Evaluate Vantage

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The US FDA shows its teeth

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With the advent of PDUFA V nearly four years ago the US regulator heralded a new era of unprecedented collaboration and transparency, and drug approvals rose. Biopharma applicants and investors alike would have been excused for thinking that happy days were here again, and the stage was set for the biotech bull market.

But after the agency's issuing of two refuse-to-file letters in the past seven days, for Catalyst Pharmaceuticals' Firdapse and PTC Therapeutics' Translarna, the message now seems to be that enough is enough (see tables below).

It could be that drug applicants had simply become too complacent in putting together data packages in an approval-friendly climate. But refuse-to-file (RTF) letters had become such a rarity after 2011 that for two to have been issued in the space of a week seems a remarkable coincidence.

The actual details of the FDA slapdowns are confidential, so we have to take Catalyst and PTC's word for it that both were the result of incomplete dossiers. Still, it is noteworthy that these are two of only five major disclosed RTF letters to have been issued since PDUFA V took effect in October 2012.

Until that point RTF letters had been relatively common, and an analysis by Leerink suggested that their issuance rose between 1998 and 2011, with deficiencies in clinical data, chemistry manufacturing and controls, and the electronic file the most common reasons.

Key disclosed US refuse-to-file letters since 2010				
Project	**Company**	**Indication**	**Reason given by applicant**	**Date**
Translarna	PTC Therapeutics	Duchenne muscular dystrophy	Not sufficiently complete	23 Feb 2016
Firdapse	Catalyst	Lambert Eaton myasthenic syndrome	Not sufficiently complete	17 Feb 2016
Dronabinol	Insys	Anorexia in Aids patients	Inadequate paediatric study plan	15 Oct 2014
Safinamide	Newron	Parkinson's disease	Organisation and navigation problems	29 Jul 2014
Undisclosed	Flamel	Undisclosed	Reformatting datasets	7 May 2013
Lemtrada	Genzyme	Multiple sclerosis	Presentation of datasets	27 Aug 2012
Perampanel	Eisai	Epilepsy seizures	Reformatting/reanalyses of datasets	29 Jul 2011
Vyndaqel	Pfizer	Transthyretin familial amyloid polyneuropathy	Not sufficiently complete	4 Apr 2011
Farydak	Novartis	Relapsed/refractory Hodgkin's lymphoma	None given	Q1 2011
Rhucin	Santarus & Pharming	Hereditary angioedema	Not sufficiently complete	28 Feb 2011
Melphalan	Delcath	Metastatic melanoma in the liver	Plant inspection, sterilisation and safety	22 Feb 2011
Truvada & TMC278	Gilead	HIV-1 infection	Analytical methodology/qualification data	25 Jan 2011
Kadcyla	Roche	Breast cancer	Failed to meet accelerated approval standard	27 Aug 2010
Ceplene	EpiCept	AML remission maintenance	Therapeutic contribution not established	23 Aug 2010
Exelbine	Adventrx	NSCLC	Insufficient data	1 Mar 2010
Pradaxa	Boehringer Ingelheim	Stroke prevention	Data integrity issues	12 Feb 2010
Menveo	Novartis	Meningococcal disease in infants	Procedural concerns	31 Jan 2010

Those hoping that the past week's developments are just a blip could argue that it is solely incompetence on the part of Catalyst and PTC that is to blame. But these letters have previously been issued to Pfizer, Novartis and Roche, companies who theoretically should know better.

Earlier RTF letters included those for Merck KGaA's cladribine, Pharmacyclics' Xcytrin and – most notoriously of all – Imclone Systems' Erbitux in 2001, leading ultimately to the conviction and jailing of the group's chief executive, Sam Waksal, for securities fraud.

The FDA lists several reasons for issuing a RTF letter, with materially incomplete or inadequately organised applications top of the list. Intriguingly, relying on a single trial if prior communication had "determined the need for more than one" is also given.

Profound absence

Cowen yesterday said that there was probably a profound absence of some type of required pivotal data in

PTC's Translarna package, pointing to the FDA's emphasis on dystrophin production in its recent damning briefing documents for Sarepta's eteplirsen; dystrophin is the only pivotal data type that PTC's study did not produce.

PTC shares crashed 62% yesterday, and investors in other Duchenne stocks took the hint, sending Sarepta and BioMarin down 7% and 4% respectively.

The implication, of course, is that the US regulator is no pushover after all, even when it comes to debilitating, poorly treated diseases. While the PTC slapdown, eteplirsen briefing papers and Kyndrisa rejection level the Duchenne playing field, rivals can only bemoan their coincidence with the market downturn.

The Duchenne muscular dystrophy pipeline

Project	Company	Pharmacology class
US filed		
Translarna	PTC Therapeutics	Transcription modulator
Kyndrisa	BioMarin	Muscular dystrophy antisense
Eteplirsen	Sarepta	Muscular dystrophy antisense
Phase III		
PF-06252616	Pfizer	Anti-myostatin MAb
Raxone	Santhera	Coenzyme Q10
Cialis	Lilly	PDE5 inhibitor
SRP-4045 & SRP-4053	Sarepta	Muscular dystrophy antisense
Deflazacort	Marathon	Corticosteroid
Phase II		
Myostatin adnectin	Bristol-Myers Squibb	Myostatin (GDF-8) antagonist
BMN 045, BMN 044 & BMN 053	BioMarin	Exon 45-skipping antisense
FG-3019	FibroGen	Anti-CTGF MAb
Givinostat	Italfarmaco	HDAC inhibitor
CAT-1004	Catabasis	NF-kB modulator
CAP-1002	Capricor	Cardiovascular cell therapy agent
AAV1-Follistatin	Milo Biotechnology	Myostatin inhibitor
TXA127	Tarix Orphan	Angiotensin (1-7)
NPC-14	Nobelpharma	Unknown
HT-100	Akashi/Grünenthal	Unknown
Source: EvaluatePharma		

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