A New Age of Pharmaceutical Innovation

IPI Speaks with Dr Patrick Larcier, Senior Director, Strategy Product Development Solutions, EU & US, of PharmaLex, on Next-generation Small Molecules

Q: Can we start with a bit of an overview of what Small Molecule Excellence from PharmaLex involves, including the types of experts involved and the overarching objective?

A: Despite the high-profile advances in the field of biotechnology, small molecules continue to be the mainstay in disease treatment. Nevertheless, these new small molecule products require expertise in order to move seamlessly through the product development process. That's where the concept of excellence comes from – it's about having that depth of knowledge in the field and across the development life cycle. With this in mind, we involve experts focused on operational excellence in every different part of the process, meaning CMC experts, non-clinical experts, as well as clinical experts, in order to build the appropriate steps, paths and studies needed in each module of the regulatory dossier, while considering time constraints and using the most appropriate regulatory pathways at all development stages. Through this expertise and extensive experience in developing small molecules, we're able to help companies save time and effort in the development of these products.

Q: Let's break down some of the areas a bit more, specific to the type of support offered to small molecule innovators (for example, non-clinical/quality, strategy, marketing authorization, scope, regulatory support)

A: It's really on a case-by-case basis, based on the experience and expertise we have. This allows us to adapt the classic development steps or recommendations to each program and provide very specific support for the development of these molecules at the CMC, non-clinical, and even clinical stages. We combine this expertise with recommendations on interactions with the health authorities. The idea is to propose smart development plans to enable successful outcomes for our customers.

Q: What is unique, or different, about the new generation of small molecules?

A: First of all, these products are typically more diverse and complex than traditional chemical entities and they target pathologies that previous generations of small molecules did not. By way of example, now we find small molecules under development in neurological conditions, such as Alzheimer's disease and multiple sclerosis, as well as in the field of oncology.[1] That's different to what we have seen previously, with companies largely focusing on the development of what we would call "classical biologics" (or large molecules) for these diseases – such as monoclonal antibodies, fusion proteins, and so on. So now some companies are, in some ways, reversing, by turning to small molecules for these pathologies. We're seeing that at companies like Bayer, which is targeting at the RNA level through small molecule innovation,[2] and Pfizer, which has had success with breakthrough small molecule treatments for arthritis and ulcerative colitis.[3] We're also observing this trend with smaller companies, such as Agios Pharma with Pyrukynd for adults with pyruvate kinase (PK) deficiency which results in chronic anemia,[4] as well as with Accent Therapeutics, Epics Therapeutics, Skyhawk Therapeutics among others.

Q: Why is a high level of expertise important when working with companies developing next-generation small molecules?

A: Some of these small molecules have come out of RNA research and are targeting RNA functions, which is why they are diverse and complex from both a technical and scientific standpoint. This requires specific knowledge and experience with working on the development of these small molecules. This is what we're seeing with new products approved for cancer, in neurological conditions, and even in some inflammatory bowel diseases, as is the case with Pfizer's tofacitinib (Xeljanz®) for ulcerative colitis and arthritis or Amgen's RNA degraders in different therapeutic areas.

What's really exciting about these breakthroughs is they are targeting difficult-to-treat pathologies and adding to the therapeutic armamentarium. It's important that these innovative therapies have the best chance of success because the need is great. Even if companies can get new biologics on the market, it seems many patients are not getting the long-term benefit that one would hope. They may respond to treatment for a period between 12 months and two years and then their condition deteriorates. Often then, the options for treatment are very limited. There might be another biologic that can be used, but these treatments may have quite similar efficacy with potentially fewer severe side effects.[5] So, the hope with innovative small molecules is not only from the efficacy side, but also from the safety perspective to enable a more patient-centric approach. Again, having that expert insight into potential safety issues is important in the development process.

Q: What are the biggest changes influencing innovation with small molecules?

A: In addition to breakthroughs in RNA research, innovation is also coming from new approaches from both the pharmaceutical and biotech industry. Traditional biotech companies like Amgen and Biogen are now developing small molecules because they see a potentially smoother path on two fronts: manufacturing and regulatory.

