

Francesco Pignatti

Walking the line between quick access and evidence

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How do you decide which new cancer drugs to approve, when statistical certainty takes too long to wait for and essential evidence on quality of life is hard to measure? The head of the cancer section at the European Medicines Agency is keen to explain his approach.



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Once upon a time, way back in the 20th century, regulating cancer drugs was a simple affair. When the European Medicines Agency (EMA) was founded in 1995, it had to balance the relative risks and benefits of one or two broad-reaching chemotherapy agents which had shown signs of activity on a wide section of the population, and then make a ruling on whether they were safe and effective enough to be marketed.

How quickly things changed. At the turn of the century, the arrival of monoclonal antibodies such as rituximab and trastuzumab marked the beginnings of a transformation not only of cancer therapies but the challenges facing those who regulated them.

A cascade of new targeted drugs that delivered high response rates in specific indications brought with them new demands for speedy access from patient groups. Ever since, the EMA has been trying to find effective ways to balance the public and professional demand to make these new drugs available with an authoritative assessment of their efficacy and safety.

Based in an airy glass tower in London's Canary Wharf, alongside prestige companies such as Barclays Bank and the State Street Corporation, the EMA's 800 staff, seven scientific committees and numerous working parties are responsible for the scientific evaluation and market authorisation of medicines for use throughout the European Union.

In charge of its cancer drug evaluation is Francesco Pignatti, an Italian medical doctor who arrived at the EMA from the European Organisation for the Research and Treatment of Cancer (EORTC) 15 years ago.

As he answers my questions thoughtfully from the 4th floor of the EMA block, gazing out at a grey London view, he identifies the challenge regulators face when considering whether the drugs presented to them by pharmaceutical companies merit market authorisation.

"Our dilemma is how to deal with the uncertainty that inevitably surrounds evidence while at the same time trying to meet the needs of patients who are in desperate need," says Pignatti, whose formal position is Head of Oncology, Haematology and Diagnostics in the EMA's Human Medicines Evaluation Division. "It's not easy, because different stakeholders have different views."

Pignatti is serious, careful in his words, but also seemingly determined not to sidestep difficult issues. During the course of our interview, he portrays an agency acutely aware that it has to be honest about the fact that balancing risk and benefit is a matter of fine judgement that leaves it constantly open to criticism. He presents an organisation looking to be innovative as it attempts to make justifiable judgements within the realms of scientific uncertainty, while the needs and demands of patients press ever harder.

Drugs regulation, he says, is changing to pay heed to research beyond randomised controlled trials and embrace the opinions and experiences of patients far more than in the past.

Today's regulators can no longer wash their hands of difficult decisions about availability and affordability of cancer drugs – decisions that loom large in national media and consciousness. Though it is for payers and health technology assessment (HTA) organisations, not the EMA, to decide how widely a drug should be made available in each country, Pignatti believes that the new world of varied and expensive cancer drugs requires regulators to work with payers and health technology assessors to convey clear messages about the kind of data needed to prove a drug's worth.

And he is at pains to dispel the myths about regulators: that they are not interested in quality of life research when assessing drugs, or that they expect the same standard of evidence for rare cancers as common cancers. Such misconceptions are standing in the way of good drug development, he tells me.

But it is the word "uncertainty" that recurs throughout our interview and provides its theme. To explain the challenges that the EMA faces, Pignatti recalls that one of the first drugs that the EMA approved was Taxotere (docetaxel) for breast cancer in 1995 – it did so under the European legal provision of "exceptional circumstances" for drugs which had not yet completed trials, or where trials were small, but there were indications of a very high response rate.

"As a regulator you have a choice. You can wait another five years, do a big trial where you show differences in survival, or you can say I am convinced by the evidence which I have today despite the uncertainty, because the drug will fulfil an unmet need. This is actually quite characteristic

of most cancer drug approvals. Almost half of them have been approved based on a response rate or an endpoint which comes with a big uncertainty.” This is known as conditional approval.

