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Pharma Ignite

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Growth in the rare disease market is outpacing that of the pharmaceutical space as a whole. In fact, around half of all the new treatments approved in the US in the past few years have been orphan drugs. There is a high level of unmet need and good incentives under current laws, while the revolution in genetic medicine has powered the development of many therapies for specific genotypes.

"We have a lot more understanding of the genome and the effects of mutations," says Will Maier, vice president and head of the research center for rare diseases at ICON Biotech. "A lot of different methods are being used. There are direct genetic insertions like gene therapy but also advances around RNA, such as mRNA therapies, circular RNA, and other variants that are useful to correct the expression, under-expression, or overexpression of a certain gene or to counterbalance it."

This, in Maier's view, is the main area of innovation in the field. It allows for the development of personalized medicines because each genetic mutation might lead to a specific genotype with different cellular function expression levels. Meanwhile, the COVID-19 pandemic has increased awareness of the possibilities of mRNA, with many biotechs developing new platforms.

Identifying Patient Populations A Challenge

The growth in rare disease R&D creates challenges too. Where ten years ago, there might have been one company active in a specific indication, now there are many. However, the number of patients is much the same, so companies must compete to find them. In addition, Maier notes there is increasing interest in very small subgroups of patient populations and very specific genotypes, which are not easy to find.

"If you are looking for a particular genetic subtype for a particular reason, you may struggle to find patients with this particular trait, These patients are not likely to be there for you to find in a database. You have to use other tools, other kinds of activities that may be ongoing to try and figure out where those patients may be," he observes.

In terms of innovation, biotech companies are responsible for most of the R&D in rare diseases. With their limited infrastructure, they have to work with global service providers to work out where the patient populations are. "It's not too difficult as an individual to figure out who some of the key opinion leaders (KOLs) are for a particular disease, but trying to operationalize and optimize where you need to do your different levels of research at different stages can be a really big challenge," says Maier.

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The Role Of Patient Advocacy Organizations

Patients with a specific rare disease may be seen very infrequently in most medical care settings so patient identification for research can be very challenging. One way of doing this is to work with patient advocacy organizations, formal or informal, and find out how they can build awareness of research opportunities and drug development within their membership and network of affiliated organisations.

These organizations have often been early champions of the need for drug development and have spent time and effort talking to scientists in order to stimulate their interest in new therapies. One example is in Duchene muscular dystrophy, where many parents of affected children became highly educated on the different therapeutic interventions and worked closely with drug developers. Other patient advocacy organizations have even started their own drug companies.

“So, there might be an institution, a lab where somebody’s developing a treatment, a group of people who are raising money, and then there’s a drug company that knows how to put it all together or be the sponsor,” Maier says. “These all need to come together to get the product moving.”

Historically, a large pharma company would do all this, perhaps with academic help. Now, the patient advocacy organization might know the most about unmet medical needs and may have a KOL involved who is well connected to researchers identifying new treatment targets or interventions. Together they can work to bring this knowledge to a drug company’s attention for the purposes of drug development and product approval. Thus, the network is wider and more complex than traditional pharmaceutical company research and development.

Artificial intelligence (AI) can help with patient identification and study recruitment by building a machine learning model, based on patient characteristics from a data set, and using it to predict where patients might be. This, Maier says, could be useful in improving patient diversity in terms of geography or other population factors. AI could also be used to map different regions of genomes from databases to drive greater understanding of potential targets for new medical interventions in rare diseases.

Regulation is something of a two-edged sword in rare disease drug development. Orphan drug legislation in the US, Europe, and Japan afford a period of exclusivity and allows treatments to be reused. Despite these incentives and support, rare disease drug development presents many challenges. The difficulties arise from the lack of precedents and standards: how to optimize opportunities; the differences between the US and Europe; how to appeal to the various different regulatory pathways; and whether the drug is an original, a variation of an original or a repurposing, among other things.

