ADVANCING PRECISION MEDICINE WITH GENE & CELL THERAPIES:

An Evolving Regulatory and Drug Development Landscape

Of the 59 new molecular entities approved by the FDA in 2018, 25 are considered personalized or precision medicine treatments, a ratio that shows an increasing trend for new approvals of personalized treatments.[1] Similarly, several other recent marketing approvals included expanded indications of previously approved treatments, highlighting the focus on individualized therapies for certain patient populations.[2]

These precision drugs, also called personalized medicines, are designed to address unique characteristics of sub-populations, a disease state or a response to a specific treatment. They are not only providing new possibilities for individualized patient care but are also propelling transformations in product development strategies, clinical trial designs and health authority initiatives.

Of course, adapting to rapid advances and keeping pace with these significant patient-centered developments in life sciences requires a major shift in strategy compared to product development over the past few decades. Drug and device developers need a comprehensive understanding of the new challenges faced in the precision medicine landscape. It is also key that they have the ability to proactively adjust to changes in this unique development arena and awareness of the regulatory nuances in marketing approval pathways.

Addressing a Persistent Lack of Precision

According to one analysis, the top 10 highest-grossing drugs in the U.S. only help between 1 in 4 (and as low as 1 in 25) of the people who take them.[3] This estimate highlights the lack of specificity for many drugs in use today and the opportunity that exists for highly targeted precision medicines.

A low rate of effectiveness in common medicines can be blamed on several factors. Conventional testing methods often require thousands of people in a Phase 3 registration program. The participants may share similarities with the same disease state but the trial may not collect information related to a patient's unique profile, data that could help determine if or why certain segments of the participants responded or didn't respond to the treatment.

Precision medicine initiatives aim to close the gap by incorporating a more systematic process into clinical trials – and beyond – to better identify responders or non-responders and aggregate highly specific datasets that can recognize patterns and provide a more holistic understanding of populations. These data sets enable a better understanding of systems biology both in the health and disease states (e.g., genetics, metabolomics, lipidomics and proteomics) and offer the promise and reality of even more targeted precision medicines.[6]

The Expansion of Precision Medicine

The idea of precision medicine to directly treat a condition is often attributed to Dr. Paul Erhlich, who believed there must be a way to treat disease without causing harm to the patient's own cells. Working as a physician and scientist in the late 1800s and early 1900s, he introduced the concept of a "magic bullet" that was targeted to the site of the disease – and only on the site of the disease. His contributions to medicine earned him the Nobel Prize in 1908.[4]

Now, more than 100 years later, following an explosion of scientific technologies in areas like Next-generation sequencing (NGS), the FDA anticipates that by 2020 they will receive more than 200 Investigation New Drug (IND) applications per year in this therapeutic space; by 2025, they predict they will be approving 10 to 20 highly targeted cell and gene therapy products per year.[5]

Precision Medicines in Practice

While there has been an explosive growth in precision medicine over the last five years, many forms of these personalized treatments have been in development for decades, namely, gene and cell therapies. In oncology, gene and cell therapies have made tremendous gains with cell-based immunotherapies such as CAR-T therapy. By removing, re-engineering and reinjecting a patient with their own immune cells, CAR-T cell therapies have been shown to induce remissions in cancer patients.

In 2018, the FDA approved expanded indications for two previously approved autologous CAR-T cell therapies, which target specific instances of B cell acute lymphoblastic leukemia and several types of lymphomas. Ongoing clinical studies are exploring CAR-T therapies in additional blood cancer types while further research has expanded into many types of solid tumor cancers. The next generation of CAR-T therapies will likely be allogeneic *off-the-shelf* products and several companies are working toward this outcome. Allogeneic products offer the promise of a more straightforward treatment paradigm for the patient and much more widespread use.

Beyond oncology, other cell and gene therapies have been part of extensive research efforts across many therapeutic areas. For example, in Type 1 diabetes, researchers are exploring how patients could benefit from genetically modified stem cells which are implanted subcutaneously to produces insulin – basically fulfilling the functions of the pancreas. In ophthalmology, the FDA recently approved a gene therapy treatment to treat patients with an inherited retinal disease. Interestingly, rare diseases might be one of the major beneficiaries of cell and gene therapies since many of the biological defects are often the result of missing or inactive genes.

Improving Technologies and Managing Big Data

Part of the rapid expansion of precision medicine has been bolstered by increasing improvements and cost-effectiveness in modern technologies, such as next-generation sequencing and gene expression technologies, which can help screen patients and identify potential treatment risks. Another source of valuable data has come from central testing laboratories that gather de-identified health information and clinical testing data to better understand patient populations, testing sites and the impact of inclusion/exclusion criteria in clinical trial protocols.

Integrated informatics systems and sophisticated analytics play a central role in helping streamline the substantial data processing that continues to drive precision medicine. These tools and techniques are changing how diseases and compounds are studied in early research, the clinical trial process and post-marketing studies.

Understanding the Impact on Clinical Trials

Testing the effectiveness of precision medicine has triggered the need for different types of clinical trials. To account for a myriad of factors and data points unique to a patient and their disease, researchers in precision medicine have moved beyond conventional Phase 3 trials to biomarker-driven trials that involve multi-level stratification.

