AN AUDIENCE WITH…

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Clinical trial programmes tend to follow a linear pathway, culminating in a go/no-go decision by regulators on whether an investigational drug is ready for the market. But, say some, this sequential and binary approach belies the complexity of clinical data and the uncertainty inherent within. Instead, adaptive licensing (AL) could provide a more flexible alternative. If drug developers, regulators, patients, prescribers and payers think through the uncertainties together, smaller 'pre-approval' trials could potentially support initial narrow approvals, and more rigorous use of 'post-approval' real-world data could then be used to incrementally broaden drug labels. Gigi Hirsch, executive director of the Massachusetts Institute of Technology's New Drug Development Paradigms (NEWDIGS) programme, has been bringing collaborators together for the past 3 years to flesh out the possibilities. As the European Medicines Agency (EMA) prepares to launch a pilot AL programme, she talks with **Asher Mullard** about the implications for drug development.

How does AL differ from the accelerated and conditional pathways?

Accelerated approval in the United States and conditional marketing authorization in Europe are regulatory pathways in a traditional sense. AL is not a regulatory pathway, nor a linear sequentially staged process, but a broader approach to all aspects of drug development.

AL is about understanding the questions that need to be answered at the different stages of each product's unique development process by each of the stakeholders. The way that we have been conceptualizing it, in AL sponsors do not just approach the regulators and deliver a proposed development plan. All stakeholders — including regulators, payers, prescribers and patients — are engaged from the beginning in planning how development will unfold.

Can you provide some examples of how development would work under AL?

In one example, there might be an initial patient population — such as severely affected patients — that is a subset of a larger population. If you look at obesity, you might initially develop and license the product for a morbidly obese subpopulation, and as more evidence is generated you might gradually expand approval into less severe obesity as long as the benefit–risk balance remains favourable.

Another strategy might be based around accepting greater statistical uncertainty. Regulators could perhaps initially grant a license on the basis of a study that is not designed to meet the conventional ≤5% significance cut-off for efficacy end points. Patients could then be informed that there is a heightened level of uncertainty for the efficacy of this product. This is something that we have seen in some of our modelling in the context of orphan drugs in particular.

A third approach could be based around the demonstration of initial effects, followed by a more comprehensive evaluation of safety and efficacy. Anti-infective drugs, for example, could initially be licensed for the treatment of infections that are resistant to other drugs, and then as more evidence of safety and efficacy is gathered, the drug could be rolled out to treat drug-sensitive infections as well.

Overall, we hope that by thinking through these and other possibilities and by prospectively planning programmes and exploring the benefit–risk trade-offs for each stakeholder, we can establish a greater degree of predictability around what might happen during drug development and establish trust among stakeholders.

Our view is also that the current binary go/no-go model is not very good at balancing uncertainty and access to medicines. We need to be able to better identify populations with different benefit–risk profiles and facilitate access accordingly. And, this is an important point, we believe that AL will ultimately lead to more and better evidence over the entire life cycle of the product because a medicine will be studied throughout its life cycle and not merely up to the time of marketing.

Given the increased uncertainty at initial roll out, do we need legislative changes to ensure better 'post-marketing' study compliance and to restrict off-label use?

We feel that there is probably room to operate without changing the legislation if trade-offs are explicitly laid out and stakeholders reach agreement through dialogue. In the 'post-marketing study' scenario, for example, an idea could be that companies could not move from an initial authorization to a full authorization if the evidence that had been required hadn't been generated. And payers could play a key role in minimizing off-label use during the initial authorization phase.

What would AL mean for drug prices, again given the initially higher uncertainty?

Answering this question is very much on our priority list for 2014. I anticipate that we will be doing modelling and simulations that are focused on identifying different ways of linking reimbursement with value, and looking at things like coverage with evidence development and lower initial pricing that could go up as new evidence comes in.

Would AL be used for every drug?

Some of our collaborators feel strongly that this way of thinking should become standard process for new and innovative drugs. At the end of the day, some assets may be more appropriate for AL than others.

How is the EMA planning to experiment with AL?

We anticipate that the EMA is going to be making an announcement where they will invite sponsors to approach them to propose AL pilot projects. These discussions are likely to be held in the context of a 'safe harbour', rather than an official mechanism for scientific advice. Working with sponsors, the EMA is expected to explore AL pathways for proposed products, and I gather that if it goes well they will move the development plans into more official mechanisms. Actual pilot projects will be an important way of better understanding AL.