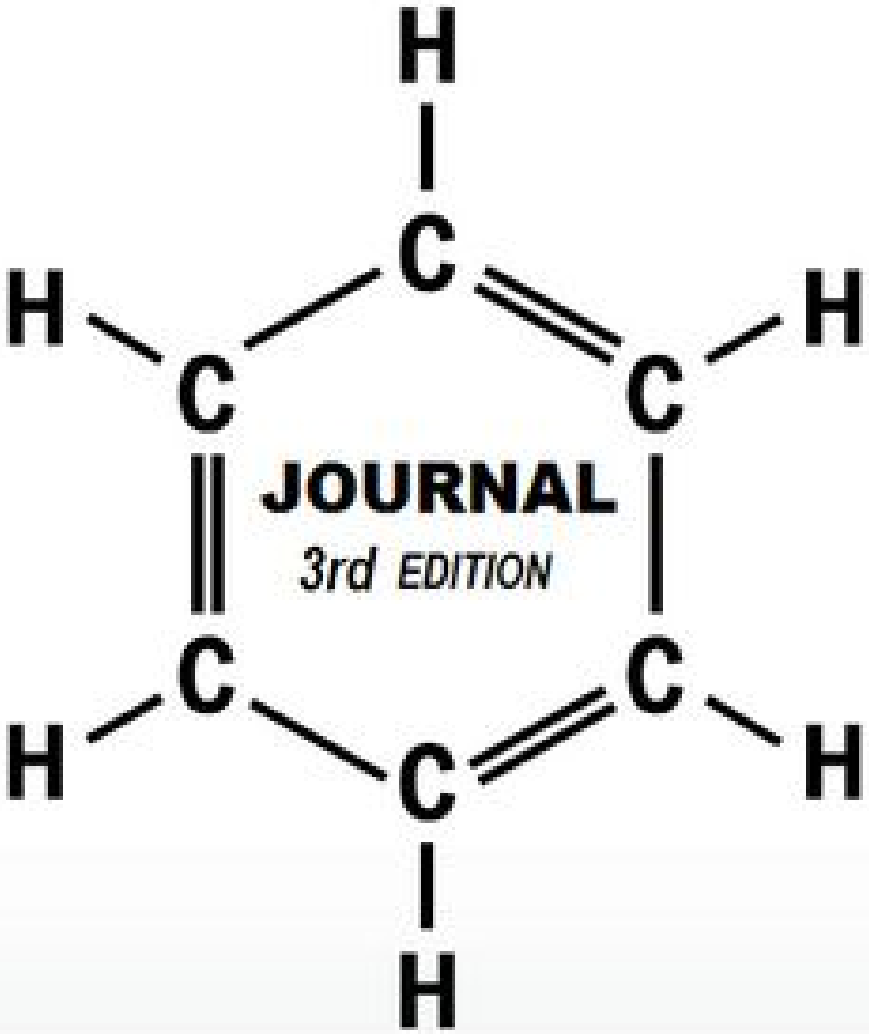
Orphan Drugs Summit

Building a Collaborative Community



Content

OPPORTUNITY OF A NEW CLASS OF BIOSIMILAR ORPHAN BIOLOGIC MEDICINES OFFERING ACCESS TO AFFORDABLE MEDICINE

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Advancement in biosimilar development and approvals EU and USA

The European Legislation for medicines has formed the basis of a regulatory pathway laid down by the European Medicines Agency (EMA) since 2004 by which biologics similar to ones already on the market can get approved with an abbreviated development programme.

By the **EMA definition** "A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA)." The US Food and Drug Administration (**FDA**) the **definition** is equivalent but more precise, namely, "A "biosimilar" is highly similar to the reference product notwithstanding minor differences in clinically inactive components and no clinically meaningful differences in terms of safety, purity and potency."

As the patents of a number of costly biologically-derived therapeutic recombinant proteins expire, among them orphan medicines, biosimilars offer an opportunity to curtail high costs of biological treatments and have consequently become increasingly attractive targets for pharmaceutical company development worldwide.

