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Leaders and laggards in FDA approval stakes

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The 22-month span between the US acceptance of the application for Merck & Co's Belsomra and its approval seems unusually long in the context of today's more eager FDA. *EvaluatePharma's* analysis of regulatory data, however, indicates that the novel sleep drug was no outlier.

Applications for central nervous system drugs have on average taken nearly 20 months to earn the agency's nod in the past decade. Lacking the urgency of oncology drugs, most of the CNS products approved in this period have been designated for a standard review schedule, a difference that can clearly be seen in the respective approval times of the two categories (see table).

More than a year

The following analysis examines approval times for CNS, oncology and cardiovascular drugs, which ought to provide a fairly broad comparison of how the FDA sets priorities in these respective disease areas.

Oncology is a field in which small patients have a clear need for life-extending therapies, and the risk-benefit analysis is tilted in favour of approval. By comparison, CNS and cardiovascular treatments are more likely to be used chronically and in larger populations, and in many cases are for diseases that are well served by existing options.

Thus these applications are not accorded the same urgency as oncology, as regulators choose to review the safety data more closely.

This is reflected in the time to approval. The 39 CNS and 18 cardiovascular drugs approved in the past decade took an average 19.7 and 21.9 months, respectively to achieve approval.

Approval time analysis by therapy area

	CNS		Oncology		Cardiovascular	
	Avg approval time (months)	Number of NMEs approved	Avg approval time (months)	Number of NMEs approved	Avg approval time (months)	Number of NMEs approved
2009 – YTD	17.7	19	9.9	48	23.1	10
2004 – 2008	21.5	20	7.1	22	20.4	8
Past decade	19.7	39	9	70	21.9	18

Some, like the blood-pressure regulator Northera and restless legs treatment Horizant, will chalk up their 20-month-plus approval timelines to first-cycle rejections.

Others, like Belsomra (suvorexant), were on regulators' in-baskets for a seemingly long time without action as the agency and company wrangled over scientific matters. In the case of Belsomra, the FDA wanted to reduce the risk of day-after driving impairment and thus authorised doses lower than those tested in clinical trials (*Safety trumps efficacy as FDA approves novel sleeping pill, August 14, 2014*).

At eight months, the fastest approval in CNS was Vanda Pharmaceuticals' sleeping pill Hetlioz, which had the benefit of an orphan designation in non-24-hour sleep-wake disorder, a condition that affects people who are totally blind. In cardiovascular disease, quickest off the blocks was Otsuka Holdings' Samsca, a pill for patients suffering heart-failure-related hyponatraemia that tore through the FDA in 5.9 months.

Slowest in CNS was the epilepsy product Aptiom, formerly known as Stedesa, which took 55 months thanks to

an FDA complete response letter in 2010; in cardiovascular disease this booby prize belongs to the varicose vein treatment Asclera, which took an incredible 10 years to earn the FDA's backing.

This outlier affects the mean cardiovascular approval time analysis; if Asclera is excluded the average falls to just under 16 months.

Priority

The ability of oncology drugs to obtain priority review has a great deal to do with their nine-month approval pace. Of the 70 NME approvals in the past decade, 53 received this accolade or, more recently, breakthrough therapy designation. This compares to four each in CNS and cardiovascular disease.

It is interesting that, despite the advent of breakthrough designation as part of PDUFDA reauthorisation in 2012, the average pace of oncology approvals has slowed in the latter half of the past decade, from seven months in 2004-08 to 9.9 months since 2009.

The fastest approval timelines for a truly novel treatment, at 2.6 months for Iclusig, has occurred since the PDUFA reauthorisation, however, so it is possible that a statistical swing of the pendulum towards the faster side is under way.

Approvals for cardiovascular drugs have also slowed in the latter half of the past decade, although CNS rubber-stamps have accelerated. It is difficult to tell whether these occurrences are random or significant of any underlying trends in the pharmaceutical sector.

What is more clear, however, is that the best way to reduce regulatory risk is to work in oncology. This is cold comfort for companies that have planted their flags in CNS or cardiovascular disease, but it goes a long way towards explaining why so much money has been invested in projects to treat cancer.

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