“Endpoints” are a subject close to Pignatti’s heart. He has discussed them extensively at international oncology conferences and written about them in a range of journals. A research fellow at the EORTC Data Centre, Brussels, from 1995, he was involved in clinical trial design, conduct, analysis, and reporting, and then from 1997 was Medical Advisor for the Gastrointestinal Tract Cancer Cooperative Group and Brain Tumor Cooperative Group.

“Conditional approvals arise typically when you are approving based on a surrogate endpoint. Obviously, when researching a drug, a true endpoint would be mortality – you find out whether a drug affects death. But if you don’t have time for that you use a surrogate which you believe to be correlated with a true endpoint, for example tumour shrinkage.”

So soon after conditional approval became embedded in European law in 2006, the renal cancer drug Sutent (sunitinib) was approved on the basis of a high response rate in two trials, and after that a stream of other cancer drugs were authorised on a similar basis. “The legislation has adapted to deal with the uncertainty that we are used to having in oncology,” says Pignatti. “And as large indications fragment into many well-defined subsets, the situation is likely to continue.”

The EMA has developed the concept further. In March 2014 it invited pharmaceutical companies to participate in a project piloting adaptive licensing, also known as adaptive pathways, staggered approval or progressive licensing. This starts with the early authorisation of a medicine in a restricted patient population, followed by phases of evidence gathering and marketing authorisation adaptation to allow broader patient populations access to the medicine. It is particularly relevant for drugs with the potential to treat serious conditions where there is an unmet need.

“No longer is regulation all about the magic moment when your drug gets on the market. It’s trying to be as rational as possible about when you have enough evidence, maybe in a small population with some uncertainty – but you can still say the benefits outweigh the risks and put it on the market for a limited group. Then you have a clear



A team effort. Pignatti with the staff of the Office of Oncology, Haematology and Diagnostics in EMA's Human Medicines Evaluation Division

plan for how to fill the uncertainty gap with data post-marketing.”

So how do you fill the uncertainty gap after marketing has started? Once a drug hits the market early, say through adaptive licensing, you can no longer complete a randomised clinical trial on the same indication because ‘equipoise’ – true uncertainty about which trial arm will benefit patients – has been lost.

This, says Pignatti, is a challenge. “We are having to look seriously into new methods. For example, observational studies have been used to assess safety for years and now the challenge is to use this type of evidence for efficacy. There are many confounders and so on, but I think it’s the beginning.”

Does he not worry that once a drug has been authorised early, the momentum for companies



JASON HARRIS

spread use. Trials in related indications or different populations may provide enough evidence to satisfy regulators, but it may not be enough for payers.

Pignatti hopes that such dilemmas will be eased by a new awareness of the need for collaboration between all the stakeholders in drug development. In 2010 the EMA launched a pilot project enabling drug developers to get joint feedback from the EMA and health technology assessment bodies (such as the EUnetHTA) about the kinds of evidence they will require for market authorisation and widespread availability. “There’s a clear opportunity to design the development in such a way that all stakeholders maximise the chances of fulfilling their objectives as quickly and rationally as possible,” he says.

He stresses that this in no way implies that the processes of regulation and HTA are being pushed together – by law, the EMA has to exclude economic considerations from its decisions. “But we can discuss evidence standards with HTAs. There’s often a lot of convergence, and even if there isn’t you can find a rational way to ensure that each stakeholder fulfils their objective. For example, a trial may deliver a certain endpoint at a certain time, but then we will continue to follow patients to observe a second endpoint which may be of interest to other stakeholders.”

Patient involvement is also becoming more integral to EMA’s decision-making – though Pignatti acknowledges it has developed gradually. He says the agency is becoming more and more aware of patients’ unique expertise and their ability to inform research assessment about what really matters to real

people – quality of life factors, for example.

Since 2005, the EMA has had a Patients’ and Consumers’ Working Group providing recommendations on matters of interest to patients in relation to medicines, and there are patient representatives for instance on the orphan drug committee.

The EMA committee that makes final decisions about drug authorisations – the Committee for Medicinal Products for Human Use (CHMP) – does not include a patient representative, but brings in scientific advisory groups of clinicians, statisticians and patients whenever the benefit–risk equation stands on a knife-edge, or there is



to follow up with authoritative, gap-filling research will be lost? The long-term effectiveness of many targeted therapies are still unknown, and there are increasing indications of acquired resistance which will surely need to be understood better.

