Achieving sustainable innovation with value-added medicines

The COVID-19 pandemic spotlighted drug repurposing as a key strategy to support traditional novel chemical entity development; yet repurposing is just one example of how off-patent molecules can be further developed to provide patients with more treatment options. Here, Arun Narayan, Chairman of the Value Added Medicines Sector Group at Medicines for Europe, discusses the value-added medicines market, its strengths and weaknesses, and how companies can capitalise on the time and financial investment in existing drugs.

"Value-added medicines are all about incremental innovation"

BRINGING CHEMICAL or biological drugs to market is well established as a costly and time-consuming endeavour. How costly? DiMasi *et al*. reported that in 2014 the estimated average pre-approval cost for researching and developing a new drug was $2,558 million (in 2013 dollars);[1] one can only assume that this figure has since risen further, especially given the increasingly widespread adoption of more complex biological products in recent years. With drug development through to marketing authorisation taking on average at least 10 years,[2,3] and the likelihood of regulatory approval being less than 10 percent for drugs entering Phase I trials,[3] every opportunity to capitalise on investment and promote the fullest extent of development for these potentially life-saving products is vital.

One of the means by which innovation can be achieved without the development of a new chemical entity (NCE) is through investing in off-patent molecules and repurposing them for new indications or adapting them to increase their benefit. Molecules adjusted in this fashion are known as value-added medicines and, dependent on the strategy used to develop them, they can offer various benefits for both patients and the healthcare sector. To find out more about the value-added market, the strategies used to enhance these molecules' benefits for patients, and how such approaches complement the traditional NCE approach to drug development, *European Pharmaceutical Review*'s Hannah Balfour spoke with Arun Narayan, Head of Global Commercial Development at Viatris and Chairman of the Value Added Medicines Sector Group at Medicines for Europe.

What are value-added medicines?

Narayan explained that at their core, value-added medicines are intended to be patient centric, focused on unmet medical need and developed through continuous innovation, rather than targeting breakthroughs. "Value-added medicines are all about incremental innovation; bringing

benefits that are accessible with what we have today, rather than waiting for that next breakthrough which may never come," he stated.

Value-added medicines are different from generics in that, though they both start from an off-patent molecule, these products include an innovative component that differentiates them from the originator. This change is aimed at providing additional benefits to all stakeholders, not just patients, whether that be through enhanced monitoring capabilities for healthcare providers or reducing the number of hospital visits needed for a course of treatment. Narayan explained that there are three strategic approaches to creating value-added medicines:

1. **Repurposing or repositioning** – used to find new indications for existing medicines, repurposing was heavily relied upon during the COVID-19 pandemic to identify beneficial interventions to combat the viral infection
2. **Reformulation** – changing the existing drug, either in terms of its route of administration or the dose, to potentially improve patient outcomes or reach new patient populations, such as paediatrics
3. **Combinations** – combining multiple therapeutics to create fixed dose regimens that can simplify treatment, enhance patient outcomes and/or improve compliance. Alternatively, digital value-added medicines are the combination of a drug with a device (such as a companion app) that enhances it in some way.

Why invest in value-added medicines?

According to best estimates by IQVIA, global sales of value-added medicines are currently $34.7 billion, two thirds of which are provided by the US market, where sales are 10 times higher than in the European Union (EU).[4] Narayan revealed that this disparity is partly because value-added medicines are relatively less well-known in the European market, and that the US has a dedicated regulatory pathway for such products, called 505(b)2,[5] which the EU has yet to establish.

In terms of the benefits to industry of value-added medicines, Narayan explained that not only do they put patients at the centre of innovation and improve their outcomes, but they also enable customisation, a trend that is emerging in the pharma industry with the rising adoption of personalised medicine and tailored approaches for patients. "They also provide better monitoring, an enhanced ability to connect with healthcare professionals and provide medical staff with more tools to deal with diseases and disease progression," added Narayan. Moreover, he emphasised that value-added medicines are about facilitating sustainable, continuous innovation at an affordable cost. He added that it is an error to believe that, especially from a patient's point of view, anything other than a breakthrough is not worth developing – "by making incremental changes, significant benefits to patients' lives can be achieved".

COVID-19: an unlikely ally

Despite the terrible impacts of the pandemic for society as a whole, Narayan highlighted that the COVID-19 crisis had in fact encouraged the value-added medicines market: "If there was any doubt about the benefits that value-added medicines can bring, whether it is repurposing or other areas, I think those doubts have been dispelled, or at least reduced significantly."

COVID-19, he said, had a particularly positive impact on drug repurposing, with dexamethasone being an example of a key drug that was repositioned to combat symptoms: "The repurposing of dexamethasone is a clear example of how continuous innovation strategies can deliver fast and affordable solutions for unmet medical need. It is estimated that treating severe cases of COVID-19 with dexamethasone led to 12,000 lives saved in the UK in the second half of 2020. Indeed, this affordable and widely available medicine was found to reduce mortality in hospitalised COVID-19 patients needing oxygen and ventilation by 18 and 36 percent, respectively."

