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EXPERT OPINION

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Working collaboratively and internationally to improve the lives of people affected by rare disease

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This month, Expert Opinion on Orphan Drugs has the pleasure of publishing a long-awaited themed issue 'Rare diseases –Detection, Treatment, Care and Research'. The issue is published in conjunction with EURORDIS – the European Organisation for Rare Diseases, and NORD – the National Organization for Rare Disorders. Both of these organisations work with rare disease patient groups providing advocacy, education and research services for their members.

Mary Dunkle is Vice President of Communications of the National Organization for Rare Disorders (NORD), with responsibility for NORD's communications and educational programs. Before joining NORD in 1999, she was assistant director of public relations for The Pennsylvania State University and Director of Public Relations for Danbury (Connecticut) Hospital.

Maria Mavris joined European Organisation for Rare Diseases (EURORDIS) in 2008 in the capacity of Drug Development Programme Manager and from 2012 to 2014 as Director of Therapeutic Development.

After obtaining a PhD in Molecular Microbiology from The University of Adelaide, Australia, she continued her postdoctoral studies at the Institut Pasteur, Paris, and the Ecole Veterinaire in Maison-Alfort. Maria was previously EURORDIS observer on the Committee for Orphan Medicinal Products at the European Medicines Agency (EMA). She was also responsible for coordinating the group of high-level EURORDIS representatives/volunteers who sit on the various scientific committees at EMA, known as the Therapeutic Action Group (TAG). Maria was also implicated in activities of the Scientific Advice Working Party (SAWP) where she was responsible for the identification of patients' representatives to participate in protocol assistance and had a supportive role for EURORDIS representatives in the Patients' and Consumers' Working Party. Her current role in the EMA continues and expands on these activities from the EMA perspective. In order to train and support patients' representatives in regulatory activities, she also co-organized the EURORDIS Summer School.

Since September 2014, she is on secondment to the EMA. Sharing her experience gained over her 6 years with EURORDIS, she now strives to improve the quality of work and communication with stakeholders in the Agency's new department dedicated to the interaction with patients and healthcare professionals.

What is the purpose of this themed issue and how did it first come about?

MM The idea for this themed issue came about in 2008 when I first joined EURORDIS. As my background was primarily as a research scientist I thought that rare diseases were a big research area that fundamental scientists didn't really have

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enough of an idea about. A lot of fundamental research is conducted into rare diseases and I think that to raise awareness by bringing in the different aspects of policy, regulation and the daily lives of patients living with the disease to many of these scientists study would be very handy. Also, due to the geographical isolation of rare disease patients, a partnership and relationship with NORD and internationally, which reaches out for collaboration and to raise awareness is very important and was the main idea behind the project.

Would this be the first time that EUORODIS and NORD have worked together?

MD Not at all! NORD and EURORDIS signed a memorandum of understanding in 2009 and that formalized a longstanding partnership between the two organisations. The purpose of the memorandum was to connect patients and patient organisations in the USA and Europe, particularly focusing on areas related to education, awareness, advocacy and public policy. As part of that memorandum we talked about doing certain specific projects together, such as NORD bringing Rare Disease Day, which EURORDIS had started in 2008 in Europe, to the USA. I believe that this current project grew out of that partnership too. The partnership goes back to the very beginning – I've been with NORD since 1999 and I remember hearing NORD's founder and first president, Abbey Meyers, talk about sharing information about the early days of NORD with the patient leaders who ultimately established EURORDIS. There is a strong history of collaboration between the two organisations. I remember when the EU regulation was enacted and how exciting it was for us here at NORD because it was one of the first times we really realised that this – the rare disease community – was becoming an international movement and was gaining momentum. We were excited for the opportunities that would come to work together with our international partners.

Do you have plans for future years or other projects that you will work on together?

MM As Mary nicely outlined, rare disease awareness has become quite an international collaboration so we are involved with NORD on many different projects, such as Rare Diseases International which EURORDIS will give information about in the coming weeks, but also the International Rare Disease Research Consortium IRDiRC. We are involved with other partners as well, such as the Canadian Organisation for Rare Disorders, and as Mary said Rare Disease Day has become an international event, growing from 18 countries in 2008 to more than 80 this year. I think rare diseases are now a much bigger international collaborative partnership. The communication, dialogue and collaboration will continue.

How did the Orphan Drug Act in the US (1983) and then the EU Regulation on Orphan Medicinal Products of 1999 improve the prospects for rare disease patients?