Pignatti nods. He argues that there is a huge incentive on industry to carry on researching their products because payers are only likely to reimburse expensive products if the evidence of meaningful benefit is strong. All the same, the problem remains of how to produce that evidence once a drug has been approved early, trial participants have switched treatments and the drug is in wide-

a disagreement on the committee. It is in this sphere that patient viewpoints are becoming more and more influential, explains Pignatti.

“Benefit–risk assessment often isn’t just about very precise quantities or statistical significance or *P* values,” he says. “There is almost always a very important subjective component. You have to use value judgements to compare two, three or four benefits to multiple risks. In the past, this exercise has been done implicitly at committee level – but it makes it less accountable.

“So we’re trying to be more transparent about why we think certain benefits outweigh the risks, or vice versa. Recently we’ve had many discussions of this kind with patients via our scientific advisory groups, and it’s often the case that they may be more concerned about quality of life than we thought they would be. There has been a lot of scepticism over the years about using quality of life measures in oncology, because the data aren’t very robust. But we are now developing a new guideline saying that quality of life measures may be imperfect, but they do tell us something about what patients think. We cannot dismiss them.

“Maybe regulators have to do more to encourage the collection of good data on quality of life rather than dismissing it as an endpoint. It can be very important for health technology assessments too.”

Patient input has been especially important in forging a way forward on rarer cancers. Last October the EMA hosted a meeting with representatives of Rare Cancers Europe to discuss RCE’s consensus paper on the methodology of clinical trials in rare cancers. Afterwards, the EMA made clear its willingness to examine evidence sources beyond randomised clinical trials – since large trials are clearly not possible for conditions that affect a small number of people.

“I hope that as a result of this meeting we will be able to plan at least two or three more meetings to figure out the problems in specific disease areas and how regulators can help. There is a lot of misconception about regulatory requirements in rare diseases, and this puts companies off invest-

ing. They believe they can never achieve the evidence standard that regulators require, but in fact we have had situations in the past where all we have had to show that a drug was safe and effective was a series of case studies.”

Equally, people wrongly assume that regulators aren’t interested in patient-reported outcomes, says Pignatti. “We will not dismiss them. However, these data are currently often poor. So the message now is: improve the quality of patient-reported data collection. There are a number of good quality of life tools, and the data collection can be done much better now using electronic means, for example using daily phone reminders prompting patients to enter information.”

Regulators need to be more open about the fact that value judgements play a part in their decisions, says Pignatti. “At the end of the day, you



have to make a decision, whether your data are robust or not. It will increase our transparency if we can say: ‘These are our value judgements, we have consulted with patients, these are their value judgements, this is the thinking that has led to our decision.’ We have never tried this, but I hope we will be able to.”

The EMA took a major step towards greater

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transparency with the announcement last October that, from January 2015, it would disclose all the trial data that has informed its decisions. Third parties will be allowed access to clinical data to verify the original analysis and conclusions, “to examine the regulatory authority’s positions and challenge them where appropriate,” states the policy.

The EMA is the first regulatory body in the world to introduce such rules, and the move has been welcomed by the founder of the All Trials campaign for greater scientific openness, Carl Heneghan, as “a real shift in favour of ensuring research data is shared routinely and re-used effectively in the public interest.”

However, the response hasn’t been universally positive. When the EMA proposed the changes in 2012, freedom of information campaigners said the EMA was lagging behind forward-thinking pharmaceutical companies, while industry expressed grave concerns that the change threatened the business value of its investments because it would reveal “commercially confidential” information. In the final proposals, the EMA allows companies to black out commercially confidential information, but now campaigners for the free availability of pharmaceutical data say this leaves the way open for wholesale censorship.

Pignatti insists that any deletions will be restricted to information about commercial aspects, such as manufacturing methods, which have no general scientific interest. “The motivation behind this new policy is to avoid duplication of research, to provide data to the community which might be useful, to find prognostic factors for future trials and so on.”