He continued that another benefit of COVID-19 was that it acted as a catalyst for change in the pharma industry, encouraging a shift away from the slow and traditional way of approaching innovation and drug development. As a result, he believes now is a great time to make changes to pharma R&D that get it closer to its goals, such as the implementation of real-world evidence or adoption of pipeline strategies aside from NCE development. »

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Drug repurposing outside of health emergencies

While certainly beneficial for tackling COVID-19, there are other crucial examples of repurposed drugs being investigated for more typical indications, such as cancer. Narayan emphasised the growing importance of implementing drug repurposing away from emergency settings, stating: "I think that COVID-19 has established the fact that repurposing is an area that is important and should be recognised. The European Commission (EC) has taken note of this; in both its recent strategy documents, The Pharmaceutical Strategy for Europe, as well as Europe's Beating Cancer Plan, the word repurposing and the concept of repurposing is evident. It is growing and the benefits of potential repurposing in non-communicable diseases like cancer or neurological diseases and equally in rare diseases, where the incentive for developing NCEs may not exist, are now recognised."

He gave two current examples of drug repurposing in a non-pandemic context: the evaluation of the expectorant ambroxol, now being tested as a treatment for Parkinson's disease despite being a treatment for respiratory diseases associated with excessive mucus; and the Anticancer Fund's CUSP9 trial, which has provided some promising preliminary data for a cocktail of nine repurposed drugs for the treatment of glioblastoma.[6] Other therapeutic areas which Narayan believes could potentially benefit from repurposing include neurological disease and mental health, where traditional innovation approaches have often failed to deliver significant improvements to patients' lives; and rare diseases (orphan drug indications), for which there would be no business case for developing NCEs.

How can companies maximise success in drug repurposing?

Despite the potential benefits value-added medicines may bring, Narayan cautioned that there are still challenges facing the sector, particularly in Europe, with such products being relatively under-recognised. The current challenges are several-fold and include a lack of clarity in regulatory processes; a lack of adequate incentives for the development of value-added medicines; and inadequate recognition of their value, coupled with disproportionate requests for data generation in Health Technology Assessment (HTA) evaluations or negotiations with payers. All of these are currently being addressed, with Medicines for Europe recently calling for the EU to provide better clarity in the regulatory processes by setting up a specific regulatory pathway for value-added medicines, similar to the US's 505(b)2, and recognising them as their own a separate category of medicines in European legislation.[7] In addition, Medicines for Europe's whitepaper[7] encourages the provision of adequate incentives for value-added medicine developers and the establishment of effective pricing and reimbursement frameworks.

Narayan explained that there are already indications that such hurdles are disappearing, with promising developments establishing more favourable environments across Europe. For instance, once it is established that a product is a value-added medicine in Belgium, it is no longer placed in the same price bracket as the generics of the same molecule; in the UK, a catalyst fund is being established to facilitate the repurposing of off-patent medicines; and in some EU member states, a framework for digital apps, such as the DiGa framework in Germany, is heralding the development and implementation of systems for the evaluation of digital value-added medicines.

To maximise success in the current climate, whether looking at repurposing biological or synthetic molecules, Narayan stated there are two key strategic points to consider:

1. Any repurposing strategy should be preceded by the identification of unmet medical need. Value-added medicine developers must collaborate with patients and several other stakeholders to ensure that the needs of the patients are heard and met.
2. When developing any value-added medicines, manufacturers should look to minimise the unpredictability of the process. Focus on three key areas: regulatory processes; pricing and reimbursement policies within the intended markets; and applicable incentives, such as data exclusivity.

Delivering sustainable innovation

While limitations exist within the European market, Narayan emphasised that there is huge potential in the value-added medicines sector, with its ability to provide significant patient benefit in a more affordable and timely manner than developing NCEs being key. He stressed that drug repurposing is a strategy that has been established as equally important and complementary to traditional R&D approaches, and that companies should be capitalising on the decades of knowledge and investment surrounding existing drugs to get new and improved options into the hands of patients. He also noted that Europe can learn from the US market, adapting the established frameworks to

suit its needs, and that the upcoming revision of pharmaceutical legislation in the EU provides a unique opportunity to shape the ecosystem for these products.

Narayan concluded: "The benefits that value-added medicines bring impact many parts of the healthcare ecosystem; they offer a means to deliver relatively quick, affordable and accessible innovation that supports patients, healthcare providers, payers, our healthcare budgets and more. They can reduce the number of visits to hospitals and exacerbation, improve compliance and adherence, all of which help, directly or indirectly, the healthcare system. There is a huge ripple effect, which we need to recognise, and this is exciting, because today we are seeing just the tip of the iceberg."

About Medicines for Europe

Medicines for Europe is an international non-profit organisation representing the generic, biosimilar and value-added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines, based on five important pillars: patients, quality, value, sustainability and partnership. Its members directly employ 190,000 people at over 400 manufacturing and 126 R&D sites in Europe and invest up to 17 percent of their turnover in R&D investment. They are working at both increasing access to medicines and driving improved health outcomes by providing high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bring to market value-added medicines.

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