Selected Developments in Biotechnology Law and the Biotechnology Industry

By STEVEN J. ZWEIG

BRISTOL-MYERS SQUIBB AND CELGENE MERGER PENDING

Bristol-Myers Squibb (BMS) shareholders approved a $74 billion acquisition of Celgene Corp. in January 2019. Since then, the proposed deal has been moving forward, with BMS selling $19 billion of corporate bonds the first week of May 2019 in order to help fund the acquisition. The combination will create a pharmaceutical behemoth with $40 billion in annual revenue. Both companies will benefit: BMS will diversify its experimental drug pipeline and become less reliant on its two currently dominant drug offerings (blood thinner Eliquis and cancer drug Opdivo), while Celgene gains protection against the pending loss of revenue when cancer treatment Revlimid, which grosses the company $10 billion per year, loses IP protection and begins facing generic competition in 2022.

“We are creating the science leader, the company that is No. 1 in oncology,” said BMS CEO Giovanni Caforio. The merger will be the largest one in pharmaceutical sector history.

BIOTECHNOLOGY SECTOR OUTPERFORMING BROADER MARKET

The on-again, off-again, on-again U.S./China trade war has been sporadically roiling the markets, especially with the recent (as of writing) threat by U.S. President Trump to increase tariffs on Chinese products to 25%. The trade dispute has been acting as a drag on Chinese and U.S. economic growth, and therefore on the global economy. Amid that backdrop, the performance of the biotechnology sector has been gratifying, with a key indicator, the NASDAQ Biotechnology Index, returning 11.5% year-to-date growth.

There are several reasons postulated for this strong performance. First are sector mergers and acquisitions. The BMS/Celgene merger discussed above is the largest one, but Eli Lilly and Company’s pending acquisition of Loxo Oncology (to fatten its oncology portfolio) has also lifted the sector, as has Roche Holdings’ acquisition of gene therapy company Spark Therapeutics and Biogen’s offer to purchase Nightstar Therapeutics.

Second, there have been promising regulatory approvals. Several of these have been for “traditional” drugs, not biosimilars or ones produced with biotechnology, but they lift the entire pharmaceutical sector. In addition, companies are pushing ahead with seeking approval for biologics, such as Celgene’s Biologics License Application for luspatercept, an erythroid maturation agent regulating late-stage red blood cell development.

Third, artificial intelligence (AI) is being implemented in the pharmaceutical market; for example, AiCure has developed an application that uses AI to determine the optimal time for patients to take medication, while SOPHiA Genetics has developed an AI system used for analysis of gene sequencing data from research institutions and hospitals. Illumina produced (and released as open source) AI-based software designed to find previously overlooked noncoding mutations in patients with rare genetic disorders. Moreover, AI is being increasingly implemented on the “back end” (non-patient-facing applications) to improve research efficiency and reduce R&D time and costs, such as licensing and using IBM’s much-touted Watson Health AI. The implementation of AI may not itself be a revenue center, but it can be used to do one or all of: reduce costs, speed time to market, and drive the use of drugs by improving how patients use them.

Steven J. Zweig is the Managing Editor of Biotechnology Law Report.
BIOTECHNOLOGY GOES TO WAR

Modern battles are won more by intelligence and analysis than by simple firepower. With that in mind, the Army is developing biorecognition sensors capable of real-time detection of environmental threats and analysis of soldier health and performance. The U.S. Army Combat Capabilities Development Command’s Army Research Laboratory (ARL) has collaborated with the California Institute of Technology and Indi Molecular, Inc. to develop a protein catalyzed capture (PCC) technology with receptors that would allow the real-time monitoring of both personal health/performance and environmental data from troops in the field.

“The Army will need to be more adaptive, more expeditionary and have a near-zero logistic demand while optimizing individual to squad execution in multifaceted operational environments,” said Dr. Matt Coppock, chemist and team lead for the ARL. “It can be envisioned that real-time health and performance monitoring, as well as sensing current and emerging environmental threats, could be a key set of tools to make this possible.” He went on to say that “PCC technology has demonstrated improvements in receptor stability, adaptability and manufacturability over standard antibody receptors, and supports the Soldier Lethality Cross-Functional Team as a potentially viable technology to monitor Soldier performance via relevant biomarkers collectable from wearable sensors.”