With an overarching protocol, a precision medicine trial can be segmented into parallel sub-trials that differ by molecular feature.[7]

- *Basket trials* test the effect of one drug on a single mutation in a variety of tumor types, at the same time. These studies also have the potential to greatly increase the number of patients who are eligible to receive certain drugs relative to other trial designs.
- *Umbrella trials* have many different treatment arms within one trial. People are assigned to a particular treatment arm of the trial based on their type of cancer and the specific molecular makeup of their cancer. These trials also offer the advantage of being able to combine dose phases into a single trial and evaluate population differences, helping researchers fulfill multiple Phase 1 objectives within a single protocol.

Precision medicines also involve several different activities as compared to traditional clinical trials. Some phases may be combined; First in Human studies are usually conducted in patients rather than normal healthy volunteers. There are often opportunities for adaptive strategies where studies can be combined into “seamless” Phase 1/2/3 clinical trials. This approach can greatly increase the speed of development toward registration. However, with gene therapy, the follow-up periods for patients can be quite prolonged, sometimes up to 15 years.[8] Regardless of the duration for following up on gene therapy trials, the changing and evolving landscape for clinical trials will definitely provide creative ways to conduct these follow-up studies using such methodologies as “virtual trials” and “mobile medicine”[9] – further examples of the impact of changing technologies on product development.

From a logistical perspective, product and delivery services must also adapt to the challenges of shipping and processing the products to specialized laboratories, sometimes across the globe. For example, with autologous T-cell therapies, cells must be isolated from the patient, shipped to a laboratory for modification, and then shipped back to the patient for administration. All of these processes must be tightly regulated and often require specialized equipment for handling extremely small samples within very limited excursion temperatures (e.g., -80 °C). In these situations, Good Manufacturing Practices (GMPs) overlap substantially with Good Clinical Practices (GCPs) – and, as a product or biological sample is manufactured, handled or transferred, the interplay between GMP and GCP documentation must be appreciated.

Accelerating Regulatory Approval

All major regulatory agencies have specialized divisions for reviewing advanced medical products; most have initiatives in place to rapidly advance development of precision medicines intended to treat life-threatening conditions (and most precision medicine products are directed toward life-threatening conditions). For example, in the United States, the FDA's Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) plays a major role in assessing advanced therapies, although many other reviewing divisions are also involved in precision medicine programs.

Interestingly, most specialized initiatives to accelerate advanced therapies build upon expedited programs already in place. Consequently, all of the potential regulatory pathways to accelerate development are available for advanced products, e.g., breakthrough therapy designations, accelerated approvals, priority reviews in the U.S.[10]; in the EU, PRIME designations and conditional approvals are available.[11]

Of note in the U.S. is the introduction of the Regenerative Medicine Advanced Therapies (RMAT) designation. This designation was introduced as part of the 21st Century Cures Act signed into law in December 2016. The purpose of this law is to help accelerate medical product development and bring new innovations and advances faster and more efficiently to patients who need them. The eligibility requirements for applying for RMAT designation are shown below:

a) The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products

b) The drug is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition

c) Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

RMAT designation enables sponsors to engage early and often with FDA to discuss the development program, especially the use of surrogate or intermediate clinical endpoints, the potential for accelerated approvals and priority reviews of their submission.

As with RMAT designations, the FDA also underscores the distinct development processes for advanced therapies used in precision medicine. For example, in the *Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (FDA)*[12] it states, "Due to the unique and diverse nature of the products employed by cellular and gene therapies, conventional pharmacology and toxicology testing may not be appropriate to determine safety and biologic activity." And indeed, many preclinical studies that would be required for a traditional drug are not required for gene and cell therapies. In other words, thoughtful selection of the preclinical testing package has the potential to accelerate development. This example serves to illustrate that for precision medicine products, it is not business as usual – one size does not fit all.

Precision Medicine Strategies

With the very real possibility to accelerate the development of advanced products intended to treat unmet medical needs, sponsors must be aware of the opportunities to create positive value inflection points in the development process. Combining many essential disciplines together early in the process to form a high-performing team will benefit all stakeholders – and definitely lessen the potential for bumps in the road. Consider the following holistic framework:

- Construct strategic development plans that maximize the impact of regulatory initiatives and the potential for adaptive/seamless clinical trial designs
- Discuss the program with regulatory agencies early with a view to gaining marketing approval as quickly as possible
- Define an appropriate (and likely streamlined) preclinical package that enables clinical studies to be initiated
- Develop a robust strategy for manufacturing and logistics for transportation
- Ask the question: "Can we develop a potential companion diagnostic (CDx) to identify patients for a targeted therapy?"
- Create an early and iterative approach to market access planning to understand potential reimbursement hurdles, a commercial strategy and how to communicate the value of the product to a specific group

The FDA acknowledges that as new classes of personalized medicines are discovered, the development paths will continue to evolve. Covance is a drug development organization that has the expertise, technologies and facilities to develop precision medicines across the entire advanced therapies paradigm. With focused solutions and over 20 years of experience in cell and gene therapies, tissue engineering and device development, Covance is already working across multiple scientific and operational disciplines to realize the promise of precision medicine to accelerate advanced therapies to market.

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The Americas + 1.888.COVANCE (+1.888.268.2623) + 1.609.452.4440
Europe / Africa + 00.800.2682.2682 +44.1423.500888
Asia Pacific + 800.6568.3000 +65.6.5686588

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