Biosimilars have substantial regulatory barriers to overcome before approval. The regulatory pathways of biosimilars require much more data than the small molecule generic medicine, due to the complexity of biological/biotechnology-derived products.

In Europe all new biologic and small molecule approvals are subject to increased mandatory pharmacovigilance surveillance and have an inverted black triangle label on the prescriber information, the SmPC and the patient information leaflet, the PIL. This requirement also applies to biosimilars and provides a safety comfort zone. EU pharmacovigilance has not identified special safety concerns or new safety signals of any of the biosimilars approved in the EU since 2006.

Nineteen biosimilar medicines have been approved in Europe (under 11 independent development programmes (grouped by colour)) **Table 1**, and one in the USA (filgastrim Zarzio) as of April 2015.

Table 1. EU Biosimilar Marketing Authorisations Landscape

(INN) substance	MA holder	EC approval	Brand name	Reference
Somatropin	Sandoz GmbH	12 Apr 2006	Omnitrope®	Genotropin®
	BioPartners GmbH[1]	24 Apr 2006[2]	Valtropin®	Humatrope®
Epoetin alfa	Sandoz GmbH	28 Aug 2007	Binocrit®	Erypo®/Eprex®
	Hexal GmbH	28 Aug 2007	Epoetin alfa HEXAL®	Erypo®/Eprex®
	Medice Arzneimittel Pütter GmbH & Co. KG	28 Aug 2007	Abseamed®	Erypo®/Eprex®
Epoetin zeta	STADA Arzneimittel GmbH	18 Dec 2007	Silapo®	Erypo®/Eprex®
	Hospira UK Ltd.	18 Dec 2007	Retacrit®	Erypo®/Eprex®
Filgrastim	Ratiopharm GmbH[2]	15 Sep 2008[3]	Ratiograstim®	Neupogen®
	Teva Generics GmbH	15 Sep 2008	TevaGrastim®	Neupogen®
	CT Arzneimittel GmbH	15 Sep 2008	Biograstim®	Neupogen®
	Sandoz GmbH	6 Feb 2009	Zarzio®	Neupogen®
	Hexal GmbH	6 Feb 2009	Filgrastim HEXAL®	Neupogen®
	Hospira UK Ltd.	8 June 2010	Nivestim®	Neupogen®
Infliximab	Celltrion (Korean)	Oct 2013	Remsima®	Remicade®
	Hospira	Oct 2013	Inflectra®	Remicade®
FSH	Teva Pharma B.V.,	Sept 2013	Ovalcap®	Gonal-f®
	Finox Biotech AG (Swiss)	Jan 2014	Bemfola®	Gonal-f®
Glargine	Elli Lilly	Sep 2014	Abasria®	Lantus®

[1] BioPartners GmbH, (an SME and virtual pharma company), source of drug substance was Korean LG Life Sciences.
[2] BioPartners GmbH Valtropin® Withdrawn 30 May 2012 (Commercial reason.) [3] Ratiopharm Filgastrim Withdrawn 20 July 2011 (commercial reasons.)

Footnote. Under EMA 2015 (June) review are etanercept (Enbrel) and infliximab (Remicade) (both Samsung Bioepis applicant), and enoxaparin sodium low MW heparin.

Though the approval of a biosimilar may demonstrate efficacy and safety to the standards of a regulatory agency, there remains a question as to whether the same level of evidence would be adequate to demonstrate the **interchangeability** of a biosimilar. Interchangeability, "changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting in any one patient" according to the European Commission in 2013, is an important consideration for clinicians in the context of biosimilars.

If interchangeability is demonstrated for a biosimilar product, the question then arises as to whether this warrants automatic substitution and hence cost sparing within the confines of acceptable risk to the patient. Many countries have introduced generic substitution for small molecule medicines, where the pharmacist is able to dispense a generic product in substitution for a branded pharmaceutical product. The Finnish Medicines Agency, FIMEA, was the first EU national authority announced on 22 May 2015 that it was recommending the

interchangeability of biosimilars for their reference biological.