How CRO Partnerships Can Support Biotechs

Biotechs need help with all these things, Maier says, and partnerships are crucial. In particular, contract research organizations (CROs) offer experience and infrastructure that are highly valuable. Although clinical trials for rare disease indications are often small-scale, they are also more complex for the same reason. The patients are few in number and scattered across the globe, often with a high disease burden – and many of them are children. Thus, a global footprint and expertise in setting up and running trials are crucial elements of the CRO’s offer.

“As a CRO, we look at the marketplace to see what’s there and build what we think the space needs,” he says. “We have a lot of capabilities in terms of operational trials, labs, and a team of people who are seasoned professionals in drug development science. They cover the gamut from early to late phase development, manufacturing, and regulatory. Those are the people who work with our teams at any one point in time to provide the best advice.”

Approaching Reimbursement Concerns

Reimbursement is inevitably a challenge when the disease is rare and the cost per patient is high. Moreover, with some treatments – notably gene therapies – patients may only use the treatment for a short period during a lifetime of disease occurrence. To address these issues, companies are putting a variety of different programs in place to help support patients. This can include patient support programs to help with drug payment and reimbursement agreements with payers that are related to the duration of treatment effect.

The US Inflation Reduction Act (IRA) has also altered the rare disease reimbursement landscape. On one hand, lawmakers have created an exemption for orphan drugs from price negotiations. However, this exemption only applies to products approved for a single indication, limiting the scope of orphan drugs to be reimbursed for treating different diseases even if effective in doing so.

"The IRA is still a work in progress, because the US wants to control drug prices, but they don't want to restrict access, especially to rare disease. It's a bit confusing, as they are restricting reimbursement after your second drug approval. The question is 'When is that going to happen and what would be a second indication approval'?" Maier says.

"One example of the potential for confusion is this: suppose I have my drug approved for the predominant genotype and then for a separate genotype. Is that a separate indication or the same one? It's causing a lot of anxiety at the moment. Over the longer term, I imagine it will be somewhat modified. It has certainly focused people's thinking around the costs associated with rare disease drug development," he continues.

Maier expects to see more novel payment mechanisms from manufacturers, especially for expensive gene therapies. Potentially, Maier adds, increasingly efficacious treatments like genetic medicines will make the treatment of some rare diseases less costly overall due to higher levels of efficacy.

At present, about 20% of rare disease drugs have more than one indication, so more clarity is needed on both sides. Regulators are wary of manufacturers continually extending the life of a product by putting a new indication on it and getting a new period of exclusivity.

"That's a good goal, because obviously we want money to be available for other patients if there's a well-established therapy," Maier says. "But at the same time, I think they will have to figure out if the way they've described it isn't rather a blunt tool and if they're going to have to be looked at on a case-by-case basis."

An Exciting Outlook For Rare Disease Development

Looking forward, Maier says: "There has been a revolution in genetic engineering, and it has accelerated the development of new medicines. It's certainly becoming more widespread, so more people understand what to do and the tools for building understanding are increasing. That's very encouraging for people who have rare diseases. We've already seen a lot of improvement in quality and length of life in all sorts of different rare diseases, and I think we will continue to see that."

Like any part of the industry, funding is vulnerable to slowdowns – as happened in late 2022 with high interest rates – or to regulatory interventions like the IRA. The challenge to drug developers, in Maier's view, could be to make their products accessible to the systems that will use them. Most rare disease drugs, he points out, are fusion-based therapies and injections, requiring specialized care.

Nonetheless, he is optimistic and not just because of the science. There is more awareness among patients of rare diseases, more support, and more opportunities for working through solutions. Social media has made it a lot easier for people to talk to each other about their disease.

"I think the kind of community that develops around patients and their families stimulates a lot of awareness about the burden of the disease, and really encourages people to try and do something about it," he concludes. "We know there will be failures, but there have also been a lot of successes. Most societies in the world are wealthy enough to pay for rare disease and I'm glad they do."

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