Image: © ag visuell - Fotolia.com

Changing Lives

With more rare diseases being discovered, there has been a dramatic industry shift towards orphan drug development – and the Middle East and North Africa looks set to be a feasible region as this neglected area of clinical trials expands

Rani Abraham and Rabinder Buttar at ClinTec International

A rare disease is considered to be one affecting only a small percentage of the global population. Different regions have different definitions of what classes as a rare disease, based on prevalence. For example, in the European Union, it is defined as a disease affecting less than one in 2,000 people; in the US, as per the Orphan Drug Act, it is a condition affecting less than 200,000 citizens each year. Overall, to classify as a rare disease, a condition must affect less than one per cent of the population.

Rare diseases – also known as orphan diseases – are frequently progressive and chronically debilitating conditions which are life-threatening if left untreated. They affect no more than five in 10,000 people, with most affecting less than one in 100,000 people (1).

To date, in the region of 8,000 rare diseases have been classified, and more are being discovered each year (2). Some 80 per cent of these diseases have been identified to be of genetic origin (3). Other diseases classified as rare include infectious diseases such as malaria, rare forms of cancer and autoimmune disorders.

Around 50 per cent of rare diseases – for example, lysosomal storage disorders – first appear at birth or during childhood, and can be rapidly progressive or almost immediately fatal. The other 50 per cent are almost exclusive to the adult population and includes conditions such as acute myeloid leukaemia, glioma and renal cell carcinoma. Additional rare diseases include spinal muscular atrophy, patent ductus arteriosus, familial adenomatous polyposis and cystic fibrosis.

For many of these rare conditions, there is no approved treatment; only palliative care is available. A disease may be considered rare in terms of the global population, but may be common in specific populations, yet the global low prevalence dictates the likelihood of commercial drug development. An example of a rare disease with localised higher prevalence is Behçet Disease, which globally affects between one and nine per 100,000 people, whereas the prevalence in Turkey is one per 1,000 (4).

Boosting R&D

Adequate scientific knowledge about causes and mechanisms of many rare diseases is lacking. However, the number of clinical trials on rare diseases is now increasing, particularly in the Middle East and North Africa (MENA) region.

Since drugs for these conditions are intended for small numbers of patients – or no return on investment can be reasonably expected – they are classified as orphan drugs.

Of the large number of rare diseases identified, only a few have the potential patient population to support commercial drug development. Therefore, incentives have been set up to encourage and increase R&D of orphan drugs. One example of this is the US Food and Drug Administration's (FDA's) Office of Orphan Products Development, whose mission is to advance the evaluation and development of products demonstrating potential benefit for the diagnosis and/or treatment of rare diseases.

Current Market

Due to the low prevalence of rare diseases, the pharma industry has little interest, under normal market conditions, in developing appropriate medicines. This is due to the fact that, in many cases, the costs of drug development cannot be recovered by sales of the resulting drugs.

However, recently there has been a dramatic industry shift in this opinion, and the spotlight is now on orphan drug development. In 2012, orphan drug sales increased by 7.1 per cent to $83 billion from the previous year. In 2012, 25 new orphan drugs were approved by the FDA (5). It is anticipated that the worldwide orphan drug market will grow to $127 billion by 2018.

Prior to Implementation

There are a number of important points to consider before implementing a rare disease clinical trial, particularly in the MENA region:

Rare Disease Day

Most regions/countries celebrate Rare Disease Day – a day dedicated to raising the awareness of these conditions. 28th February 2013 marked the Sixth International Rare Disease Day.

Since the first event in 2008, Rare Disease Day has seen an ever-growing number of participating countries. More than 70 nations participated in 2013, including many MENA countries such as Bahrain, Iran, Lebanon, Palestine, Saudi Arabia and the United Arab Emirates (6).

About 80 per cent of rare diseases are genetic in origin. Therefore, when considering a region or country for inclusion in a trial, local customs must be considered. There is a high rate (25-60 per cent) of consanguineous marriages in MENA, resulting in a higher risk for genetic disorders than in other regions. This makes MENA a good region for the investigation of rare genetic conditions (7).

Attending regional rare disease programmes can help to raise awareness of the research that the company plans to conduct in the country/region. The national alliance or country organiser should be contacted to discuss interest in participation.

Natural History Studies

Studying the natural course of a disease – from the pre-symptomatic phase and through the different clinical stages to the endpoint (cure, chronic disability, or death) – is important, especially with rare diseases. An essential role for natural history (NH) studies in rare disease drug development (the investigational new drug phase) is facilitating efficient clinical development.

Ideally, this knowledge should be available before the implementation of trials in the region. NH studies help characterisation of the disease process, including variability in disease severity, symptom stability and outcomes. Such studies also serve to assist with clinical trial design, improve diagnosis, provide insight to disease prevalence, and help enhance commercial understanding of the patient community.

Study Design and Documents for Submission

A well-defined protocol is central to the study design. Key opinion leaders (KOLs) and regional experts can provide valuable guidance on the adaptation of the global protocol to regional requirements, as well as site selection. KOLs can also advise on what rare disease networks exist in the region.

