

A BREAKTHROUGH YEAR FOR UNMET DISEASES

Perhaps breakthrough therapy designation seemed like little more than an FDA publicity stunt when it came into force in mid-2012, but a year and a half later no one can be in any doubt about how seriously biotech and pharma now takes it.

Industry has sat up and taken notice: FDA data indicate that no fewer than 141 breakthrough therapy designations (BTDs) have been applied for, of which 37 have been granted. On the other hand, little can be gleaned from the three breakthrough-designated products to have already received US approval, and many uncertainties still abound.

Among matters that have yet to come out in the wash are what it actually means in practice for a project to be designated a breakthrough therapy.

The jury is out on whether receipt or non-receipt of the accolade is a material, disclosable event – only two of 72 applicants slapped with a rejection have owned up to this – and several controversial designations call into question the agency's criteria for issuing such an award.

But at least some mists have started to clear, helped for instance by draft FDA guidance issued a year after PDUFA V brought the BTD into effect. Practical benefits include a boost to the dynamics and frequency of an applicant's interaction with the regulator, and "intensive guidance" that the FDA has promised to offer on issues such as trial design must be helping some applicants.

The FDA's Definition of Breakthrough Therapy Designation

VI. BREAKTHROUGH THERAPY DESIGNATION

Section 506(a) of the FD&C Act provides for designation of a drug as a breakthrough therapy "if the drug is intended, alone or in combination with 1 or more other drugs, to treat a *serious or life-threatening disease or condition* and *preliminary clinical evidence* indicates that the drug may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically significant endpoints*, such a substantial treatment effects observed early in clinical development."

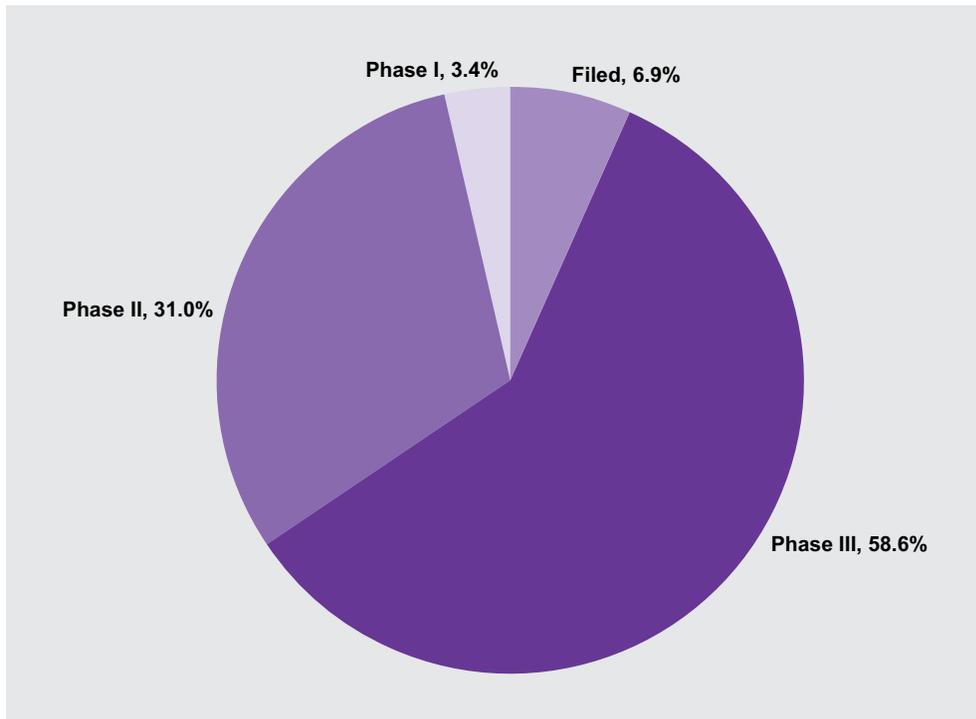
Source: June 2013 FDA draft guidance document

Attempts to highlight evidence of shortened approval times for BTM products look premature.

True, the three BTM drugs approved so far – Roche’s Gazyva, J&J/Pharmacyclics’ Imbruvica and Gilead’s Sovaldi – were green-lighted in an average 181 days, versus 246 days for the six oncology drugs approved in 2013 that are not known to have received a BTM. This average is also well within the FDA’s 240-day performance goal, Leerink analysts have noted.

