Evaluate Vantage

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Vantage Point – One year on, breakthrough designation remains an enigmatic accolade

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For Scioderm it was a no-brainer. Once the private biotech group became aware of the US FDA's new breakthrough therapy designation it realised that its epidermolysis bullosa project SD-101 ticked all the boxes and – just two months after filing – the agency approved its application.

Others have not been so lucky. But one year after the new category was enacted by legislation much secrecy remains, and it is far from clear whether receipt or non-receipt of the accolade is a material, disclosable event. If anything is clear it is that the main beneficiaries have been big pharma and big biotech.

It was perhaps not supposed to have been this way. The FDA has, for instance, promised to work closely with successful sponsors on clinical trial design and provide "intensive guidance" on development as early as phase I – a benefit surely aimed at small, cash-strapped biotechs (*FDA not such a soft touch on breakthrough therapies, June 26, 2013*).

Yet almost 90% of the 19 granted breakthrough therapy designations (BTDs) that have been disclosed so far have benefited mid and big-cap firms – an imbalance boosted by Tuesday's receipt by Novartis of BTD for bimagrumab.

Granted breakthrough therapy designations (disclosed)			
Date disclosed (all 2013)	**Project**	**Indication**	**Applicant company**
January 6	Kalydeco	Cystic fibrosis*	Vertex Pharmaceuticals
January 6	Kalydeco + VX-809	Cystic fibrosis*	Vertex Pharmaceuticals
February 12	ibrutinib	Mantle cell lymphoma	Pharmacyclics
February 12	ibrutinib	Waldenstrom's macroglobulinemia	Pharmacyclics
April 8	ibrutinib	Chronic/small lymphocytic leukaemia	Pharmacyclics
March 15	LDK378	Non-small cell lung cancer (ALK-positive)	Novartis
April 10	palbociclib	Breast cancer (ER-positive, HER2-negative)	Pfizer
April 24	lambrolizumab	Melanoma	Merck & Co
April 25	daclatasvir + asunaprevir + BMS-791325	Hepatitis C	Bristol-Myers Squibb
April 29	SD-101	Epidermolysis bullosa	Scioderm
May 1	daratumumab	Multiple myeloma	Johnson & Johnson
May 6	ABT-450 + ABT-267 + ABT-333	Hepatitis C	AbbVie
May 15	obinutuzumab	Chronic lymphocytic leukaemia	Roche
May 20	sebelipase alfa	Lysosomal acid lipase deficiency	Synageva BioPharma
May 28	asfotase alfa	Perinatal, infantile and juvenile onset hypophosphatasia	Alexion Pharmaceuticals
June 21	serelaxin	Acute heart failure	Novartis
June 27	drisapersen	Duchenne muscular dystrophy	GlaxoSmithKline
July 25	sofosbuvir + ledipasvir	Hepatitis C	Gilead Sciences
August 20	bimagrumab	Sporadic inclusion body myositis	Novartis
**Vertex has not disclosed the setting in which its two compounds have been granted breakthrough designation*			

Rejected breakthrough therapy designations (disclosed)			
Date disclosed (all 2013)	**Project**	**Indication**	**Applicant company**
7 August	AP26113	Non-small cell lung cancer (ALK-positive)	Ariad Pharmaceuticals

“We were the first small biotech to get it,” Robert Coull, Scioderm’s chief operating officer, tells *EP Vantage*. The group has subsequently had an exchange of emails with the FDA and is scheduling a meeting, which it expects to take place in November.

Interestingly, the company had had no interaction with the agency before its BTD was granted. In contrast, Genmab’s daratumumab got a push from the agency itself. “We had a meeting earlier on in the year with the FDA where they actually advised us to go for [BTD],” says Genmab’s chief executive, Jan van de Winkel.

But this does not explain the dearth of small biotech representation in the list of BTD approvals so far. And, although Mr van de Winkel insists that Genmab was “absolutely” involved via a joint clinical development team, daratumumab’s BTD filing was formally handled by its partner Johnson & Johnson.

One obvious link is that the compounds that have received BTD so far appear all to be in phase II to III – big pharma’s natural domain – but there is no reason why BTD should preclude earlier-stage projects. If it is a question of a lack of regulatory expertise, an obvious opportunity now exists for consultants to offer smaller businesses regulatory advice regarding BTD 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 BTD 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 BTD application for Prosensa's drisapersen. Synageva BioPharma, the only other small biotech known to have received BTD, refused to discuss the issue with *EP Vantage*.

Secrecy

Synageva playing its cards close to its chest typifies an area in which disclosure 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.

True, immediate share price reactions to a BTD announcement have so far been impossible to discern. But the fact remains that only two companies have owned up to receiving a BTD rejection – 35 have been handed out so far. Even more curiously, eight of the 26 BTD recipients have yet to trumpet the fact.

FDA's action on BTD applications received so far

Agency division	Time period*	Received	Approved	Rejected	Outstanding
CBER	9 July 2012 to 31 July 2013	8	0	7	1
CDER	9 July 2012 to 9 August 2013	79	26	28	25
	Total	**87**	**26**	**35**	**26**

**BTD was legally enacted on July 9, 2012*

The prize for openness and transparency goes to Ariad Pharmaceuticals and its phase I/II oncology project AP26113. "We made the disclosure [that BTD 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 says. "We believe in honest disclosure and wanted to be proactive."

J&J has also stated that it had a BTD application denied, but has not identified the relevant project.

There had been suggestions that the FDA had declined to pass Ariad's BTD 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 BTD can be granted to two projects for the same use, and only once one gains approval will the second lose its designation.

As such Prosensa's rival Sarepta apparently had nothing to lose in applying for BTD for eteplirsen, which it has said it has no intention of doing. It is possible that having a request rejected presented too great a risk for relatively little reward, though Sarepta boasts already having engaged in dialogue with the FDA over its phase II study, and it might have felt that BTD would therefore not have given it any further advantage.

Breakthrough benefits

Scioderm is still trying to determine the precise benefits of BTD, 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 Mr Coull.

And Genmab highlights another little-appreciated point: help in manufacturing and scale-up of commercial-scale material. "One of the real advantages [of BTD] 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 Mr 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.

The jury is still out on the issue of disclosure, and it is clear that for bigger companies a BTD is share-price neutral. But the last word on the small biotech view should probably go to Mr Coull, who is in absolutely no doubt as to the material nature of receiving BTD.

He says BTD "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 BTD successful applicants receive a priority review voucher, which can be redeemed with any product filing – not necessarily the one that received BTD – resulting in review within six months instead of the usual 12 to 18.

As with the priority review procedure itself, such a voucher is transferable, and could thus hold value in its own right.

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.

(This story was amended to add Gilead's disclosure of BTD for its hepatitis C combination.)

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