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Gene therapy clinical holds take centre stage

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An analysis of company disclosures reveals a sharp rise in US FDA-imposed halts on clinical work involving gene therapies.

After the recent flurry of US clinical holds you might be excused for thinking that such setbacks are on the rise; in fact, data from the past three years do not bear out such a view. What they do show, however, is an alarming increase in the number of holds imposed specifically on gene therapies.

This could simply reflect the increased work on novel approaches versus three years ago, but the inescapable fact is that holds imposed on gene therapies increased from one in 2017 to four last year and eight so far in 2019. This includes a few repeat offenders, most notably Solid, of whose clinical hold on SGT-001 investors were again reminded this week.

Remarkably, Solid is now on its third clinical hold. Yesterday the group played up the fact that the adverse event that had led to this had now resolved, and that two earlier subjects were seeing microdystrophin expression potentially supportive of a therapeutic benefit in Duchenne muscular dystrophy.

However, the hold remains in place, and on an analyst call Solid would give no guidance on when it might be lifted. And, when it is, investors have to deal with the separate question of why so far the microdystrophin expression levels SGT-001 has been yielding have lagged those of Solid's rival, Sarepta.

Three years of US clinical holds			
	2017	**2018**	**2019**
By project type			
Small molecule	9	3	5
MAb/protein	5	6	2
RNA	2	0	2
Car-T/cell therapy	1	2	2
Gene therapy	1	4	8
By hold type			
Full	10	11	11
Partial	8	4	8
By reason for hold			
Toxicity	11	10	7
Manufacturing	3	3	3
Administrative	2	1	4
Undisclosed	2	1	5
TOTAL	18	15	19
Source: company statements, filings & EvaluatePharma.			

The above analysis of the past three years' holds was carried out using *EvaluatePharma*, by way of a database search of disclosures made by biopharma groups in press releases, quarterly reports and SEC filings, as well as those reported in stories published by *Vantage*.

The list might not be exhaustive though it should present an accurate picture. It likely omits work under way at academia and at private companies, which naturally have a lower disclosure burden than those traded on the public markets.

There is also the risk that the searches missed some announcements that did not specifically mention the phrase "clinical hold", or indeed that some listed biotechs have not even disclosed such information – an inexplicable decision given the market-sensitive nature of such setbacks.

That this is a possibility was illustrated by recent holds imposed on Regenxbio, Abeona and Marker Therapeutics, the last not involving a gene therapy, all of which sat on FDA notification of a clinical hold for weeks. Most famously, perhaps, Solid itself initially did not disclose a clinical hold while trying to complete its Nasdaq flotation (*DMD-day for investors, January 26, 2018*).

With some companies choosing not to reveal a clinical hold until a quarterly SEC filing, or until they respond to the FDA's imposition of such a hold, if anything the absolute number of clinical holds in place might be higher.

US clinical holds involving gene therapies, 2017-19				
Date	**Company**	**Project**	**Hold type**	**Reason**
Nov 2017^	Solid Biosciences	SGT-001	Partial	Manufacturing
9 Mar 2018	Advaxis	Axalimogene filolisbac	Full	Death of respiratory failure
14 Mar 2018	Solid Biosciences	SGT-001	Full	Bleeding & complement activation
30 May 2018	Vertex/Crispr	CTX001	Full	Unknown
25 Jul 2018	Sarepta	DMD gene therapy	Full	Manufacturing
23 Jan 2019	Advaxis	Axalimogene filolisbac	Partial	Manufacturing
15 Apr 2019*	Adverum Biotechnologies	ADVM-022	Full	Manufacturing
10 Sep 2019	Prevail Therapeutics	PR001	Full	Modified clinical design
23 Sep 2019*	Abeona Therapeutics	EB-101	Full	Needs stability data
18 Oct 2019**	Regenxbio	RGX-314 (wet AMD)	Partial	Third-party devices
18 Oct 2019**	Regenxbio	RGX-314 (diabetic retinopathy)	Full	Unclear
30 Oct 2019	Novartis	AVXS-101 intrathecal	Partial	Preclinical toxicity
12 Nov 2019	Solid Biosciences	SGT-001	Full	Toxicity

*Note: ^not disclosed until Jan 2018; *company had been notified some time before this disclosure date; **not disclosed until Nov 2019.*