But interaction with the regulator on study design could not possibly have helped these products since they all received BTM when filed or about to be filed, possible FDA help on manufacturing development and scale-up as benefits notwithstanding.

Status of Disclosed Projects at the Time When Breakthrough Designation Was Granted



Source: EP Vantage

Moreover, the agency does not need special instructions as to what should be fast-tracked, and knows precisely which therapies matter. The non-BTM drugs Xofigo and Kadcyra, approved in 152 and 179 days respectively, surely show that if the FDA likes a product it will bust a gut to get it on the market – breakthrough status or no breakthrough status.

BIG GROUPS FAVOURED... SO FAR

A look at the list of the 30 disclosed BTB projects reveals an unexpected but by now extensively publicised fact: the vast majority have favoured big pharma and big biotech.

It was perhaps not supposed to have been this way. The FDA's promises to work closely with successful sponsors on clinical trial design and provide intensive guidance on development as early as phase I were certainly aimed at small, cash-strapped biotech that likely lacked such expertise.

Yet over 80% of the 30 granted BTBs that have been disclosed so far have benefited mid and big-cap firms. In a recent update the FDA's Center for Drug Evaluation and Research was moved to point out its expectation of a shift to earlier development stages as the BTB programme matured.

Granted Breakthrough Therapy Designations (Disclosed) To January 1, 2014

| Date disclosed (all 2013) | Product | Indication | Phase | Company |
|---------------------------|---|---|-----------|---------------------------------|
| January 6 | Kalydeco | Cystic fibrosis* | Marketed | Vertex Pharmaceuticals |
| February 12 | Kalydeco and VX-809 ibrutinib | Cystic fibrosis* | Phase III | Vertex Pharmaceuticals |
| | | Mantle cell lymphoma | Phase III | Pharmacyclics/Johnson & Johnson |
| March 15 | LDK378 | Waldenstrom's macroglobulinemia | Phase II | Pharmacyclics/Johnson & Johnson |
| | | Non-small cell lung cancer (ALK-positive) | Phase III | Novartis |
| April 8 | ibrutinib | Chronic/small lymphocytic leukaemia | Phase III | Pharmacyclics/Johnson & Johnson |
| April 10 | palbociclib | Breast cancer (ER-positive, HER2-negative) | Phase III | Pfizer/Onyx Pharmaceuticals |
| April 24 | lambrolizumab/MK-3475 daclatasvir, asunaprevir and BMS-791325 | Melanoma | Phase II | Merck & Co |
| April 25 | | Hepatitis C | Phase III | Bristol-Myers Squibb |
| April 29 | SD-101 | Epidermolysis bullosa | Phase II | Scioderm |
| May 1 | daratumumab (HuMax-CD38) | Multiple myeloma | Phase II | Genmab/Johnson & Johnson |
| May 6 | ABT-450, ABT-267 and ABT-333 | Hepatitis C | Phase III | AbbVie/Enanta Pharmaceuticals |
| May 15 | obinutuzumab (RG7159/ GA101) | Chronic lymphocytic leukaemia | Phase III | Roche/Biogen Idec |
| May 20 | sebelipase alfa | Lysosomal acid lipase deficiency | Phase III | Synageva BioPharma |
| May 28 | asfotase alfa (ENB-0040) | Perinatal, infantile and juvenile onset hypophosphatasia | Phase III | Alexion Pharmaceuticals |
| June 21 | serelaxin (RLX030) | Acute heart failure | Phase III | Novartis |
| June 27 | drisapersen | Duchenne Muscular Dystrophy | Phase III | GlaxoSmithKline |
| July 01 | sofosbuvir + ledipasvir | Hepatitis C | Phase III | Gilead Sciences |
| August 20 | BYM338 | Sporadic inclusion body myositis | Phase II | Novartis/MorphoSys |
| August 27 | Firdapse | Lambert-Eaton Myasthenic Syndrome (LEMS) | Phase III | Catalyst Pharmaceutical |
| September 11 | entinostat | Breast cancer | Phase II | Syndax Pharmaceuticals |
| September 13 | Arzerra (ofatumumab) | Chronic lymphocytic leukaemia (first-line use) | Phase III | GlaxoSmithKline |
| September 17 | volasertib | Acute myeloid leukemia (AML) | Phase III | Boehringer Ingelheim |
| September 23 | alectinib/RG7853/AF802 | metastatic NSCLC (ALK-positive) | Phase II | Roche |
| October 22 | MK-5172/MK-8742 | Hepatitis C | Phase II | Merck & Co |
| October 24 | ALXN1101 | Molybdenum cofactor deficiency (MoCD) type A | Phase I | Alexion Pharmaceuticals |
| October 25 | sofosbuvir | Hepatitis C | Filed | Gilead Sciences |
| November 25 | andexanet alfa (PRT4445) | Factor Xa inhibitor antidote | Phase II | Portola Pharmaceuticals |
| November 25 | idelalisib | Relapsed chronic lymphocytic leukaemia | Filed | Gilead Sciences |
| December 20 | tafenoquine | <i>Plasmodium vivax</i> malaria | Phase III | GlaxoSmithKline |

