NEWS IN BRIEF

Time to rethink dose-finding study design

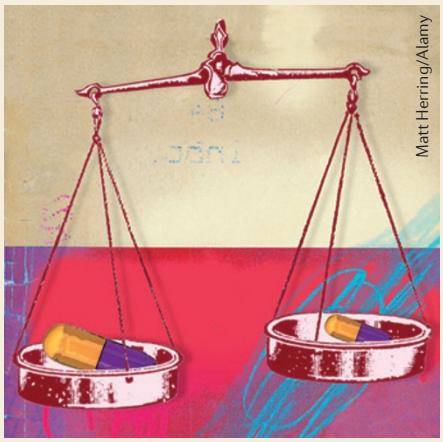
Model-based Phase II dose-finding studies offer benefits over traditional approaches, say European regulators.

The lowdown: Most dose-finding Phase II studies are currently designed around selecting one out of two or three doses of a drug, based on a head-to-head comparison of each dose with placebo. But sponsors could benefit from shifting the emphasis of these trials to instead focus on understanding the dose–response relationship, says the European Medicines Agency (EMA) in a new draft qualification opinion.

With the Multiple Comparison Procedure-Modelling (MCP-MOD) approach, sponsors first select plausible possible dose–response relationships for their drugs (based, for example, on data from similar compounds or an agent's mechanism of action) and then design the Phase II study and select their dosing levels to test these models. The resulting studies can test more doses of a drug (perhaps four to seven active doses across over a tenfold dose range), in a similar number of patients as traditional trials.

"While a traditional approach might test 20, 40 and 60 mg per kg against placebo, here we can think about the whole dose–response relationship from 0 to 200 mg per kg," says the EMA's Robert Hemmings. With the traditional approach sponsors usually end up advancing one of the doses they have already tested, but with MCP-MOD they get enough data to be able to choose a more optimal dose that may not have been tested explicitly in patients before.

"We are rather excited about this qualification opinion," says Hemmings. "It is extremely rare to see something as comprehensive and sophisticated as the MCP-MOD approach. We hope that publishing this qualification opinion will vastly increase the interest in modelling-based approaches, whether it is this one or another one."


Matt Herring/Alamy

With great speed comes great need for post-marketing oversight?

An analysis of US drug approvals suggests that expedited drug development pathways are working, but asks whether post-marketing review is keeping pace.

The lowdown: Clinicians, drug developers, politicians, investors, patients and regulators all have an interest in accelerating drug development, and have been working hard to introduce new pathways and policies that can speed up the process. Just last month, the US Food and Drug Administration (FDA) approved the first breakthrough drug candidate (see page 891). A *JAMA Internal Medicine* article now quantifies some of the benefits of the multitude of expedited drug pathways.

To compare expedited and standard drug development programmes, Thomas Moore, of the Institute for Safe Medication Practices in Virginia, USA, and a colleague analysed data from 20 drugs approved in 2008. They used the Freedom of Information Act to get data on when human testing began for each drug, and various other sources for data on clinical trial programme sizes and post-marketing requirements. Eight drugs approved in 2008 via expedited pathways spent an average of 5.1 years (varying from 1.6 to 10.6 years) in the clinic, compared with 7.5 years (4.7 to 19.4 years) for those that followed a standard route. The expedited drugs were tested in significantly fewer subjects: 104 (23–599 patients) versus 580 (75–1,207). The FDA has said that these findings show the expedited programmes are working as intended.

The paper also found, however, that 5 years after approval only 26 out of 85 (31%) of the post-marketing study commitments for these 20 drugs had been fulfilled. This points to "emerging troubles in the regulation of pharmaceuticals", writes Daniel Carpenter, of Harvard University, in a linked commentary article. "It is concerning that the FDA may alter the terms of the implicit approval contract with pharmaceutical manufacturers, that is, less clinical testing of drugs before approval with quicker review in exchange for more reliable and rigorous post-approval testing, and not enforce the post-approval requirements as it should," he writes.

VC and non-profit unite to launch new companies

Puretech Ventures has teamed up with non-profit JDRF in bid to launch a new model of company creation.

The lowdown: Venture capital (VC) biotech funding has flagged since 2007, forcing entrepreneurs to find other backers to bankroll their projects. Puretech Ventures' Valley of Life initiative — and a recently announced partnership with JDRF — could see non-profit charities stepping into the breach, and being rewarded for the risk.

For the first Valley of Life undertaking, JDRF has committed US$5 million to launch T1D Innovations, a "venture-creating entity" that will found four to ten companies focused on developing drugs, diagnostics and devices for type 1 diabetes. Puretech is working to raise a further $25 million from other investors and will oversee project selection. T1D aims to launch its first company within 6–12 months.

Puretech's David Steinberg says that most non-profits typically use grants to drive their research agendas, and do not receive a return on their investments for fear of violating their tax-exempt status. The Valley of Life initiative generally, and T1D Innovations specifically, is instead designed to potentially reward charity investors for their contributions without violating their tax status. A paper published last year in *Trusts & Trustees* outlined the model.

Some non-profits have found other ways to get returns on their investments, including the Cystic Fibrosis Foundation, which earns milestones and royalties from the $75 million it invested into Vertex's ivacaftor. But whereas these solutions have been useful for funding science in established companies, the beauty of T1D Innovations is that it will offer aid to entrepreneurs who are starting from scratch, says Steinberg.

Puretech is looking to set up more Valley of Life programmes in other disease areas as well, especially in those that have been neglected by the pharmaceutical community.