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Pandemic Windfall Upends Status Quo For Top-10 Best-Selling Drugs

by Daniel Chancellor

This article reveals the top 10 pharmaceutical products by revenues in 2022 and discusses the major themes affecting the highest-grossing drugs and the companies behind their continued development.

Now that the books for 2021 are closed, *In Vivo* has crunched the numbers and can report on the best-selling pharmaceuticals last year. And what a year it was, with expectations for drug launches having been completely rewritten. Humira lost its record for peak annual drug sales, not to Keytruda as had seemed inevitable for the past couple of years, but to a product that transitioned from bench to bedside to $40bn+ dollars in under two years.

Pfizer Inc.'s Comirnaty, licensed from *BioNTech SE*, along with *Moderna, Inc.*'s mRNA COVID-19 vaccine Spikevax, capitalized on the once-in-a-generation (or longer?) opportunity by allying life-saving clinical data with tremendous manufacturing scale, aided by large government purchases. These two newcomers have propelled the class of 2021 to a collective $157bn, representing a dramatic increase over the $101bn that was itself a record in 2020.

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The COVID Windfall

Sitting at the top of the leaderboard as the best-selling drug during 2021 is Comirnaty. It is difficult to state how remarkable it is that in only its first year on the market, a single product can achieve more in annual sales than any other in the history of the pharmaceutical market. The $41.1bn in revenues that Pfizer reported are not just a record, but this number is almost twice as large as Humira's peak annual sales of $21.2bn. Furthermore, Humira and its peers are supported by an incredible wealth of clinical data across a large number of indications, while Comirnaty's success is almost entirely underpinned by a single Phase III trial conducted over the course of a few months.

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Moderna, being unable to match Pfizer's scale of manufacturing and international exporting, can console itself with equally astonishing Spikevax sales of $17.7bn in a single year, despite having no prior experience of drug marketing.

Of course, the pandemic has rewritten the status quo for government expenditure on public health interventions, and it should be noted that vaccine purchasing accounts for only a small proportion of COVID-19 response budgets. Comirnaty and Spikevax sales are arguably better viewed in the context of similar contracts for personal protective equipment (PPE) and mechanical ventilation devices, where usual procurement methods were cast aside in the interests of haste and urgency.

It remains to be seen how durable sales will be through 2022, as many individuals in western countries completed their primary vaccination courses during 2021. However, with recommendations slowly expanding into younger age groups, and booster programs being favored to counter subsequent waves of new variants, these two drugs will certainly feature prominently as we adjust to COVID-19's endemicity. Most forecasts indicate that 2022 will be another highly lucrative year for vaccine developers, with new pricing models through 2023 offsetting a strong decline in volume thereafter.

Although not in the top 10, it is worth giving an honorable mention to other notable beneficiaries of the COVID windfall. This includes *Regeneron Pharmaceuticals, Inc.*'s antibody cocktail Ronapreve, whose $6.2bn in 2021 revenues are short-lived as the emergence of variants has blunted efficacy within the class. *AstraZeneca PLC* reported $4.0bn in sales for its adenoviral vaccine Vaxzevria, despite having non-profit pricing. Launched in the final weeks of 2021, Paxlovid has not made an impression on this list, but Pfizer is guiding for sales of $22bn in 2022 for its oral antiviral against all variants of SARS-CoV-2.

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Diverging Fortunes For Mature Drugs

Excluding the COVID-19 vaccines from Exhibit 2, there is a clear divergence that creates two discrete sets of drugs: those that have more or less peaked (Humira, Revlimid, Opdivo) and those that are still sustaining >10% growth rates. All of these drugs have risen to the top of the pyramid based on many years of stellar growth, but time on market is inevitably accompanied by the saturation of the commercial opportunity and the rise of competitors. How soon this comes is a function of lifecycle management, such as seeking out new patients with additional indications or geographies, and blunting the effect of competitors through continued product development and intellectual property protection.

Stelara, Eylea and Eliquis are shining examples of longevity, with impressive year-on-year

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increases despite being in their twilight years. Both Stelara and Eylea have collected broad labels in their respective autoimmune and retinal disorders, with competitors failing to make impressions on their market shares. Eliquis will likely continue to grow through to its expiry in 2026 as the chief beneficiary of the transition away from warfarin to novel anticoagulants owing to its excellent data in preventing the risk of stroke and major bleeds.

Keytruda continues to collect new indications and solidify its position as the PD-1 inhibitor of choice across the spectrum of solid tumor indications. Its dominance is signified by the length of its prescribing information document – currently standing at 125 pages – and it is leading the wave of immuno-oncology clinical trials involving novel combination strategies and in the adjuvant/neoadjuvant setting for earlier stages of tumors with curative intent.

