Obesity matters for drug developers

JANUARY 2023

ARTICLE

Evaluate
a norstella company

Obesity matters for drug developers

Expanding waistbands are on many people's minds in January. This year, R&D and business development execs across the industry should take note. Obesity is now so prevalent that the US FDA is considering whether drug sponsors should include patients with obesity in clinical trials of any drug – not just those that address the condition.

Any such action would introduce another factor into clinical strategy decisions, on top of the broader pricing considerations thrown up by the 2022 Inflation Reduction Act. It would also add significant cost and complexity to development, not least given the physiological changes and co-morbidities associated with obesity.

Yet these differences are precisely why studying obese patients should be mandatory, according to David Greenblatt, professor at Tufts University School of Medicine. He was speaking at an FDA co-hosted workshop in November 2022, "Bridging Drug Efficacy and Safety to the Obese: Considerations and Scientific Approaches". The workshop set out to address whether people with obesity should be studied as a "special population" in new drug development programs.

In reality, this is no longer a "special population": close to 40% of the overall US adult population is now obese or severely obese, with figures reaching 50% or more in some ethnic groups, according to the Centers for Disease Control and Prevention. Childhood obesity has increased eightfold in the last 40 years, and now affects more than 380 million children worldwide. Understanding how drugs may behave in differently in patients with obesity relative to normal-weight patients, and adjusting dosing and regimens accordingly, is vital to ensure drug efficacy and safety.

> Childhood obesity has increased eightfold in the last 40 years, and now affects more than 380 million children worldwide

Some of that understanding already exists in the medical literature. Studies show that it can take longer for obese people to achieve effective drug concentrations, which is why oral contraceptives are less effective in obese individuals, for example. The half-lives of some treatments - how long they remain in the body - can be over five times greater in obese patients than normal weight individuals, according to Greenblatt. He also pointed to recent work studying drugs' pharmacokinetic and pharmacodynamic (PK/PD) behaviour, revealing higher distribution volumes for lipophilic (fat-soluble) treatments such as benzodiazepines, NSAIDS, corticosteroids and some

statins. As far as Greenblatt is concerned, labels on lipophilic drugs must be updated to incorporate these variations. “We know what to do. We just need to put it in the regulations.”

FDA is unlikely to move fast to add “obesity” as a special category on drug labels, as is the case for pregnancy or paediatric use. The agency in December 2022 said it couldn’t speculate on any potential regulatory actions resulting from the workshop, but that internal discussions were ongoing on this “important topic”.

The direction of travel is clear. New guidance on increasing racial and ethnic diversity in clinical trials appeared in April 2022, to encourage better treatments for diseases that “often disproportionately impact diverse communities.” Obesity is one such condition: it affects half of all non-Hispanic black adults, and a similarly high proportion of Native American Indians and Alaskan natives, yet “only” 41% of white adults and 16% of Asians.

The racial and ethnic diversity guidance recommends rather than rules. It suggests that sponsors submit plans on how to achieve such diversity early on in clinical development. It’s unclear whether or what penalties will hit those that fail to do so. But the Agency is clamping down in other areas, like Accelerated Approvals. It may be prepared to do the same here. *(See Box: Accelerated Approval clampdown)*

ACCELERATED APPROVAL CLAMPDOWN

Accelerated Approval approves new treatments for conditions with few or inadequate current options based on surrogate endpoints, subject to confirmatory trials. The trouble is, almost 40% of sponsors don’t complete those trials, according to a US Department of Health and Human Services (HHS) study published in September 2022. The pathway was already under the spotlight following the controversial accelerated approval of Biogen’s Alzheimer’s treatment Aduhelm in 2021. In 2022, it was the turn of Covis Pharma’s pre-term birth drug, Makena, approved in 2011 but which still hasn’t generated conclusive positive results.

FDA has clamped down, even though formal legislation to sharpen its claws failed to pass in 2022. The tightening has already prompted several sponsors (including Roche and GlaxoSmithKline) to withdraw products or submissions.