Currently, the majority of countries do not permit **automatic substitution** of biosimilars, largely based on the fact that biosimilars are 'similar' and not identical to the reference product. However, this is likely to change in future for example the FDA 'Purple Book' listing is a publication of decisions on biosimilar approval and if they can be substituted. By substitution is meant the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

Some orphan biosimilars in development

Orphans that are being currently developed at the clinical stage include palivizumab, eculizumab, taliglucerase alfa, interferon beta, Factor VIIa and rituximab.

Palivizumab, is a recombinant humanised monoclonal antibody, originator product Synagis. Synagis is indicated for the *prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease*.

Eculizumab is a humanised monoclonal (IgG2/4κ) antibody, originator product Soliris, indicated in the EU for *Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions*. And *Atypical haemolytic uremic syndrome (aHUS).* In the US Soliris is indicated for the "treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis." And the *"treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy."*

Taliglucerase alfa, Elelyso, is approved only by the FDA and not EMA for the treatment of Type 1 Gaucher Disease.

Interferon beta (Avonex or Rebif) is indicated in relapsing multiple sclerosis and in a single demyelinating event with an active inflammatory process.

Factor VIIa, NovoSeven, is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures.

Rituximab, MabThera in the EU or Rituxan in the US, has orphan indications of chronic lymphocytic leukaemia and severe, active granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis, also rare but non-orphan (that is, non-designated) indication of stage III-IV follicular lymphoma, follicular lymphoma and CD20 positive diffuse large B cell non-Hodgkin's lymphoma.

Development programmes of orphan biosimilars

All these orphans under biosimilar development are conducting extensive campaigns of comparative studies against the originator medicine in a stepwise Quality-Nonclinical-Clinical fashion. This work began with many comparative physicochemical, biophysical, bioanalytical and biological testing studies, then animal pharmacology and toxicology, proceeding finally to comparative bioavailability in man (determines exposure and effect of the body on the biologic), and pharmacodynamics in man (how the drug acts on the body) studies, and finally a comparative clinical phase 3 safety.

Developing all biosimilars is always complicated and risky but has additional challenges for orphan medicines. There are many barriers to development such as the difficulty of recruiting patients and ethics, and sparsity of supplies of originator medicine as comparative reference product. The regulatory burden is substantial in the EU and the US, and the assessment of the final data packages submitted to the EMA as a Marketing Authorisation is closely scrutinised by 28 EU authorities.

Conclusion

Due to their uniqueness and their market exclusitivity once approved by the FDA and EMA, orphan medicines tend to be costly treatments. Affordability and market accessibility will fulfil unmet needs in all European countries and the US once lower cost biosimilar versions of the originators orphan are approved. Orphans have market and data protection exclusivity, and sometimes patent protection too, so that entry of the new class of medicines of orphan biosimilars will be gradual.

Orphan mice: a case study on how rare disease patient organizations can make it easier to develop new orphan drugs.

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The challenge of choosing an orphan indication.

When it comes to developing an orphan drug, there are between 6000 and 8000 rare diseases to choose from. For a drug developer, the decision to pursue one of these rare diseases as an orphan indication is often a complex one, and the answer is not always the one with the largest market size. Scientific reasons such as knowing the underlying genetic cause of the disease, the availability of animal models, and the existence of well-defined clinical endpoints, also play a major role in the decision by making the development pathway easier for some of the rare diseases.

At the current rate of approval of orphan drugs, it could take hundreds of years for many of the rare diseases to have a drug approved. This situation has led to a patient revolution, where rare disease patients and their loved ones get organized to try to beat the odds, influence the field and accelerate the development of orphan drugs. Well-organized patient groups have a unique understanding of patient needs and can facilitate clinical data gathering and patient recruitment, making their field more attractive to drug developers.

Patient groups also have a global view of the field that allows them to identify the key challenges and opportunities. In our conversations with researchers and drug developers we identified disease mouse models as a critical resource for drug discovery and development. Having access to a suitable mouse model makes it possible for drug developers to de-risk their programs and prioritize orphan indications prior to clinical trials, directly influencing the number of trials for that particular rare disease. Therefore when faced with a choice between multiple potential orphan indications for a particular compound, the one with the best-characterized and more easily accessible mouse model is much more likely to come at the top of the list.

When the mouse model is a bottleneck.