Traditionally, biological receptors for sensors were based around animal antibodies, but despite the precision of antibody-based detection methods, there are problems. Said Dr. Coppock: “The gold standard receptor work is based around antibodies, which are fantastic at target capture and selectivity, but their detection capabilities are somewhat limited due to their instability, limited shelf life and batch-to-batch performance variation.” To get around those practical issues, the ARL and its collaborators have followed a different approach: “As an alternative, peptide-based receptors are smaller, simpler to produce, inexpensive and much more robust to environmental stresses, while still retaining the desirable binding properties of an antibody,” Coppock said. “We utilize an entirely synthetic approach to receptor development, which allows for much more control over the incorporation of unique building blocks to guarantee stability and permit straightforward modifications for sensor integration.”

Biosensors are being developed to enhance human performance, health, and therapeutics; food and water safety; and vigilance against environmental biothreats.

BIOSIMILAR APPROVAL AND THE BIOSIMILAR MARKET

Samsung biosimilar to Amgen’s Enbrel (etanercept), Eticovo (etanercept-ykro), was recently approved by the U.S. Food and Drug Administration (FDA). This does not necessarily guaranty that patients will see Eticovo any soon, however. For example, Eticovo is the FDA’s second approval of an Enbrel biosimilar; the first was Sandoz’s Erelzi, which was approved in August 2016 but which still (almost three years later) has not launched in the U.S. Erelzi has been tied up by a several-year court battle between Amgen and Sandoz, with no end currently in sight. Analysts are predicting that Erelzi will finally reach the U.S. market anywhere from 2021 to 2029.

The often-lengthy gap between FDA approval and biosimilar launch substantially reduces biosimilars’ hoped-for potential to reduce drug costs. Sandoz U.S.’s president, Carol Lynch, recently said that:

We actually got approval for Erelzi in August of 2016 and yet we’re still not allowed to market this product because we’re in litigation and we can’t bring it to market until that court case has been resolved. At this rate, it looks like it will be around $3 billion of savings that have been missed, and for patients in the system and for the healthcare system as a whole, I think that’s something that we all need to take on.

Litigation to delay biosimilar launch is not uncommon, especially in the U.S. (where litigation is often the “go to” tactic for companies seeking strategic advantage), given how much money is involved: even a relatively short delay in competitor launch preserves a lucrative market for the reference drug creator.

Despite delays in the U.S., globally, biosimilars are gaining traction, albeit still more slowly than hoped. For example, biosimilar revenues at Biogen, which partners with Samsung on biosimilars, saw a year-over-year increase to $175 million in the first quarter of 2019, as compared to $128 million in the first quarter of 2018. Biogen’s gains came from the launch of Imraldi (adalimumab) in Europe and $124 million in sales of Benepali (etanercept) worldwide. Once regulatory approval is obtained and legal challenges (if any) are dealt with, biosimilars have considerable potential for their creators.

Meanwhile, a Russian drug manufacturer, Generium Pharmaceutical, whose specialty is “orphan
drugs” (drugs for rare diseases with relatively few sufferers), recently received Russian marketing approval for its biosimilar eculizumab, which references Soliris, a treatment for a rare red-blood cell disease, paroxysmal nocturnal hemoglobinuria (PNH), and atypical hemolytic uremic syndrome (aHUS), an extremely rare and life-threatening condition. Soliris is currently the most expensive orphan drug in Russia, so a biosimilar for it, which may drive down treatment costs, is very big news to patients and the health care system.

Despite the comparatively small number of potential orphan drug patients, the lack of treatment options often results in very high drug prices—when your life or quality of life is on the line, you pay what is required for treatment. Since a biosimilar can cost only a fraction of the reference drug’s R&D price but can command—even at a discount *vis-à-vis* the reference drug—a still-high price, orphan drugs are becoming a popular target for biosimilars manufacturers.

• • •