Evaluate Vantage

June 26, 2013

FDA not such a soft touch on breakthrough therapies

Jacob Plieth

The US FDA has recently been bending over backwards to charm pharma, and after Novartis's less-than-stellar heart failure project serelaxin was deemed a breakthrough therapy observers would have been excused for thinking that all a sponsor had to do to obtain such a designation was apply for it.

But the agency's long-awaited draft guidance, released yesterday, paints a harsher picture, spelling out what will not qualify as a breakthrough therapy and even proposing scenarios under which such a designation, once granted, will be revoked. Indeed, data show that less than half of the applications sought so far have actually been allowed.

The FDA's guidance document actually deals with all expedited approval procedures, including fast-track designation, accelerated approval and priority review. But, given the huge interest that breakthrough designation has generated, it is this most novel category that will be most closely watched.

And, given the interest, industry will doubtless find it fascinating that, just like orphan drug status, breakthrough designation is not immutable. For instance, the FDA cites the possibility of subsequent clinical data showing a project to yield a much worse response rate than initial trials had suggested.

Even more interestingly, the agency says breakthrough status can be granted to two projects for the same use; if one of the drugs gains approval the second would lose its designation unless it was shown to be a substantial improvement over the first.

Sponsors no longer pursuing development of a breakthrough therapy are told to inform the FDA. On the other hand, when breakthrough therapy designation is revoked the agency may – but apparently does not have to – send a letter notifying the sponsor.

21 rejections

Since the breakthrough designation was enacted in the Food and Drug Administration Safety and Innovation Act on July 9 last year, 21 such designations have been granted – interestingly all by the CDER and none so far by the FDA's biologicals arm, the CBER. Some concern the same projects several times over.

Meanwhile, 21 have been rejected, the agency states, while 22 remained pending as of June 14, 2013. Thus the picture seems rather less rosy than made out by FDA officials who remarkably had been sent in person on a diplomatic mission to Asco to talk up the breakthrough designation (*Asco – FDA charms industry with talk of faster approvals, June 3, 2013*).

Still, many of those initial comments at Asco have been echoed in the draft guidance. For instance, the document spells out the agency's commitment to "work closely with the sponsor to provide guidance on subsequent development" – something that small, cash-strapped biotechs should find particularly reassuring.

Preliminary evidence

The key difference between breakthrough therapy designation and other expedited procedures is the need to provide "preliminary clinical evidence" of substantial improvement over existing therapies on one or more clinically significant endpoints. In contrast, fast-track designation can be sought at any point before an approval filing.

The agency further stipulates that preliminary evidence cannot take the form of a theoretical or mechanistic rationale, or evidence of non-clinical activity. Ideally it should come from a clinical study that shows the investigational project to be superior to an available therapy – if none is available placebo will suffice – or comparing the new treatment plus standard of care to standard of care alone.

However, breakthrough therapy requests can be submitted as early as at the time of the IND filing - ideally no later than the end-of-phase-II meeting, and certainly not after an NDA/BLA filing. The agency commits to acting within 60 calendar days by issuing either a designation letter or a non-designation letter.

The latter will explain the reasons for the decision. It will be interesting to see how many companies formally disclose receipt of a non-designation latter, let alone spell out the reasons.

What does it mean?

Again the FDA has tried to explain what breakthrough designation means in practice. For instance, because a project that qualifies as a breakthrough therapy would also meet the standard for fast-track designation, all the benefits of the latter will be available to the former.

“Intensive guidance” on development will begin as early as phase I. If the clinical effect is large compared with available therapies the programme could be “considerably shorter” than for other drugs in the disease, although adequate data must still be generated to demonstrate safety and efficacy; omitting necessary components of drug development can delay or preclude approval.

Potential proposed strategies include adaptive trial designs, an enrichment strategy and use of historical controls. A sponsor should be prepared for quicker development of manufacturing infrastructure or a necessary companion diagnostic.

And, if a company has not requested breakthrough therapy designation, the FDA might itself suggest it upon review of early data submitted. While the honeymoon period for breakthrough therapies might therefore be coming to an end there is still lots for industry to be optimistic about.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter