

The European Medicines Agency looks to the future

At the end of 2010, the European Medicines Agency (EMA) published a road map that laid out a 'strategic vision for the operation of the European Medicines Agency' from 2011 to 2015.¹ According to this document, there are three strategic areas where much of their effort will be spent in the coming years: addressing public health needs, facilitating access to medicines, and optimizing the safe and rational use of medicines. As a follow-up to the road map, the EMA has published a document explaining how it will go about achieving its goals in each of the strategic areas mentioned above.² Interestingly, there is the candid recognition that we are living through a difficult economic situation, and this will have an impact on the availability of resources and the achievement of the stated goals. Below, I discuss a couple of aspects that most caught my eye.

The efficacy–effectiveness gap

The EMA seems to be increasingly aware that there is a difference between 'efficacy', that is, how well a drug works in the controlled setting of a clinical trial, and 'effectiveness', that is, how it does in a clinical practice setting. There are many reasons for this so-called efficacy–effectiveness gap, but perhaps the most important are differences in clinical trial populations and the ultimate target population (the former are usually free of factors such as multimедication and comorbidities that might blur the results of a trial) and poor adherence to treatment in real life (a drug will not work if you do not take it, and adherence is usually much better in clinical trials, which are often designed to obtain good adherence).³

The remit of the regulators is to generally assess efficacy, even though patients and national health authorities may be more interested in whether the drug will actually work in the clinic. With a broader regulatory remit, sponsors could, in principle, be forced to design clinical trials that better reflect real life.³ However, even as it stands, the health authorities are privy to information that

could be useful to health authorities and other payers to make their decisions, and that information could be made more readily available without redesigning the whole process. Indeed, according to the road map, the EMA does aim to 'focus on increasing the role of the Agency as an information provider and on greater collaboration with health technology assessment processes [that is, the bodies responsible for determining cost-effectiveness, such as the National Institute of Clinical Excellence in the UK]'. In addition, there is a commitment to improve the 'focus on the needs of geriatric patients', which is recognition that patients over 65 years are often excluded from clinical trials (for example, because they are multimедicated) when such patients will form a sizeable portion of users of many drugs (for example, hypertension therapies). Such changes, if they occur, will bring the regulatory approval closer to real life.

The menace of antibiotic resistance

The road map also mentions antibiotic resistance. This problem is by no means new. For example, in 1992, in an article titled 'The crisis of antibiotic resistance', Neu⁴ outlined how some of the microbes that cause conditions such as diarrhea, urinary infection, and sepsis are now 'resistant to virtually all of the older antibiotics', largely due to inappropriate use of antibiotics. Is the current situation really any worse than it was 20 years ago?

This time round, there are perhaps more causes for pessimism than before. In this more globalized world, outbreaks of infection have the potential to travel faster. In addition, the increasingly widespread use of antibiotics makes it harder to properly control their use and so avoid resistance. This is compounded by the lack of new antibiotics and, importantly, fewer first-in-class antibiotics coming through the pipeline than before. The reasons for this are partly commercial – developing antibiotics that will be used generally for a few days does not seem as attractive as developing, say, a lipid-lowering compound that will be taken for life. Bacteria might also quickly develop resistance to the antibiotic leading to a potentially short useful lifecycle.

It may also be that there are only a finite number of viable molecular targets for drug development, and many of the most useful ones have already been exploited, leaving only the more difficult (and less effective) ones for development.

These reasons aside, there are also certain regulatory hurdles that can hinder approval and deter development. For example, the regulatory requirement to demonstrate that an antibiotic is equivalent to what is already on the market is difficult in that the epidemiology of bacterial resistance varies from place to place and over time. So even though an antibiotic might be inferior to another in most situations, this might not always be the case. Often, the clinician is interested in having a range of options from which to choose according to susceptibility testing or epidemiology.

The EMA will encourage pharmaceutical companies by 'Reviewing existing options to promote development of new antibiotics to treat multi-resistant bacteria including adaptation of clinical guidance documents, consideration of the balance between the amount of prior data needed with enhancing post-marketing surveillance, use of orphan legislation, etc'. Although somewhat vague, the general idea seems to be one of reconsidering the burden of proof prior to approval (as is the case with orphan products), while paying close attention to the drug once it is on the market. It is not clear to me whether the reference to orphan legislation also includes the financial incentives

associated with these products (access to scientific advice, exclusivity, etc.). Like the EMA road map, the Generating Antibiotic Incentives Now (GAIN) Act, introduced in the US in 2011, also intends to tweak the regulatory approval process. In this case, the act also explicitly recognizes that there is little financial incentive to develop new antibiotics and proposes ways to make development of antibiotics more profitable, in the form of favourable licensing conditions (for example, extensions of exclusivity) rather than actually spending tax dollars. It remains to be seen how much of an impact these measures will have, particularly as the potentially short lifetime of these products will render any extended exclusivity effectively useless.

References

1. Road map to 2015: The European Medicines Agency's contribution to science, medicines and health. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf.
2. Implementing the European Medicines Agency's Road map to 2015: The Agency's contribution to Science, Medicines, Health 'From Vision to Reality'. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/10/WC500115960.pdf.
3. Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens H, *et al.* Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov* 2011;10:495-506.
4. Neu HC. The crisis in antibiotic resistance. *Science* 1992;257:1064-73.

Greg Morley
Freelance and Contract Medical Writer
greg.morley@docuservicio.com