Conversely, Keytruda's great rival Opdivo is stuttering. While it returned to growth in 2021, its sales of $8.5bn are now less than half those of Keytruda's. The advantage first ceded with the failure to show efficacy in first-line non-small cell lung cancer has grown larger each year, and it appears unlikely that Opdivo will challenge the upper echelons of this leaderboard in the future. Rather, Opdivo may find itself falling out of the top 10 drugs list sooner rather than later. Nevertheless, with protection from biosimilars until 2028 in the US, *Bristol Myers Squibb Company* and *Ono Pharmaceutical Company, Ltd.* will still enjoy a prolonged exclusivity period, and should remain confident that continuing to expand Opdivo's therapeutic potential will provide a return on investment.

Facing a generic threat rather more imminently is Revlimid, meaning that its $12.8bn in 2021 revenues will certainly represent its peak. This brings about the end of one of the most lucrative oncology drugs in history, which revolutionized the treatment paradigm for multiple myeloma. As an oral small molecule, sales erosion will be particularly keen, with *Teva Pharmaceutical Industries Ltd.*having launched the first copy in March 2022.

Humira has the final word in this section on mature drugs, as it remarkably continued to grow its global sales by 4%, despite low-cost competition affecting sales in Europe. With US biosimilars not slated to enter the market until 2023, *AbbVie Inc.* may be able to enjoy a final swansong of growth in 2022, buying critical time to continue to build the clinical case for Humira's immunology successors, Rinvoq and Skyrizi.

Mega-Blockbuster Success Is A Double-Edged Sword

For drug developers, creating blockbuster products is no longer sufficient to ensure commercial success. Novartis, which markets 14 different drugs with >$1bn in sales, is shaking up its commercial operations with the goal of transitioning its portfolio away from such diversity and instead generating a smaller stable of drugs that crosses into mega-blockbuster territory. (Also see "*Can Novartis Break Back Into The US Top Five? It Is Going To Need Bigger Blockbusters*" - Scrip, 6 Apr, 2022.)

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While *Novartis AG* may be looking enviously at some of its peers and their assets in the top 10 list, placing such a strategic emphasis on single drugs carries a considerable degree of risk. Exhibit 3, below, shows the overall portfolio balance of those companies that are supporting the top 10 drugs, with the sales of these mega-blockbusters shown as a proportion of total revenues for each. Moderna and BioNTech are for all intents and purposes single-asset companies, with such a distortion being an inevitable trade-off for the success of their COVID-19 vaccines. Apart from these emerging biotechs, along with Pfizer and its COVID windfall, companies such as *Gilead Sciences, Inc.*and Regeneron are also highly dependent upon sustained revenue growth for their leading products.

For Gilead, Biktarvy represents a continuation of its strategy of creating and dominating the market for a single disease, and then aggressively managing the lifecycle of its products through follow-on developments. The oral HIV drug was only launched in 2018 but has rapidly gained a market-leading position through cannibalization of older Gilead drugs, as well as effectively competing with incumbents. Its $8.6bn revenues represent 32% of Gilead's total, and so its prospects have an outsized effect on Gilead's future positioning. Gilead will be well versed in the risks of an imbalanced portfolio, having seen its total revenues and share price underperform following the decline of its once-stellar hepatitis C franchise.

Regeneron faces a similar predicament with its share of Eylea sales in the US accounting for 36% of its total revenues of $16.1bn. Given it is a mature drug, the near-term need to replace Eylea revenues is pressing, even more so considering that Regeneron will have negligible sales for its COVID antibodies in 2022 and beyond. Much hope is pinned on the continued success of the atopic dermatitis biologic Dupixent, which is poised to break into the top 10 best-selling drugs soon. Regeneron shares a portion of the economics with its collaborator Sanofi, and it has also recently reclaimed full possession of the PD-1 inhibitor latecomer Libtayo. These two growth drivers are central to the investment thesis for Regeneron, meaning that risk is highly concentrated in a strategy that management is now fully committed to.

At the other end of the scale, *Bayer AG* and*Johnson & Johnson* are two of the largest conglomerates in the life sciences space, where pharmaceuticals represent just a portion of total revenues. Considering their broad remits, it is to both companies' credit that they have been able to create single assets that rank among the highest selling on the market. Both are well positioned to weather any turbulence, as Eylea and Stelara respectively account for just 7% and 10% of their total revenues.

Bristol Myers Squibb is also notable for possessing three drugs in the top 10 list: Revlimid, Eliquis, and Opdivo. This diversification is the result of a conscious decision to manage overall portfolio risk through its $74bn acquisition of *Celgene Corporation* in 2019. In doing so, the combined company possesses much more stable foundations as it navigates the Revlimid expiry.

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