On the manufacturing side, biological products, including both "complex biologics" (such as cell and gene therapies) but also "classical biologics", typically face manufacturing challenges that can require more time and resources to overcome. Our regulatory expertise leads us to conclude that it's likely that small molecules will face fewer questions from the health authorities, meaning those interactions might be shorter and questions regarding the future dossier might be easier to address. Fewer questions and a more seamless regulatory pathway inevitably mean shorter timelines for approval and faster availability of these treatments to patients. And that's

particularly important when a company is targeting conditions with huge unmet medical need.

Q: Can you describe any regulatory incentives that can help to create opportunities for the developers of novel small molecules?

A: Regulatory authorities offer a number of incentives to support innovation, particularly when tackling unmet medical need. In the EU, the PRIME scheme provides enhanced support for innovative therapies,[6] as does the UK's Innovative Licensing and Access Pathway (ILAP)[7] and Fast Track Designation (FTD) or Breakthrough Designations (BTD) in the US.[8] There are also Orphan Drug designations (ODDs) in many jurisdictions that companies should consider.[9] All these kinds of programs may help small molecule innovators with their next steps.

There are also collaborative efforts such as the FDA-run Project Orbis,[10] which developers of innovative oncology projects can take advantage of to gain access to several markets, and therefore propose new treatments to patients and generate revenue earlier, and in more jurisdictions.

These and other types of incentives or programs need to be considered in a global light, which is why working with an experienced service provider is important. Companies need that global perspective and the expertise required to solve CMC quality challenges that might be encountered, the right insight to define the non-clinical and clinical strategy for developing a small molecule, and the ability to put all of that into perspective in order to leverage appropriate regulatory tools, like Project Orbis or PRIME, particularly for the products in the field of oncology.

Q: What are the biggest challenges companies face when navigating the development and regulatory landscape with innovative new molecules?

A: While the challenges on the CMC side are less pressing than with biologics, there are still issues to overcome because these small molecules are structurally diverse and complex. For example, when working on RNA functions, there will be complexities that need to be addressed. That's not just on the CMC quality side, but also pharmacological considerations, since companies must be able to demonstrate the effects and benefits their product is expected to have on a specific disease, especially when we talk about neurological disorders such as Alzheimer's and multiple sclerosis, which are difficult to treat diseases. As I mentioned earlier, there are a number of regulatory tools such as PRIME, ILAP and Project Orbis (the latter for oncology developers, when appropriate), among others, that might be helpful, so getting the right advice and recommendations from an experienced service provider can be extremely helpful.

Q: What role does technology, including AI, play in supporting small molecule innovation, and what technologies is PharmaLex focused on for this purpose?

A: Through our Global Statistics and Data Science team of experts, PharmaLex supports artificial intelligence/machine learning from discovery to manufacturing of small molecules. Areas of expertise span:

- Target identification and related processes using real-world "omics" data
- Leveraging knowledge in pharmacology and pharmacometrics for the distribution, metabolization, elimination, dose, mechanism of action of new structures

- Using modeling and ML for the "manufacturability" of new compounds.

In summary, AI plays an important role in supporting small molecule innovation.

Q: What is the vision of the PharmaLex small molecule team in terms of supporting the industry and raising the profile of small molecule innovation?

A: The vision is to support companies developing these small molecules to address treatment of patients suffering from diseases with high unmet medical need. One area, in particular, where small molecules could be particularly helpful is in the fight against antimicrobial resistance (AMR). This is an issue we are already facing and one that could be even more difficult to manage in the coming 25 years. We have an initiative at PharmaLex to support companies developing small molecules (in particular that target these pathogens) as we are committed to being part of the fight against AMR. By this, I'm not just talking about antibiotics, but also antifungals, anti-malarials, antiprotozoals – all these pathologies are emerging and could potentially result in more deaths than cancers by 2050.[11]

Unfortunately, despite this threat, there has been very limited research into fighting these pathogens and currently there are only around 30 new compounds under development in this area, which is tiny when compared with the field of oncology or autoimmune disorders, with about 4,000 agents. By being part of this fight and playing a key role in product development to address AMR, we believe we can really help to make a difference.

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