INTERVIEW

Enabling patient access to CAR-T cell therapy in India

David McCall, Senior Editor, Cell & Gene Therapy Insights, speaks to Shashwati Basak, Vice President, Cell and Gene Therapy, Intas Pharmaceuticals, about the availability of autologous CAR-T cell therapies in India, the current state of regulatory guidance in the country, and the phase-appropriate analytical control of cell therapy manufacture. As engineered cell therapy products rapidly increase in complexity, it is critical that costs are reduced to ensure affordability to patients worldwide, including those in India.

Q What are you working on right now?

SB: Currently, my team and I are focused on developing novel gene-modified cell therapy and gene therapy (CGT) products. The idea is to develop otherwise inaccessible and expensive advanced therapies at a fraction of the cost of current commercial products in order to provide accessibility and affordability to the Indian patient population.

Q Tell us more about the R&D pipeline for cell and gene therapies at Intas Pharmaceuticals

SB: Intas Pharma was the first Indian company to establish cell and gene therapy development programs in India. The company began with the vision to develop the next generation
of cell- and gene-based therapeutics to treat a wide range of genetic disorders and cancers. The CGT unit is involved in the drug discovery and process development (with full-fledged analytical support) of various gene and cell therapy products, including CAR-T cell therapy.

Q What is the current situation in India in terms of the availability of autologous CAR T cell therapies to patients? How is Intas seeking to help in this area in particular?

SB: At the moment, eligible patients for CAR-T cell therapy must travel to the USA, or other countries that offer these therapies at an exorbitant price. There is no accessibility to these therapies in India for patients, and the majority of such patients would not afford these therapies even if they were able to travel. There is a huge unmet need in India.

Although the evolving regulatory aspect needs attention given the novelty of CGT here, support from the government and other funding agencies, combined with the efforts of a few industry visionaries, has enabled several start-up companies and hospitals to get involved. They are dedicated to working on bringing autologous CAR-T cell therapies to Indian patients. In addition to Intas, there are two other companies leading this effort—ImmunoACT, a spin-off of an academic lab in the Indian Institute of Technology, Bombay, and Immuneel Therapeutics, which is located in Bengaluru. Both these companies have conducted phase 2 trials in India. ImmunoACT recently received the approval of its indigenously developed CD19 CAR-T cell therapy product in India. I believe this milestone is just the beginning for Indian companies.

At Intas Pharma, our team is developing several CAR-T cell products, including one targeting CD19 alone and two more targeting CD19/20 and CD19/22. The former is in the preclinical stage while the latter two are in the discovery stage. We also have a collaboration with the Tata Medical Center (TMC) in Kolkata and Miltenyi Biotec in Germany to allow us to initiate our phase 1 trial with Lentigen/Miltenyi’s CD19 LV soon.

The collaboration with TMC serves as a demonstration of proof of concept to establish a point-of-care unit, following the decentralized manufacturing model. This will be a fully functional and self-sufficient manufacturing unit with both QC and QA capabilities in a hospital setting. We believe this can speed up the vein-to-vein or turnaround time, which is crucial for the patients’ survivability since most of these patients are terminally ill with no other treatment options available. Intas Pharma is actually unique in that the parent company is located in the Westernmost part of India, while the medical center is in the East part of India, which contributes to the appeal of a point-of-care manufacturing unit.

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In parallel, we are developing a novel CD19 CAR-T product and also building the capability to manufacture plasmids and LVs in-house—an important consideration in terms of bringing down costs and increasing accessibility for Indian patients. Both of our autologous CAR-T cell therapy initiatives are being funded in part by a grant from the Biotechnology Industry Research Assistance Council under the National Biopharma Mission of the Government of India’s Department of Biotechnology. This is a great example of government support to both industry and hospitals expediting the launch of these therapies.

Q: What is your perspective on recent regulatory guidance relevant to the cellular immunotherapy space, particularly that which relates to QC and release testing of T cell therapy products? What are the key considerations for cell and gene therapy developers such as Intas?

SB: In terms of Indian regulatory guidance, the first draft of the national guidelines for gene therapy product development and clinical trials was published by the Indian Council of Medical Research in 2019. Due to a few unique features of these therapies, the aim of this guidance was to provide a framework to Indian cell and gene therapy developers over and above the guidelines already outlined in the existing Drugs and Cosmetics Act, which is more suitable for small molecules and biologics.

Since CAR-T cells and other CGT products are categorized as drug products, the quality expectations for product release remain the same as those for any other drug product. All the critical quality attributes (CQAs) must be identified during the development phase so that all relevant analytical tests can be identified, developed, and qualified or validated as fit-for-purpose prior to conducting the trials.

However, there are few exceptions to the rule given the living nature of the cell-based products. For example, the compendial sterility testing as per USP <71> takes a long time, which can pose a challenge. Fortunately, the regulators have recommended alternative strategies for the testing and release of living drug products. The US Pharmacopeia now has chapter 1071, which includes a risk-based approach to rapid sterility testing for product release. Examples of other alternative methods that may be needed for live cells include rapid mycoplasma and rapid endotoxin tests.