Most rare diseases have a genetic cause. This makes them ideally suited to be modeled in mice by genetically modifying them to carry the same mutations that cause the disease in humans. This is indeed the case of Dravet syndrome, a rare disease where most patients carry mutations in a gene encoding for a neuronal sodium channel, the Scn1a gene [1]. There are seven different

strains of Dravet syndrome mouse models generated by academic groups that either lack a portion of Scn1a (knock-out mice) or carry mutations in the gene (knock-in mice) [2-8]. All seven recapitulate the clinical phenotype, characterized by a very aggressive form of epilepsy that is aggravated by fever, cognitive and behavioral problems, as well as an increased risk for sudden death [1-8].

The high degree of conservation of the neuronal sodium channel and its function in the brain makes Dravet syndrome a lucky disease when it comes to being modeled in animals. The field faced, however, a bottleneck due to limited access to the existing Dravet mice. When we begun talking to researchers and drug developers we learned about multiple therapeutic programs that were not being tested in Dravet syndrome, even though they look promising, because of not having access to the mouse model. This included new anti-epileptic drugs, compounds with a potential to treat the non-epileptic aspects of the syndrome for which there are currently no treatments, and even projects using gene therapy and cell therapy. All of these groups and companies had been unable to negotiate access to the existing Dravet mice under acceptable terms. We also failed at trying to get some of these mice hosted and distributed through an open-access repository.

As a patient organization we understood it was not the responsibility of any particular academic group or company to create a resource that would make it easier for everyone else to also work in that field. We also understood that was precisely the value that patient groups could bring to the community: having a view of the entire field and strategically removing the bottlenecks.

That is when we embarked on the generation of the eighth mouse model for Dravet syndrome.

Creating an open-access mouse model for Dravet syndrome.

In 2013 we initiated the design and generation of an open-access mouse model for Dravet syndrome that is now available for everyone around the world [9].

To do that, we partnered with the Jackson Laboratory, a nonprofit organization expert in the creation of disease mouse models that manages the largest mouse repository in the world. We designed a new strain of Scn1a mutant mice that would not only be shared with the entire community, but would also address some disease-specific challenges that due to the severity of the phenotype made it difficult to work with most of the previous Dravet models. These new mice are in the process of being characterized and can already be requested through the Jackson Laboratory repository, joining another Dravet mouse that became also available recently.

Beyond the scientific aspects, generating these mice represented an opportunity for us as a patient organization to directly influence the field by being an active part of it. Hundreds of families in the Dravet syndrome community came together to finance the generation of the open-access Dravet mice through a crowdfunding campaign. Joining forces allowed us to remove this key bottleneck and hopefully accelerate the development of orphan drugs for Dravet syndrome. And we trust we are in the right path - the first request from a pharma company to have access to the new mice came in just forty minutes after we announced their launch.

The role of impatient patient organizations.

Rare disease patient organizations can and want to contribute to developing new drugs for their diseases as active partners. In our organization we refer to them as impatient patient organizations. Developing research tools, coordinating and providing a focus to academic research, partnering with drug developers and creating patient registries and networks, are just some of the many ways in which impatient patient organizations can accelerate the development of new drugs for their disease.

Traditionally, patient organizations focused on raising funds, and relied on individual academic groups to propose the projects that they want to pursue and on external advisors to select projects for funding based on their scientific merit. This researcher-initiated, or bottom-up, funding model means the most important decisions – research directions and how to spend the funding – are made by scientists external to the organization. Today, most successful patient organizations regardless of their size have internalized these decisions. The result is a strategic top-down model where the organization identifies roadblocks along the therapeutic development pipeline and targets their funding to these critical gaps, ensuring that their investments translate into benefits for patients.

We advise patient groups to sit down with scientists and drug developers and ask them about what is slowing their progress and what will help them move forward. We also advise them not to stop at the “we need more money” answer and to look for broader emerging themes that will give them an idea of where the field bottlenecks are. Free of the pressure to publish for career advancement of academia, and from the need to grow the bottom line of private companies, nonprofit foundations can play a strategic role in getting the entire field forward. And it is only through informed strategic investments that this will happen.

