, patients will need to have a strong voice in the regulatory process to ensure their voice is heard. Traditionally, Europe has lagged far behind the US in this respect, but EMEA has been trying hard to catch up. A Working Group with Patients and

Consumers Organisations now enables these groups to have a formal consultative role. Though for some patients this falls far short of the partnership they would like, the European Cancer Patient Coalition and other patient groups have welcomed the move.

Pignatti sees a cultural shift away from the 'gatekeeper' model towards a constructive communication among stakeholders more appropriate to today's rapid progress of basic science and cancer therapies. "In this context, CMA makes a lot of sense – it weighs the need for a comprehensive clinical development with high unmet need and public health interest in getting beneficial drugs quickly to patients in desperate need."

Pignatti envisages the use of surrogate endpoints so long as they are considered "reasonably likely" to predict an effect on a clinical endpoint such as survival, and so long as the effect on the surrogate is great enough. "There are some surrogates where the prediction is sufficiently high that if the effect is big enough, and looking at all the supportive evidence, you know that it will be very likely also to mean something in terms of clinical benefit."

Minimum data sets

Asked about what he would envisage to be the minimum specifications in terms of trial size and design required to grant approval, Pignatti said, "It is not about the minimum. It is about giving yourself the chance in a comprehensive development of deciding at which point there could be sufficient evidence to go for approval."

He is cautious about spelling things out in detail, because there are so many possible variables: the rarity of the indication, the level of toxicity, whether alternative therapies are currently available, whether the drug shows dramatic or less-pronounced activity and so on. He recognises, however, that the window of opportunity for performing a randomised study in a certain indication may only exist before approval, and he ventures some general comments.

"To aim for early approval, one should randomise early in the clinical development. Preference should be given to study designs and endpoints that can capture convincingly a clinical benefit as early as possible. In the standard approach we would certainly say 'do a randomised trial, and if appropriate plan for an interim analysis when you have a sufficient number of patients when it is meaningful to draw some conclusions, in case the treatment effect is much larger than initially expected.'

"I would not recommend a strategy focussing on single-arm studies for approval. However, if one happens to observe a dramatic effect in a single-arm study, it may be that randomised trials are no longer needed. But this should be the exception, and there may be

THE SUNITINIB PRECEDENT

Sunitinib is the only drug so far approved by CMA.

Trial design

The demonstration of efficacy in patients with metastatic renal cell carcinoma (mRCC) who were refractory to prior cytokine therapy with interleukin-2 or interferon α was based on the proportion of patients achieving an objective response observed in two single-arm studies. The studies were conducted in a homogenous group of progressive patients with a predictable outcome of the disease.

Results

The estimated proportion of responders was 36.5% (95% CI 24.7%–49.6%) and 35.8% (95% CI 26.8%–45.7%).

EMEA's opinion

EMEA's Committee for the Evaluation of Human Medicinal Products (CHMP) considered the effect in terms of tumour shrinkage to be unprecedented, even with the most active available agents in a non-refractory population for which response rates in the order of 5 to 15% have been reported. They found that the efficacy results provided sufficient confidence to believe that treatment with sunitinib would translate into some effect in terms of progression-free survival or overall survival in patients who have failed prior cytokine-based treatment, although they were unable to assess the exact size of the effect on these clinical endpoints.

Post-approval studies

At the time of approval, the CHMP considered that data from an ongoing randomised trial of sunitinib as a first-line treatment in mRCC patients could help to confirm that treatment with the drug is associated with an effect on important clinical endpoints. Although the ongoing trial involved an active control and patients in an earlier stage of treatment, based on pharmacological and biological grounds, the demonstration of a favourable effect as a first-line treatment would be considered relevant also for patients with mRCC who have failed prior cytokine-based treatment. This would confirm the existence of an effect in terms of relevant clinical endpoints even if the precise magnitude of this effect would not be known.

Upgrading to full approval

The randomised trial has now been completed and in October EMEA's Committee for Medicinal Products for Human Use recommended that sunitinib's CMA should be upgraded to full approval, with the approval being extended to cover first-line use in mRCC patients.

No drug approved via CMA would be withdrawn purely because the conditions were not fulfilled

different perceptions about what constitutes a 'dramatic' effect. Indeed in our experience, lack of an adequately randomised controlled trial has been an important reason for rejection."

A look at EMEA's track record, however, shows that 16 (44%) of the 38 oncology new drug applications that were granted marketing authorisation in the last 10 years were approved on the basis of single-arm trials, and Pignatti acknowledges that this is an issue of concern in some quarters.

In the case of sunitinib, approval was based on the results of two single-arm trials. There were, however, early supportive data from an ongoing randomised trial in a different category of patients. Completion of that randomised trial was one of the conditions EMEA set for giving sunitinib conditional marketing approval.

A POWERFUL TOOL

The power to set these sorts of conditions is something new for EMEA. How that power will be used is one of the big question marks relating to the new approval procedure.

Pignatti points to the second criterion under the Requirements section of the implementation regulation, that it must be "likely that the applicant will be in a position to provide the comprehensive clinical data," (post-approval), and he argues that getting agreement with the drug sponsors over what studies are feasible and appropriate will be key to overcoming compliance problems.

He is clear that there will be strict limits to what post-approval studies are asked for. "You shouldn't be imposing more requirements than necessary. So if for instance we have a drug that works in refractory disease, and then we are interested in knowing whether it would also work early on, that should not really be a CMA type of question. But if we have some uncertainty in the indication in which it is currently approved, and we think we could extrapolate information from an earlier indication to reduce that uncertainty, then we can ask that question."

This is what was done in the case of sunitinib (see box, p27).

Regulations are being drafted that will allow EMEA to impose fines for non-compliance. Doubts have been expressed in some quarters over whether financial penalties are an appropriate way to deal with issues like clinical trials, and time will tell how much use EMEA will make of these powers. Pignatti is clear, however, that although approval is conditional on the required studies being carried out, no drug approved via CMA (i.e. positive benefit–risk had been established) would be withdrawn from the market purely because the conditions were not fulfilled.

The key, he believes, is to ensure that patients and prescribers understand the implications if a therapy they are using has conditional rather than full marketing authorisation.

In the case of sunitinib, the information says: "This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine, in particular in the treatment of kidney cancer. Sutent [sunitinib] has shown to shrink the tumour. However, more information is awaited on the duration of this effect. The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary."

Pignatti believes that this kind of clear information to physicians and patients will be an incentive for companies to finish the required post-approval studies to upgrade to standard approval.

Is it realistic to rely on clear communications to make the regulatory system work, or will EMEA's voice be drowned out by the heavy guns of pharma advertising, at least among the non-specialists who are still responsible for prescribing cancer drugs in many parts of Europe? Should CMA be used sparingly to avoid non-compliance, and if so, what of the patients who need quick access to new therapies? Once positive risk–benefit has been proved to the standard required for CMA, has EMEA any business demanding any further data? But if they don't, then who has responsibility for carrying out the trials needed to find out how best to use the drugs and in whom?

Clinicians, patients, health administrators, policy makers and members of the public who have an interest in the new drug approval regulations should look out for the draft Notes for Guidance document scheduled to be published on the EMEA website www.emea.eu.int. It will be a consultation document, and EMEA wants your views.