“We’re already quite transparent about the decisions we have made, publishing reports, often hundreds of pages long, describing the data we have examined. This goes one step further, allowing secondary analysis of the data by researchers who want to use them for further research or to scrutinise our decisions.”

The EMA has also been in the firing line about how long its drug authorisation process takes. A review published in the *British Journal of Clinical Pharmacology* in 2013 found that approval times for tyrosine kinase inhibitors (TKIs, such as Glivec/ imatinib) were on average twice as long as in the US – 410 days as opposed to 205. How does Pignatti feel about that, when patients are crying out for the new treatments?



JASON HARRIS

“I very much understand the expectation of patients when they are in that situation and I think we have to do our absolute best to meet those expectations,” he says. “I think the FDA has been very effective in reducing the review time for a number of cancer drugs. We also have provisions in legislation that allow us to accelerate an assessment of drugs that represent major therapeutic innovations, but these have been used only rarely.” One example of fast approval was for Glivec for chronic myeloid leukaemia in 2001. “It is difficult for me to comment on why the CHMP has not decided to avail itself of these mechanisms more frequently.”

But when people compare the speed of the EMA

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review times with those of the FDA, they are perhaps concentrating on the wrong thing, says Pignatti.

“Maybe we should look instead at the speed of the whole development. What are the mechanisms to bring effective drugs to patients before approval?” Pignatti says that pharmaceutical companies should find efficient ways beyond clinical trials for people to access drugs that have been heavily hyped in the media. It is wrong, he says, that often the only access route to a promising new agent in the absence of any valid alternatives is through randomised clinical trials, where a patient might find themselves on the non-active arm. When equipoise is lost, drug companies could provide access to at least some patients and investigators through observational studies, which, in addition, can still provide meaningful data.

“If pharmaceutical companies are afraid to open up a compassionate use programme because they are worried about losing the patient population for their trials this is the wrong approach.” Pignatti apologises for soundings defensive on the subject.

Comparisons with decisions and timing by other regulatory bodies around the world have also led to criticism. A number of papers in oncology journals have pointed out that, despite the submission of identical supporting data from clinical trials, the EMA and FDA have come to subtly different findings which are not obviously explainable.

In 2011 the *Journal of Clinical Oncology* published research showing that of the 100 indications for 42 cancer drugs evaluated by the EMA and FDA between 1995 and 2008, 19 indications were not approved by one or other of the agencies and 10 had different label wording with significant clinical meaning. For example, in 2011 the FDA withdrew an authorisation for using Avastin (bevacizumab) for advanced breast cancer following new data, while the EMA kept its use in combination with chemotherapy.

But Pignatti points out that these decisions are not made randomly or in isolation. What people might not know is that the EMA is constantly col-

laborating and comparing notes with the FDA, and other regulatory authorities in Canada, Japan and elsewhere, through monthly teleconferences.

“We go through the products we are assessing, and though we don’t try to achieve common decisions it’s very important that we don’t think in isolation. Drug development is on a global scale so regulation has to be aware on a global scale. Our processes and the efficiency of our processes may be different, but I think it’s very important that on methodological issues we achieve good alignment.”

“If there is a divergence, it will often have been discussed with our colleagues before we make a decision. If we think there is a justifiable reason why we should do differently than another regulator, then we make every effort for this to be understood. As I said, you are dealing with a lot of uncertainty here, and balancing benefit and risk there can be a narrow line between going one way or another.”

And so we come back to uncertainty. It is 20 years since the EMA was set up, and Pignatti believes that moving forward on cancer drugs over the next 20 must involve acknowledging and embracing methods to deal with uncertainty – for all the challenges that creates. It is, he says, always worth keeping in mind the end goal.

“Obviously there is a very high responsibility and no one person can take this on, which is why we have experts and committees and work in a very European-style bureaucratic system. But it works. If all the legal requirements are met in terms of safety and efficacy, and a drug receives a marketing authorisation, you see the end stage of all the successful drug developments for people with cancer. It is a very nice place to be.” ■