In the case of Dravet syndrome, a key bottleneck was the access to the mouse model. Today, the open-access mice will make it easier to develop specific therapies for Dravet syndrome and to repurpose existing or previously failed therapies for which companies are now facing the challenge of choosing new potential orphan indications.

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‘Rare Disease Groups: Scaling Up From The Kitchen Table’

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The Rare Disease Field

There are 7000 rare diseases, affecting 350 million people worldwide. Together, they would form the third most populous country on the planet. Within the UK, these conditions collectively affect 6% of the population, approximately 3.5 million people.[1]

Yet these conditions are neglected due to the small patient numbers of each individual disease. Of the 7,000 conditions, only 200 have licensed treatments. Patients are often left with low health outcomes, suffering from debilitating diseases, kept from work or being active due to complications. The unmet need is so huge and still so unrecognised that many people call these rare diseases by the name of ‘orphan diseases’: orphaned from society, orphaned from the medical profession, orphaned from research.

There is a chronic lack of support for rare diseases among the medical profession. Patients experience a diagnosis odyssey, on average spending 8 years visiting 10 specialists to receive an accurate diagnosis.[2] Even once they have been diagnosed, they face an uphill struggle. In a 2013 study by Shire, 62% of patients stated they needed to provide their healthcare professionals with information on their disease.[3]

As a result, patients often turn to patient groups as their main source of information, of community, of empathy, and of support. Researchers also report that patient groups are their first port of call when preparing research to develop treatments and clinical trials. However, Global Genes Project has found that 50% of the thousands of rare diseases do not even have a disease-specific group to turn to.[4] To access the challenges facing rare disease patient groups, Findacure conducted multiple surveys with relevant stakeholders throughout 2014 and in early 2015.

Situation for Patient Groups

Our research found that where patient groups do exist, they usually come in the form of ‘kitchen-table’ organisations, set up by people living with rare conditions or those who have an affected family member.

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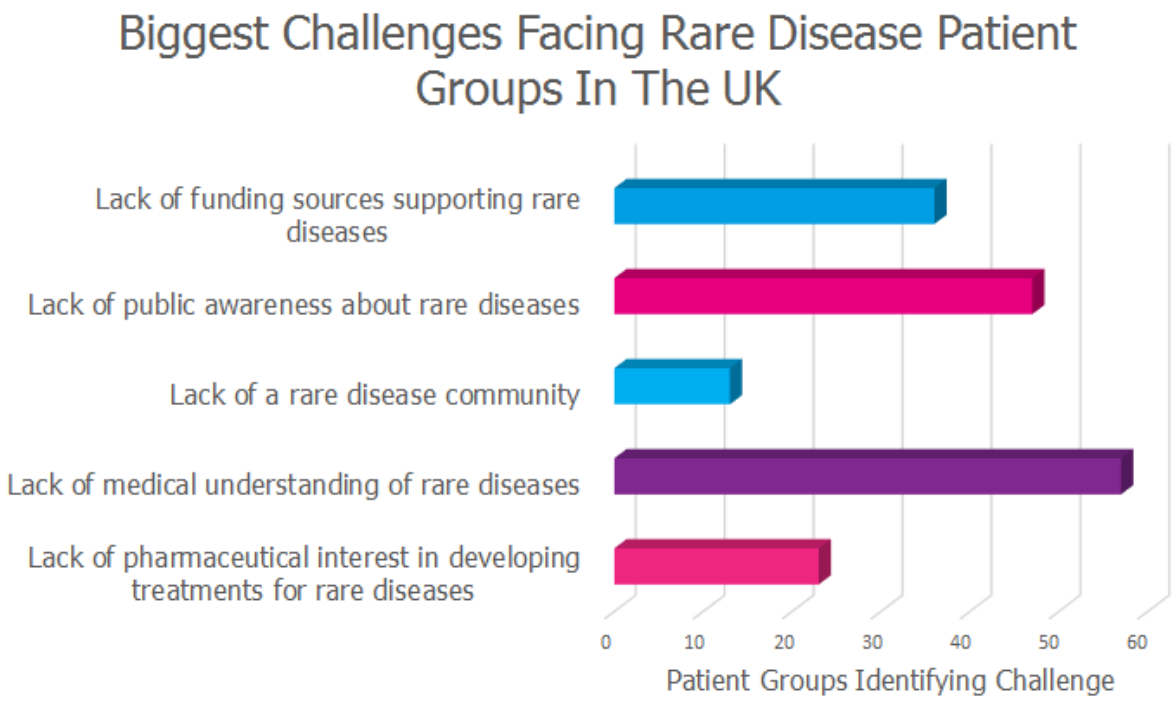
These patients and advocates face significant barriers and challenges when attempting to establish patient groups.[5]