*Vertex has not disclosed the setting in which its two compounds have been granted breakthrough designation

The apparent imbalance could to some extent be a function of which companies choose to disclose and which do not – a contrast with fast-track status, for instance, where most disclosures are made by small companies.

Another clear trend is oncology's large share of BTDs disclosed so far. Dr Richard Pazdur, the FDA's director of the office of oncology drug products, remains very much a champion of BTB, and made an appearance at last year's ASCO meeting to promote the new designation.

"One could argue that, even for the large companies, which clearly have not made a habit of disclosing milestones such as fast-track designations, BTB is seen as a pre-approval victory worthy of public announcements, perhaps consistent with the idea that BTB is now the highest order of these special FDA designations," says Mark Mathieu, Parexel's director of strategic research.

Parexel's consulting division has studied emerging trends in several FDA accelerated development pathways, including BTB, and more recently has been discussing its observations and findings with pharma and biotech companies.

DISCLOSURE

The issue of disclosure also goes to the heart of an area where the rules are apparently still being written. Current practice is that the FDA discloses total numbers of applications, but it is up to sponsors to identify their projects publicly.

Mr Mathieu says disclosure rules for BTB seem to mirror those for fast-track status, in that the FDA is not permitted to disclose the sponsors, and the only way granting of BTB gets into the public domain is through disclosures by the companies themselves. Orphan drug designations – arguably not an accelerated pathway – which are compiled in a publicly available FDA database, are the exception.

Secrecy abounds, even among BTB applicants that have made a disclosure. One small biotech, Synageva BioPharma, refused to discuss with EP Vantage anything about its granted BTB for sebelipase alfa, and would not say whether it had applied for BTB for any other project or indication.

The issue of disclosure must turn on the market sensitivity of the BTB accolade, and in fairness the jury on this is still out. Immediate share price reactions to a BTB announcement have so far been impossible to discern, for instance.

But the fact remains that only two companies have owned up to receiving a BTB rejection – 72 have been handed out so far. That seven of the 37 BTB recipients have yet to trumpet the fact is perhaps even more curious.

The prize for openness and transparency must surely go to Ariad Pharmaceuticals and its phase I/II oncology project AP26113. "We made the disclosure [that BTB had not been granted] due to the fact that we had communicated earlier in the spring that we would be filing for breakthrough designation," an Ariad spokeswoman told EP Vantage. "We believe in honest disclosure and wanted to be proactive."

J&J has also stated that it had a BTB application denied, but has not identified the relevant project. The FDA cites lack of clinical criteria, insufficient patient numbers,

lack of “substantial improvement”, reliance on a novel biomarker and post hoc analyses as common reasons for BTB denials.

There had been suggestions that the FDA had declined to wave through Ariad’s BTB because Novartis’s LDK378 had earlier received it for the same indication. But this seems an extremely unlikely reason, and the agency has stressed that BTB can be granted to two projects for the same use, and only once one gains approval will the second lose its designation.

As such Prosenza’s rival Sarepta apparently had nothing to lose in applying for BTB for eteplirsen, but it has said it has no intention of doing so. It is possible that having a request rejected presented too great a risk for relatively little reward, though Sarepta boasted of already having engaged in dialogue with the FDA over study design, and it might have felt that BTB would therefore not have given it any further advantage.

BREAKTHROUGH BENEFITS

So what are the advantages of a BTB? Scioderm, a successful sponsor that did agree to be interviewed by EP Vantage, says it is still trying to determine the precise benefits, but the clear expectation is that there will be much more interchange with and access to the US regulator.

