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Big pharma tightens its grip on breakthrough designations

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Four years seems ample time to judge the progress of a new regulatory procedure, and approvals of drugs blessed with US breakthrough status since this accolade was introduced in July 2012 have shown striking reductions in average FDA review time.

If this is one clear trend, another has emerged more slowly: breakthrough therapy designations (BTDs) are accruing mainly to big pharma. And now an analysis by *EvaluatePharma* links the two, showing how reduced review times have also largely favoured big pharma over smaller groups with BTDs under their belts (see tables below).

True, the sample size is small; only six of the 31 drugs with BTD that were approved between July 2012 and the 2016 half-year point are solely in the hands of small or mid-cap companies. Indeed, of the 145 granted BTD applications just 39 are known to belong to non-big pharmas – though there could be more that have not been disclosed, of course.

But the trend is there: small company drugs with BTD have got to market in an average 8.2 months, seemingly much longer than the 5.5-month average it has taken big pharmas.

BTD products that have secured US approval*					
		US sales ($m)			
Product	**Company**	**2015**	**2022e**	**FDA approval**	**Approval time (mth)**
Opdivo	Bristol-Myers Squibb	823	7,123	22 Dec 2014	4.8
Imbruvica	AbbVie	659	3,683	13 Nov 2013	4.5
Darzalex	Johnson & Johnson	9	3,497	16 Nov 2015	4.3
Tecentriq	Roche	-	3,456	18 May 2016	4.2
Ibrance	Pfizer	718	3,111	03 Feb 2015	5.7
Keytruda	Merck & Co	393	2,783	04 Sep 2014	6.2
Harvoni	Gilead Sciences	10,090	2,515	10 Oct 2014	8.0
Orkambi	Vertex	351	2,152	02 Jul 2015	7.9
Gazyva	Roche	79	1,736	01 Nov 2013	6.3
Zepatier	Merck & Co	-	1,378	28 Jan 2016	8.1
Ofev	Boehringer Ingelheim	244	1,286	15 Oct 2014	5.5
Empliciti	Bristol-Myers Squibb	3	1,253	30 Nov 2015	5.1
Venclexta	Roche	-	1,146	11 Apr 2016	5.4
Alecensa	Roche	67	1,108	11 Dec 2015	3.1
Viekira Pak	Abbvie	1,639	1,034	19 Dec 2014	8.0
Nuplazid	Ipsen/Acadia	-	1,018	29 Apr 2016	7.9
Sovaldi	Gilead Sciences	2,388	863	06 Dec 2013	8.0
Tagrisso	AstraZeneca	15	817	13 Nov 2015	5.3
Esbriet	Roche	401	781	15 Oct 2014	59.4
Epclusa	Gilead Sciences	-	560	28 Jun 2016	8.0
Kalydeco	Vertex	372	515	21 Feb 2014	4.7
Strensiq	Alexion	4	420	23 Oct 2015	10.0
Trumenba	Pfizer	19	326	29 Oct 2014	4.4
Zykadia	Novartis	75	314	29 Apr 2014	4.1
Kanuma	Alexion	-	307	08 Dec 2015	11.0
Xalkori	Pfizer	231	307	11 Mar 2016	2.8
Bexsero	GlaxoSmithKline	26	292	23 Jan 2015	6.0
Blincyto	Amgen	45	225	03 Dec 2014	2.5
Arzerra	GSK/Novartis	89	158	17 Apr 2014	4.9
Praxbind	Boehringer Ingelheim	-	-	16 Oct 2015	7.9
Xuriden	Wellstat Group	-	-	04 Sep 2015	7.9
**between 9 Jul 2012 and 30 Jun 2016.*					

As before, this calculation excludes the anomaly of the Roche drug Esbriet. This had been filed in 2009 before

being subjected to a five-year delay, and only after Roche applied for the newly introduced breakthrough designation did it get approved.

Across all 31 approvals the average review time is 6.1 months, or 7.8 if Esbriet is included; a year ago average review time for BTD drugs was 5.7 months (*FDA's high bar for breakthrough therapy designations, June 8, 2015*).

Either way this shows how BTD can speed a drug's path, since US review times overall are running at between nine and 10 months. So it might be surprising that BTD applications have been holding steady over time, and at present 145 have been granted, with the US agency giving the OK to about 40% of those submitted.

BTD applications to date*			
Time period/agency division	**Received**	**Granted**	**Denied**
1 Oct 2015 - 30 Jun 2016 (CDER)	82	29	31
1 Oct 2015 - 30 Jun 2016 (CBER)	18	5	9
1 Oct 2014 – 30 Sep 2015 (CDER)	93	32	43
1 Oct 2014 – 30 Sep 2015 (CBER)	20	8	9
1 Oct 2013 – 30 Sep 2014 (CDER)	96	31	51
1 Oct 2013 – 30 Sep 2014 (CBER)	26	7	19
1 Oct 2012 – 30 Sep 2013 (CDER)	92	31	52
1 Oct 2012 – 30 Sep 2013 (CBER)	11	1	10
9 Jul 2012 – 31 Sep 2012 (CDER)	2	1	1
Total		145	225
**between 9 Jul 2012 and 30 Jun 2016.*			

That said, one obvious question is whether the FDA would in any case have fast-tracked a drug that is clearly highly promising, or is showing efficacy in an unmet need – with or without the existence of BTD.

This has long been an imponderable, but a new analysis seems to support this hypothesis. The trick is to look at two drugs – Vertex's Kalydeco and Pfizer's Xalkori – whose approved BTD uses were not their first registered indications.

Kalydeco was approved in 4.7 months for treating cystic fibrosis patients with non-G551D gating mutations, having first been approved for the non-BTD use of G551D-mutated cystic fibrosis. For Xalkori, BTD approval in Ros1-mutated lung cancer came in just 2.8 months, after first being approved in Alk-mutated tumours.

But how long did these to drugs take to negotiate the regulatory pathway in their initial uses, which both occurred before the BTD pathway was in effect? The answer is just 3.5 and 4.9 months respectively.

This is not to deny the benefit to an applicant that BTD brings in terms of interacting with the regulator and planning a robust pivotal programme. But the FDA clearly does not need to have its hand held, and smaller companies still need to work harder to turn breakthrough designation into faster approval.

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