If the regulator does push for obese patients in some drug trials, sponsors would have to navigate the impact of co-morbidities such as diabetes, hypertension, heart and liver disease, depression and osteoarthritis as well as underlying inflammation in individuals with obesity. Stigma associated with the condition, plus socio-economic, educational, racial and gender disparities, present further hurdles to recruitment. Non-hispanic black women are more affected than men, for instance, according to Frank Hu of Harvard Medical School.

All these complexities explain why obese patients are currently under-represented; many of the co-morbid conditions above are currently exclusion criteria in drug trials. As of September 2022, just 32 US drug labels included information relevant to obese patients, according to Raj Madabushi, associate director in FDA’s Office of Clinical Pharmacology. Only 13 of those contained alternative, bodyweight-based dosing recommendations.

Workshop participants discussed the use of cost-saving technologies such as in silico modelling and virtual patients to generate drug-specific dosing guidelines for adults and children with obesity, and FDA Commissioner Robert Califf was alert to the need to limit additional costs. Such methods are still in their infancy, though.

Efforts to combat obesity itself have ramped up in the last 18 months. Novo Nordisk's Wegovy (semaglutide) was launched in the US in mid-2021; supplies quickly ran out as demand outpaced even the company's own projections. This year, Eli Lilly's tirzepatide, already sold for diabetes as Mounjaro, will likely follow suit. It may help people achieve even greater weight loss than Wegovy, which itself marked a new high-point in drug effectiveness.

Wegovy and tirzepatide are expected to sell a combined $18.5 billion by 2028, according to Evaluate consensus forecasts, fuelling over 36% compound annual growth rate (CAGR) for obesity treatments between 2021-2018. Evaluate Omnium counts another almost two dozen obesity candidates in Phase 3 or Phase 2 development, worth an additional $6 billion in peak (risk-adjusted) worldwide sales.

These efforts, if valuable, are unlikely to turn the tide of obesity anytime soon – not enough to dilute the need to include more patients with obesity in drug trials. Sponsors should expect to hear more on trial diversity and inclusion during 2023 and beyond. As Califf declared at the start of the November event: "The implications of obesity cannot be overstated."

Evaluate

a norstella company

Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

Evaluate Pharma offers a global view of the pharmaceutical market's past, present and future performance with best-in-class consensus forecasts to 2028, unique broker forecasts, and the application of proprietary methodologies to support highly robust, detailed and accurate analysis.

Evaluate Omnium provides a complete, dynamic view of development risk and commercial return across all phases of the clinical lifecycle – including early-phase and privately-developed drugs not covered by analysts' forecasts. With product-specific data including Predicted Peak Sales, Probability of Technical and Regulatory Success (PTRS), R&D Costs, Net Present Value, Time-to-Peak and more, Evaluate Omnium makes it easier than ever to quantify and compare risk and return across the full pipeline landscape.

Evaluate Epi is curated by epidemiology experts and delivers comprehensive, global epidemiological data in granular detail, on a highly interrogatable platform. Customers have access to impartial data for 15 therapeutic areas, and over 230 indications and 9,500 sub-populations across 27 core markets (up to 49 for some countries).

Evaluate Medtech provides a transparent and trusted source of market intelligence and consensus forecasting for the global medical device and diagnostic landscape, using the same proprietary methodologies as Evaluate Pharma. Customers can quickly understand how the market views products and portfolios – and where their opportunities, risks and priorities lie.

Evaluate Consulting & Analytics are specialists in solving unique and complex biopharma pipeline, portfolio and commercialisation challenges with best-in-class datasets, powerful analytical capabilities, and deep therapy and commercialisation expertise.

Evaluate Vantage provides award-winning, thought-provoking news and insights on current and future developments in the pharma, biotech and medtech industries, and is the only news service underpinned by Evaluate's commercial intelligence and data.

www.evaluate.com | **@Evaluate** **@EvaluateVantage**

Evaluate Headquarters
Evaluate Ltd.
3 More London
London SE1 2RE
United Kingdom
T +44 (0)20 7377 0800

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

Evaluate Asia Pacific
Evaluate Japan KK
Holland Hills Mori Tower 2F
5-11-2 Toranomon, Minato-ku
Tokyo 105-0001, Japan
T +81 (0)80 1164 4754