“The hope is that this is not just an expedited review, but that it may offer an expedited development process,” says Robert Coull, the group’s chief operating officer.

FDA’s Action on BTB Applications Received So Far

| Time period/agency division | Received | Granted | Denied | Pending |
|---------------------------------|------------|-----------|-----------|-----------|
| 9 Jul - 30 Sep 2012 (CDER) | 2 | 1 | 1 | 0 |
| 10 Jul - 30 Sep 2012 (CBER) | 0 | 0 | 0 | 0 |
| 1 Oct 2012 - 30 Sep 2013 (CDER) | 92 | 31 | 52 | 9 |
| 1 Oct 2012 - 30 Sep 2013 (CBER) | 11 | 1 | 10 | 0 |
| 1 Oct 2013 - 3 Jan 2014 (CDER) | 27 | 4 | 6 | 17 |
| 1 Oct - 31 Dec 2013 (CBER) | 9 | 0 | 3 | 6 |
| TOTAL CDER | 121 | 36 | 59 | 26 |
| TOTAL CBER | 20 | 1 | 13 | 6 |

Source: www.fda.gov

Meanwhile, Genmab highlights the little-appreciated FDA argument about help in manufacturing and scale-up of commercial-scale material. “One of the real advantages [of BTM] is that when the FDA sees real potential they can actually help you to use two types of batches of material in the same trial, which can easily shave off a year to a year and a half in drug development timelines,” says Genmab’s chief executive, Jan van de Winkel. “That could be the real advance.”

Genmab’s partner J&J has likewise highlighted the possibility of rate-limiting steps such as chemistry, manufacturing and controls being addressed earlier in the process.

Others are less complimentary. One pharma insider who declined to be named says that, while the rare disease community is over the moon about the possible advantages of BTM, others just “roll their eyes. Most industry people think this is just another label to make the FDA look proactive,” he told EP Vantage.

As far as interaction goes, the FDA division director calls each successful sponsor to congratulate them – one anecdote even has Dr Pazdur in person phoning a company. The agency then spells out what types of meeting are now available, and makes itself open to routine monthly meetings. But there is “no ‘bat phone’... no private cellphone number to call” in an emergency, the insider said.

Scioderm’s Mr Coull told EP Vantage that his company had had no interaction with the agency before its BTM was granted. In contrast, Genmab’s daratumumab got a push from the agency itself. “We had a meeting earlier on in [2013] with the FDA where they actually advised us to go for [BTM],” says Genmab’s Mr van de Winkel.

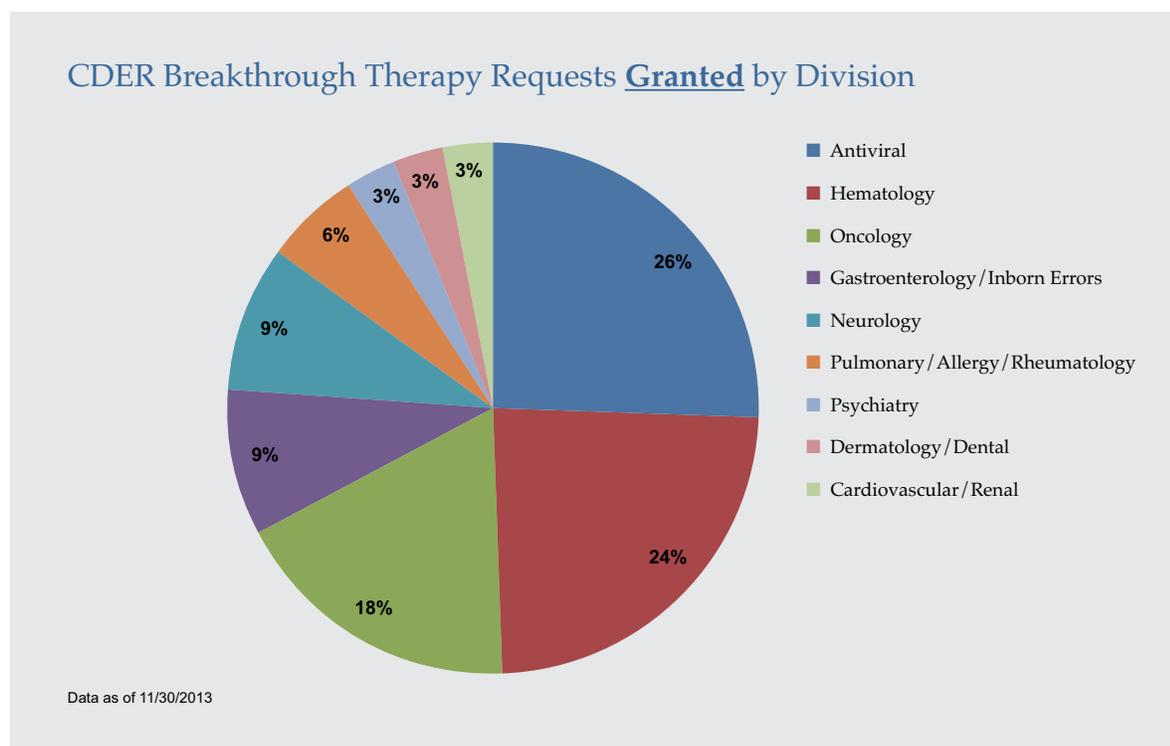
Mr Coull says Scioderm was the first small biotech to be awarded BTM, adding that, for him, making the application was a no-brainer. Once the private biotech group became aware of the new pathway it realised that its epidermolysis bullosa project SD-101 ticked all the boxes and – just two months after filing for BTM – the agency approved its application.

