Cell And Gene Therapy Rapid Approvals Can Pose Commercialization Challenges

World Courier, a part of AmerisourceBergen, helped Novartis overcome the unique logistical hurdles associated with commercializing Kymriah.

AmerisourceBergen (ABC) is positioning itself as the go-to partner for the growing number of manufacturers facing rapid preclinical-to-market transitions for cellular and gene therapies.

The pharmaceutical services provider has a collection of integrated global units, including its World Courier clinical trials logistics business and third-party commercial logistics operation ICS, that are targeting the burgeoning cell and gene therapy sector. ABC recently moved its commercialization services businesses under a single operating group called Global Commercialization Services and Animal Health, as part of a company-wide realignment.

In addition to World Courier and ICS, AmerisourceBergen's commercialization group includes a variety of businesses, such as Lash Group, a patient support services company, and Xcenda, a strategic consultancy with expertise in health economics and outcomes research, market access consulting and reimbursement. AmerisourceBergen outlined how each of the businesses can address commercialization challenges specific to cell and gene therapy in a recent white paper.

The reorganization in part reflects the recognition that the U.S. health care market is on the brink of a revolution in cell and gene therapies. The U.S. Food and Drug Administration (FDA) approved two such treatments, known as chimeric antigen receptor T cell (CAR-T) therapies, in the past two months.

Novartis AG's pediatric leukemia therapy, *Kymriah* (tisagenlecleucel) was approved August 30, 2017. (*Also see Novartis CAR-T Therapy's Swift Approval Aided By REMS And New US FDA Review Mode - Pink Sheet, August 30, 2017.*) Kite Pharma Inc.'s *Yescarta* (axicabtagene ciloleucel) for certain B cell lymphomas was approved October 18, 2017. (*Also see Gilead/Kite Pricing For Yescarta Undercuts Novartis's CAR-T Kymriah - Scrip October 18, 2017.*) And two more cell and gene therapy candidates could be cleared for marketing over the next 14 months (*see box*).

Accelerated clinical development schedules and shortened regulatory reviews for cell and gene therapies in the US require manufacturers to assemble a complicated commercialization process in a compressed timeframe. The FDA was able to approve both Kymriah and Yescarta more than a month ahead of schedule by taking advantage of cross-agency collaboration involving its Oncology Center for Excellence.

"If you've got a novel therapy, the good news is, many times the review is being expedited," said Doug Cook, President of

Global Specialty Logistics at AmerisourceBergen. "We've had manufacturers say, 'That's great but I'm not ready.'...That's a unique opportunity for us to make sure that we pull together the solutions." In his role, Cook oversees the World Courier and ICS businesses.

Cell and gene therapy developers "are going from pre-clinical to commercial in four to five years, which is just so fast," World Courier President Sam Herbert added. "Normally you have a Phase III [research stage] that's a multi-year process, when you can start thinking about all your commercial plans."

"This has moved so quickly" that "the people who are commercializing now have had to address a lot of commercial questions in very short order."

Novartis approached World Courier two years ago to talk about collaborating on Kymriah in anticipation of a rapid transition to market, Herbert said. "They put a lightbulb on for us about this space" in terms of the "complexity of the whole thing and all the big stakes."

World Courier is providing global commercial logistics for the launch of Kymriah, "mainly because of the global commercialization capabilities or logistics capabilities we have," Herbert explained. World Courier offers a suite of services, such as coordinated peripheral scheduling to pinpoint pickup, real-time product tracking and temperature monitoring, as well as advanced cryoshipping technologies.

The company said it has demonstrated its ability to develop solutions for the complicated logistics involved by working with Novartis on Kymriah's clinical trial. Currently, more than half of the active cell and gene therapy innovators trust World Courier with their personalized supply chain.

"We can be your partner on the clinical side but if we do a great job for you, guess what? You don't have to look for another partner. We can also be your partner on the commercial side," Cook commented. "It's an easy baton hand-off from World Courier to ICS and the rest of our commercialization services."

DOUG COOK
President,
Global Specialty Logistics,
AmerisourceBergen

SAM HERBERT
President of World Courier
(an AmerisourceBergen company)

PETE BELDEN
President of ICS
(an AmerisourceBergen company)

There's a lot at stake in managing the logistics for the treatment, Herbert pointed out. It's not just "picking up from a manufacturer, bringing it into a country, and storing it, where you have a lot of lead time and if something goes wrong, you just replace it with a different box."

With many cell and gene therapies, "the patient, or some individual, is in the supply chain, which is totally different," Herbert explained. For autologous treatments like Kymriah, "you have a very sick patient" and "if anything goes wrong in the supply chain, the stakes are that patient's life."