Those looking to establish patient groups face the major difficulty of a lack of medical understanding of their condition. This hinders their ability to identify other patients, build a community, and offer accurate health information to patients. In addition, there is a lack of awareness and consequently a lack of funding for running their organisation.

As a result, these organisations are very small, heavily relying on volunteers and have very few full time members of staff. On average, patient groups have eight people involved, with 71% as volunteers. This paints a picture of a group comprised of three members of staff and five volunteers attempting to meet patient support needs and promote research.[6] This suggests that although these groups are innovative and entrepreneurial, they are running on a very small scale, and likely do not have the professional capacity to fulfil the multiple services expected of patient groups.

To identify how best to meet the needs of these groups, we conducted a further survey with our beneficiaries. 98% of the respondents[7] believed it is critical to provide training to rare disease patient groups in order to meet the challenges they face. It was argued that patients and family members who establish patient groups transfer their skills with no previous experience in the third sector or in healthcare. There is little help available for these people, and they are the very people most in need of a support group.

[5] Results of feedback surveys filled out by 74 patients, advocates, and patient group representatives throughout 2014 and early 2015. Respondents were asked to select all the challenges they experienced setting up and/or running patient groups.
[6] Results of survey conducted in January 2015 with 18 additional patient groups.
[7] We received 41 responses from patients, carers, patient group representatives, clinicians, pharmaceutical representatives, and researchers.

Meeting Patient Group Need

Findacure aims to meet that need through innovative programmes for rare disease patients and advocates. We aim to unite fragmented and isolated patients into a concerted effort to take control of their diseases and meet the challenges of medical research and drug development. In undertaking this mission, Findacure follows in the footsteps of William Bateson, the father of modern genetics, who reminded us that it is worthwhile to 'treasure our exceptions'.

Since 2013, Findacure has been building the rare disease community to drive research and develop treatments. We organise training workshops in areas such as fundraising, how to interact with academics, patient identification and recruitment. In 2014 we organised four workshops, attended by 124 patient group delegates representing more than 62,550 patients across the UK. In feedback, 93% agreed the workshops were relevant to their needs, with 95% reporting increased knowledge and skills.

We launched a pilot peer mentoring scheme in late 2014, recruiting 16 patient groups and expert mentors. As part of this scheme, new patient groups are linked to experienced organisations and experts to nurture the development of key skills and knowledge. Feedback from both mentors and mentees has been incredibly positive, with real progress being achieved in a short period of time. Several mentees have stressed having a mentor has empowered them and given them the confidence to develop their patient groups and push for patient rights.

Our most recent project is an easy-to-navigate online resource portal, where patients and advocates can acquire the skills and access tools needed to run their patient groups. We have worked closely with volunteers from established patient communities, international rare disease advocacy organisations, and academic institutions to develop credible and accurate guides for new patient groups. Patients and advocates are able to access free information, connect through moderated forums, and contribute to increasing the collective knowledge of the rare disease community.

By supporting patient groups with our empowerment programmes, we aim to increase the development of individual patient groups, improve support capability, deliver better health outcomes for thousands of patients around the country, diminish stress and isolation for group leaders, and ultimately offer hope by driving research into treatments. In addition, we are working to build the community of rare disease stakeholders, to enable cross-condition collaboration and strengthen the collective voice of these long overlooked conditions.

Disclaimer: this article was originally published on PharmaPhorum in April 2015, available at http://www.pharmaphorum.com/articles/rare-disease-groups-scaling-up-from-the-kitchen-table