For non-compendial tests, the US FDA recommends qualification or validation to ensure they are fit for their intended use. In addition, the guidance states that for ex vivo genetically modified cells administered immediately following manufacturing, in-process sterility testing of a sample can be performed 48 to 72 h prior to final harvest. This may include a Gram stain and a sterility test compliant with 21 CFR 16.12. Under this approach, the release criteria for sterility would be based on a negative result and no growth resulting from the 48 to 72-h sampling.

At Intas Pharma, we are incorporating both the Indian guidance and the global guidances in the early product development phase so that we are aligned with both global and local regulatory expectations to ensure safe and high-quality products for our patients.
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Q Are novel cell therapy analytical tools and technologies delivering the required degree of repeatability and precision, for you (e.g., cell counting)? If not, where are the key innovation shortfalls at the moment?

SB: Cell counting measurements are used in cell and gene therapy applications to evaluate cell viability and concentration in order to assess the quality and quantity of cells for use in a variety of processes. This also determines the dose that needs to be infused into the patient. Automated cell counters are used in combination with flow cytometry-based absolute cell counts to cross-validate the data in order to avoid manual counting, which is prone to errors.

Real-time cell counting while the cells are in different phases of the process would be a key innovation to track critical in-process parameters, rather than just the endpoint.

Q What does phase-appropriate analytical control of cell therapy manufacture look like, particularly in the early stages of development?

SB: Analytical methods are critically important throughout process and product development. They are used to support manufacturing investigations and characterize process changes. As the CQAs for most cell therapies are poorly defined and vary from product to product, selecting assays for process development can be challenging. Given the complexity in using a living cell as a product, it is important to develop many orthogonal assays early on in the product development pathway. This approach ensures we characterize and measure the unique physical and biological characteristics of the product that may affect the CQAs.

The idea is to identify the matrix that is both biologically meaningful and sensitive to variations in the process. As the product advances through the different clinical development phases, our understanding of the process and the product characteristics will increase. In parallel, an understanding of the manufacturing process and test methods is expected to evolve. Manufacturers are constantly looking to simplify the process without compromising on quality and capacity with the overall aim of reducing the cost of goods. As the sequence becomes clearer, the assays will be refined and improved, and new assays will be identified to reduce both the turnaround time of these living drugs and the cost of goods to increase patient affordability.
Where and how are you applying automation in your cell therapy processing? And how can we move further towards the automation of data analysis in cell therapy manufacture?

SB: At Intas Pharma, we have not yet delved very deeply into automation, as we are in the discovery and early clinical stages. However, the field as a whole is clearly moving towards the adoption of automation, mainly to reduce variability in the manufacturing process. This is important because of the nature of cells, especially in the autologous setting where the starting material itself is inherently variable.

There are already a few fully automated, closed, and integrated systems available on the market that can be used for manufacturing cell therapies such as CAR-T cells. These include Miltenyi’s Prodigy, Lonza’s Cocoon, and OMPUL by Orgenesis. The latter is a fully integrated, closed-loop, all-in-one mobile bioprocessing unit encompassing the entire GMP suite. Another example is Cytiva’s Chronicle automation software, which is GMP-compliant software providing a unified digital platform to monitor cell therapy manufacturing operations and supply chain logistics. The field is moving in the right direction in terms of automation.

What are the keys for you in formulating and executing a successful CMC compliance strategy, particularly in light of the ever-increasing complexity of engineered cell therapy products?

SB: The key is to align with the regulatory expectations for successful CMC compliance. An ongoing conversation with regulators at each stage of the product development process is helpful to understand their perspectives, especially as the area is relatively new in India. In addition, as drug developers, we need to provide regulators with the scientific rationale to increase the awareness of these novel products and their uniqueness.

We need a back-and-forth dialog between drug developers and regulators so that everyone can be on the same page in terms of successful CMC compliance. In India, we can always take guidance from the already well-established FDA and EMA guidance.

Finally, can you sum up one or two key goals or priorities, both for you in your own role and for Intas Pharma as a whole, over the next 12–24 months?

SB: The major goal would be to progress a few of these cell and gene therapy programs into the clinical phases in India.

BIOGRAPHY

SHASHWATI BASAK is the Vice President and Head of the Cell and Gene Therapy Unit at Intas Pharmaceuticals (Biopharma Division), Ahmedabad, India. She is leading the development of several programs in gene and cell therapies, spanning from early-stage research to clinical stage. Prior to this, she served as the Head of Quality and Regulatory Operations at another leading Indian CGT company called Immuneel Therapeutics Ltd, focused on...
developing CAR-T cell therapies. Basak has a PhD in Molecular and Cell Biology from the Indian Institute of Science, Bangalore. She did two postdoctoral fellowships from the Salk Institute for Biological Sciences and Stanford University, studying gene expression and regulation, and cancer signaling pathways. She has over 20 years of scientific leadership experience in translational research, clinical biomarkers, analytical assays, technology platforms, quality and compliance. She has worked in several Biotech and Biopharma companies, including Biocon Bristol Myers-Squibb R&D Center, Aurigene Discovery Technologies and Immuneel Therapeutics Ltd, and held positions of increasing responsibilities in varied roles.

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