Quoted organization:
ISCT International Society Cell and Gene Therapy
Publication:
BioWorld
Publisher:
Clarivate Analytics
About publication:
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Geographical focus:
North America, EU, Middle east, Asia
Founded:
1991
Readership:
25,000
Readership details:
Subscription publications only. Subscribers from 72% of top biopharma companies, 92% board and C-level. Also VPs of business development, regulatory affairs and analysts, investors.

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Clarivate Analytics

May 16, 2018
Volume 29, No. 95
Special Reprint

CBER head Peter Marks weighs in on cell, gene therapy pricing debate

By Cormac Sheridan, Staff Writer

DUBLIN – Last week Philadelphia-based Spark Therapeutics Inc. reported $2.4 million revenue for the debut quarter of Luxturna (voretigene neparvovec-rzyl), its gene therapy for an inherited form of vision loss, which gained FDA approval last year. Novartis AG also recently reported its first quarterly sales figure for Kymriah (tisagenlecleucel). The chimeric antigen receptor T-cell (CAR-T) therapy took in $12 million in the first quarter, its second on the market since its approval last August for children and young adults with B-cell precursor acute lymphoblastic leukemia (ALL). Gilead Sciences Inc. reported Q1 sales of $40 million for Yescarta (axicabtagene ciloleucel), the CD19-directed CAR-T therapy approved for diffuse large B-cell lymphoma, following sales of $7 million in Q4 2017, its first quarter on the market. Although modest, the numbers demonstrate that the new era of cell and gene therapy has – after several false dawns in Europe – finally arrived.

These therapies – and several others in the late-stage pipeline – have reached a level of maturity at which they are having a real impact on patients. Their roll-out adds a new urgency to the ongoing pricing debate, but the economic questions arising from their incorporation into clinical practice are still far from settled.

Payer pressure is likely to rise as the list of approved therapies starts to grow. "It may limit the more widespread adoption of some of these, at least in the near term," Peter Marks, director of the FDA's Center for Biologics Evaluation and Research (CBER), told *BioWorld*. As a regulator, the FDA's remit is confined to assessing the safety and effectiveness of new medicines. But it also is charged with fostering competition and is actively engaging with the pricing controversy. "I wish I had a solution to the payment issue. I don't have a quick and dirty one," Marks said. "We don't have a magic wand, but we're trying to use the levers at our disposal."

The usual levers of encouraging the development of generic drugs and biosimilars (still a work in progress) – and combating anti-competitive behavior – will not operate in the world of cell and gene therapy, however. It's difficult even to contemplate what a biosimilar CAR-T therapy would look like, but in any case the technologies are evolving so rapidly that the normal patent terms are not very relevant. The commercial life span of today's CAR-T therapies is likely to be much shorter than those of a kinase inhibitor or an antibody drug. In that respect, they resemble complex devices more than traditional therapeutics, said Marks.

"I would be shocked – I could be wrong – if 10 years from now we haven't evolved to some better alternative," he added.

The FDA aims to help the evolution toward a better alternative by supporting internal and external research aimed at improving the efficiency – and reducing the cost – of CAR-T manufacture. Its efforts at present are on a small scale. "We're trying to get additional funding in this area for future years," Marks said. Because the budget process for 2019 is currently underway, he said, he was unable to comment further on the funding side of the strategy. The technology vision, in contrast, is quite clear. "We would really like to see this continued trend towards this 'cassette-based' manufacturing, where it's very scalable," he said. This requires a paradigm shift, to move away from classical processes that involve a gradual scale-up from pilot to commercial-scale processes toward a modular approach, which typically involves single-use bioreactors. "What it lacks in efficiency in some regards, it makes up for in uniformity and a decrease in time required to accomplish what's needed," Marks said.

Ordinary competition may drive prices down

The relationship between cost of goods and the actual price of cell and gene therapies is opaque – and controversial. A report which the Boston-based Institute for Clinical and Economic Review issued in March concluded that the wholesale acquisition cost (WAC) of both Kymriah ($475,000) and Yescarta ($373,000) in B-cell ALL and DLBCL, respectively, were justifiable in terms of the clinical benefit they provide. An alternative analysis, published on Feb. 8, 2018, in the *Health Affairs Blog*, estimated that Kymriah would still be profitable at a WAC of $160,000.

Ordinary price competition between rival products may help to drive pricing downward in certain settings. "One can't guarantee that, but I certainly hope that will happen," Marks said. It's not a dynamic that usually operates in the biopharmaceutical industry. However, Basel, Switzerland-based Novartis, following its May 1 FDA approval for Kymriah in large B-cell lymphoma (including DLBCL), matched Gilead's pricing of Yescarta in that indication. Novartis is not offering outcomes-based pricing in DBCL, however, although it does so in B-cell ALL, albeit in a limited fashion. Patients who fail to respond to therapy within 30 days are not charged.

"Based on our experience with Kymriah in the pediatric ALL indication, the slower complete response time in large B-cell lymphoma makes an outcomes-based contract model complex and unsustainable for many parties involved," a spokeswoman for Novartis told *BioWorld* by email. The company continues to work with the Center for Medicare & Medicaid Innovation on "to find the best and most effective path forward for indication- and value-based pricing", she stated.

Walter Colasante, vice president in the life sciences practice of the Boston-based consultants Charles River Associates, is concerned that the pricing debate does not fully take account of the fundamental differences between potentially curative cell and gene therapies and more traditional drug therapies. "Everybody's using the same model from the past and hoping for the best," he told *BioWorld*. "People believe if you do the right thing, other people will find the money." The perverse incentives that hamper antibiotic development suggest otherwise.

Colasante questions whether existing payer systems are configured to accommodate high-cost therapies, even if they offer clinical value. "The problem will come not from the economist but the accountant," he said. Colasante chaired a panel on the issue at Bio-Europe and polled the audience on a series of key questions, including the potential involvement of third parties, such as financial institutions, insurers or charities, in tackling the affordability problem. Fully 83 percent of respondents agreed on this – Colasante readily acknowledged that the sample was biased. The response could indicate an unwillingness – or an inability – on the part of industry to shoulder the commercial risks attached to innovative therapies.

Miguel Forte, CEO of Oslo, Norway-based T-cell receptor therapy firm Zelluna Immunotherapy AS and chair of the commercialization committee of the International Society for Cellular Therapy, expects to see some business-model divergence in on the supply side. Bigger firms are better able to absorb large up-front development and manufacturing costs – and may also be able to enter annuity-based pricing agreements, which would spread out the cost of therapy over a long time period. Smaller firms may have to sacrifice some of the upside by bringing in third parties to carry some of the financial load. "Everybody is considering it and discussing it," he said. To succeed, participants need to understand their position in the complex matrix involving patients, payers, care givers and biotech firms. "This cannot be a single-side effort," he said.

For individual companies attempting to navigate their way through a complex market, the end game is far from clear. "There will be a way through, but it will be turbulent in some markets – and will be too late for some patients," Colasante said. There will be winners and losers – some technologies will be adopted, but some will be under-utilized. "It will not be rosy for all," he said. "What bothers me is why do we accept this as normal?" Whichever way it plays out, 2018 will be a key year in the adoption of cell and gene therapy. The commercial performance of Kymriah, Yescarta and Luxturna will be closely watched over the next three quarters. ♦