For example, treatment with Kymriah involves removing T-cells from patients, engineering them to target cancer cells expressing CD19 and then injecting the cells back into patients. Cryopreservation stabilizes the cells as they're shipped to and from Novartis' manufacturing site and systems are in place to track the products closely as they're shipped across borders.

In general, the integration of ABC's commercialization services facilitates a natural progression from clinical trial to the marketplace, ICS President Pete Belden pointed out.

"It's been really interesting for us, as we go deeper with the manufacturers in clinical phases, to begin to navigate all the complexities of the commercial launch of a product," Belden said.

ABC encourages "real white boarding-type sessions to help [developers] think forward two or three years, if possible." The proactive planning enables developers "to start to apply what we are learning in the clinical phases about the logistics of the product movement, the patient scheduling and coordination, the manufacturing of using the patient material, the provider readiness and awareness and ability to deliver the therapy when it gets there," he added. "All of that is very complex, more complex than any of the therapies that we traditionally deal with on a day-to-day basis."

As a big pharma, "Novartis knows how to commercialize," Belden observed. "But even with that, the requirements for a unique process and product like a cell therapy brings in multiple different levers of unique customized and tailored commercial services."

'Managed Access' Opportunities

AmerisourceBergen's ability to transition from clinical trials to commercialization has led to opportunities in managing access to novel treatments in countries outside the US where a therapy may not yet be approved, Cook observed.

"There are patients in those countries that will need to get access to those therapies," he said. "But if it's not available, the grey market enters the picture and prices skyrocket, double and triple in some cases." In addition, he asked, "how do you know when it's been through the grey market and that the product has been kept under proper temperature control and storage?"

Today, such circumstances involve traditional specialty products, as well as rare and orphan products. However, as the specialty pipeline continues to evolve, and more and more complex products – such as cell and gene therapies – reach the market, the problem and demand for a solution will grow.

The company sees a need for a "bridge to commercialization" in such circumstances. As a result, "we've put together an offering through the World Courier footprint where we are now

going to be offering global managed access programs" to "get the drug to commercial patients who will pay for it," Cook said.

Global markets "allow you to do this, based on what the requirements are to get the drug into the country to the patient. You just have to have the expertise in knowing what the physician needs to get local country approval for their patient," he explained.

"This is an unmet need and a problem that manufacturers know" and "the need is going to get much bigger, quickly."

Provider Confidence In Supplier As Competitive Advantage

In countries where cell and gene therapies are approved, provider confidence in the supply chain could become a competitive advantage for some products, according to the executives.

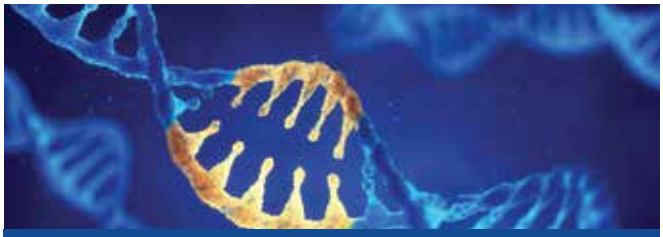
"The efficacy and side effect profile are always going to matter. But at the end of the day, if the physician is very comfortable with how you order, that it's going to go according to plan, that they're going to get the data they need and they're confident of the treatment schedule, it's going to be a very big differentiator down the line," Herbert maintained.

Not all cell and gene therapies in the pipeline are as complicated as Kymriah so the commercialization model will continue to evolve as the field develops, he predicted.

"We think of these now for acute conditions but cell and gene therapy has widespread applications – everything from tissue regeneration to low acuity" conditions affecting large numbers of patients. "So I think you're eventually going to have more stakeholders involved."

There may be "more community hospitals, maybe community-based specialty physicians that are going to use some of these products, and that's going to be a whole new set of challenges," he said, "The reimbursement won't be as high. But there will be so many people that are relying on it that the model will have to keep evolving."

Belden agreed. There are "a number of gene therapies that aren't quite as complex, where the patient might not always be providing material for their own therapy, but that pose similar complications in terms of the logistics and the patient, provider and reimbursement journey that's going to be needed."



CELL & GENE THERAPY PIPELINE IN U.S.

- Novartis' Kymriah approved August 30, ahead of its Oct. 3 approval deadline, following priority review.
- Kite Pharma's axicabtagene for B-cell lymphoma in adults approved Oct. 18 ahead of Nov. 29 deadline, following priority review.
- Spark Therapeutics' Luxturna for inherited blindness in children under priority FDA review: decision deadline Jan. 12, 2018.
- Juno Therapeutics' JCAR017 in non-Hodgkin lymphoma registration trial ongoing; U.S. filing targeted in second half 2018 and approval possible in 2018.