Translation of patient-related documents into the native language is required; it is advisable to have this done locally to avoid delays due to external review and revision. Partnering with a contract research organisation with a good track record of conducting such trials in the region can help provide strategic solutions to shorten start-up times.

Drug Development Challenges

Trial stakeholders must also overcome various challenges when planning and delivering studies and developing orphan drugs.

Orphan Drug Designation

In order to receive orphan drug designation, sponsors must demonstrate that the population of patients to be treated meets the appropriate regulatory requirements regarding prevalence. In addition, orphan designation may be granted if the sponsor can demonstrate that there is no reasonable expectation to recover development costs of the product.

Study Design and Execution

Diagnosis of rare disease can be challenging, and misdiagnosis can often result in poor quality of life for the patient. Even when the correct diagnosis is made, the majority of patients are faced with the reality that there is no treatment. An FDA-approved therapy is available for only about five per cent of the 8,000 rare disorders and diseases (8).

Implementing a clinical trial in rare disease requires strategic regional solutions, as well as good knowledge of the region and culture – including a careful analysis of disease prevalence and treatment patterns in the region – as ethnicity is often a significant risk factor. As these are complex trials requiring multiple sophisticated tests, sometimes sites that regularly treat such patients may not have the infrastructure required for participation in global studies.

Patient Recruitment and Retention

Recruitment of patients for long-duration trials can be difficult due to the very low prevalence of rare diseases. There is a need to initiate trials quickly, particularly for rapidly progressing diseases, as patients may be lost. It may therefore be of great benefit to transport patients from nearby regions to existing sites, and provide support and accommodation for the patient for the duration of the visit.

If the patient is a minor, then one must also consider the costs of the legal guardian or representative travelling along with the patient. Significant effort and time must also be invested in patient follow-up and support.

Regulatory Requirements

The regulatory environment in MENA is well-established, with ongoing reforms posing a challenge for long-duration trials. It is imperative, for the duration of the trial, to remain updated with current regulatory requirements – for example, import licences and ethics approvals. In keeping with the regulations, necessary approvals should be sought in advance, to avoid delays which may lead to patients falling outside of protocol requirements, as symptoms may recur if the investigational medicinal product is withheld pending updates to the regulatory approval.

Vendor Management

Rare disease trials are complex and may require multiple vendors to provide services. It is preferable to have prior experience in managing regional vendors, or to collaborate with partners that have past experience in managing such trials.

The vendors should have gone through a vendor qualification process and are required to sign a confidentiality agreement. Sometimes changes in the political situation can cause steep and unexpected revisions in costs by vendors; this should be taken into account when budgeting and forecasting.

Significant Needs

With the recent developments in the pharma and biotech industries, research and interest in rare diseases is on the rise. Collaboration with local partners with the ability to provide strategic solutions and intelligence can save time and costs, while retaining study personnel is an important consideration in long-term studies to ensure continuity.

In addition, patient recruitment support, close oversight of vendors, coordinating patient transport and payments, and locally-based contract research associates with a sound understanding of the local regulatory environment play crucial roles in the success of rare disease trials.

Acknowledgements

The authors wish to thank Sophie Totten and Dr Sabita Srivastava for their input in the preparation of this article.

References

1. The Global Genes Project, RARE facts and statistics. Visit: http://globalgenes.org/rarefacts
2. Heemstra HE *et al*, Translation of rare disease research into orphan drug development: Disease matters, *Drug Discovery Today* 14(23/24): pp1,166-1,173, 2009
3. Campos-Castello J *et al*, Orphan drugs and orphan diseases, European Paediatric Neurology Society, pp141-149, 2000
4. Yurdakul S and Yazici Y, Epidemiology of Beçhet's Syndrome and differences in disease expression, *Beçhet's Syndrome*, pp35-52, 2013
5. Visit: www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_results_2.cfm
6. Visit: www.rarediseaseday.org/country/finder
7. Almalki ZS *et al*, Access to orphan drugs in the Middle East: Challenge and perspective, *Intractable and Rare Diseases Research* 1(4), pp139-143, 2012
8. White W, Building bridges to rare disease patients, Siren Interactive, 2012

About the authors

Rani Abraham is ClinTec International's Regional Director – Regulatory Affairs and Operations MENA. She joined the company in 2008 and has over 18 years of experience in clinical research. With a strong regulatory expertise across the MENA region, Rani has worked on multiple multinational trials across a variety of indications and therapeutic areas. She has a Master's degree in Pharmacy, majoring in Immunopharmacology and Cancer Chemotherapy.

Email: rabraham@clintec.com

Dr Rabinder Buttar is Chief Executive Officer and Founder of ClinTec International. She holds a PhD in Immunology from the University of Strathclyde, and was awarded Doctor of the University from the University of the West of Scotland in 2010 for her 20-year contribution to life sciences. Rabinder is a Fellow of the Royal Society of Medicine and a Member of the Institute of Directors.

Email: rbuttar@clintec.com