CONTROVERSY

Of course, rare diseases are not the only ones to qualify, as evidenced by Novartis’s acute heart failure project Serelaxin, whose award of BTM must presumably have been due to the unmet medical need of the indication. The move was controversial though, since the clinical data around Serelaxin could at best be described as mixed.

Not as controversial as the BTM granted to Catalyst Pharmaceuticals’ Firdapse (amifampridine phosphate) for treating the extremely rare condition Lambert-Eaton myasthenic syndrome, however. Amifampridine phosphate is already provided for free on a compassionate-use basis to many US patients, and the BTM granted to Catalyst’s project could be seen as tacit support for a corporate plan to establish orphan – or as some critics have said: very high – pricing.

FDA Divisions Handling Granted Breakthrough Applications



But none of these individual cases help explain the dearth of small biotech representation in the list of BTDA approvals so far. And, although Mr van de Winkel insists that Genmab was “absolutely” involved via a joint clinical development team, daratumumab’s BTDA filing was formally handled by its partner Johnson & Johnson.

One obvious link is that the compounds that have received BTDA so far appear all to be in phase II to III – big pharma’s natural domain – but there is no reason why BTDA should preclude earlier-stage projects. If it is a question of a lack of regulatory expertise, an obvious opportunity now exists for consultants or CROs like Parexel to offer smaller businesses regulatory advice regarding BTDA filings.

Nevertheless, Scioderm managed the process entirely in house, though it was fortunate to have a chief executive, Robert Ryan, who is a regulatory expert thanks to extensive experience at PPD and Quintiles.

The procedure of applying for BTDA was “relatively straightforward, but took a fair amount of time”, says Mr Coull. Scioderm “carefully put together a sophisticated, well-written document” including full clinical data and statistical analyses and some preclinical data. “It wasn’t a one-day job.”

Mr van de Winkel thinks that for Genmab the procedure would not have been more difficult without J&J. Meanwhile, GlaxoSmithKline is understood to have been wholly responsible for the BTDA application for Prosensa’s drisapersen.

And, while for bigger companies the award of BTDA is share-price neutral, Mr Coull is in absolutely no doubt as to the material effect on a small biotech.

He says BTDA “definitely puts us on the radar screen”, especially with bigger groups that might be more willing to take an early risk on partnering. Moreover, there is a clear financial reward in that as part of BTDA successful applicants can receive priority review.

For Scioderm, which had spent some time trying to secure funding, a lot happened very quickly. The group managed to close a \$16m series A financing round on April 26, and just three days later received notice from the FDA that BTD had been granted for SD-101. Had the FDA decision come a little earlier, “we might have raised more”, says Mr Coull.

“One thing is clear,” says Parexel’s Mr Mathieu. “It’s simply no longer reasonable to have a productive discussion of trends in drug and biologic development and approval without addressing ... the various accelerated pathways that have become so much a part of the product development landscape.” BTD is clearly one such pathway.

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