MD In the USA, in the decade before 1983 there were only 10 products for rare diseases developed by the pharmaceutical industry. There really was a great need for some sort of federal incentive to encourage the development of treatments and make it possible for the companies to recover their investment. Patient organisations in the USA did play a very crucial role in getting the orphan drug act enacted, they went and testified before Congress and told their stories. They worked with the media; there was a very popular TV show called Quincy about a medical examiner – they connected with the star of the show who was very supportive and eventually went and testified on Capitol Hill on their behalf. But in the years since 1983, I think it has been considered a very successful piece of legislation and in just going by the numbers; there have been more than 3000 orphan designations and approximately 470 orphan approvals. These include some truly life-saving and life-changing products, which are very important for patients.

Henry Waxman, who is still in Congress and will be retiring at the end of this year, was the principal author of the Orphan Drug Act. He is coming as one of the keynote speakers to our conference next week (Rare Diseases and Orphan Products Breakthrough Summit, 21st –22nd October, 2014) when he will be talking about the Orphan Drug Act, its importance over the years, what he sees as the future for the Act and in general on the legislative front. In a book he wrote a few years ago, he identified the Orphan Drug Act as one of the achievements he considers the most important in his career. At NORD, we see the impact of it every day on the lives of patients.

MM Absolutely, I think our experiences have also paralleled that of the USA in some aspects, but only a few years later. The number of products that had been developed for rare diseases prior to the orphan drug regulation was very low compared to what we have seen since the implementation of the regulation. There are incentives as Mary mentioned as well, in this case fee reductions and fee waivers, especially for small- to medium-sized enterprises. Research coming out of the EMA has shown that most of the orphan products are developed by these small- to medium-sized enterprise and the fee reductions/waivers are critical to them. There is also of course the market exclusivity – so protection from the same type of products for their indication once the product is on the market is very important. As Mary also mentioned, patients were extremely instrumental in the orphan drug regulation in the EU. This is also demonstrated by the fact that in the EU – where there is a committee that makes a decision on orphan designations made up of one representative from each member state – there are also three patient

representatives that are included as full voting members on this committee. They are present at the monthly committee meetings, and this shows the commitment and importance of the patient voice in regulatory decision making in Europe. The Committee for Orphan Medicinal Products (COMP) was the second committee to be formed at the EMA, following the Committee for Human Medicinal Products, and since then there have been three subsequent committees with patients involved as full members as well. I think the voice of patients in all of this legislations has been quite clear and they are certainly well heard.

So you mention the patients and the patient organisations, what are the current estimations of the total numbers of rare diseases and how does this compare to the number of patient organisations that you engage with?

MD The number of diseases has continued to go up over the years. We use the numbers from the National Institutes of Health (NIH) in the USA, and when I first joined NORD in the late 1990s, NIH was saying that there were 5000 diseases considered rare and that they affected 20 million Americans. That number has continued to go up over the years so that today NIH has identified more than 7000 diseases and these are believed to affect 30 million Americans.

MM In Europe as well, because the number is a moving target, at EURORDIS we say that there is greater than 6000 rare diseases. If you look on the Orphanet website (www.orpha.net) then today there are 6760. These diseases are diagnosed, and then due to the genetic testing and information we now have they might be reclassified, so that one new disease might mean another disease is reassigned into a different group – a bit of a moving target but we always go with over 6000.

How frequently are patient groups launching and joining your respective organisations?

MD NORD formally has 220 patient organisation members, and these are primarily disease-specific organisations or umbrella groups for small classes of related diseases. We also work with many other organisations – there is a database on our website where people can type in their disease and find an organisation – I believe we have approximately 1000 organisations for people with specific diseases. We may work with these to help them to become a member of NORD by becoming a 501C3 non-profit organisation. For smaller groups or ones organised for specific purposes, it might not make sense to go through these types of processes but that does not mean that we do not work with them. For instance, we frequently partner with other organisations that are not necessarily members of NORD on specific public policies where our interests coincide. We also help patients to form organisations if there is not one for their disease; we actually launched an organisation yesterday for an extremely rare disease that previously had no patient organisation. We will work with them and nurture them until they are able to stand on their own and fly away from the nest to become a free-standing organisation. We also work with small or new organisations that are trying to grow and we help them to learn best practices; we connect them with other members so that they can learn from each other and share information.

MM We also have currently over 630 member organisations representing 59 countries. We do not only have European countries, but have member organisations from other countries as well, for example Australia and Uruguay. These organisations represent over 4000 different diseases and some of these will be grouped together as umbrella organisations. We have also encouraged and supported national alliances as well and once a year they get together and have exchanges of information. We have membership meetings where groups can learn from each other – similar to NORD we encourage organisations to form to get people suffering from the same disease together. Another thing we have done is launch an online patient community– RareConnect (https://www.rareconnect.org/) – which has tackled the issues of geographical dispersion and language barrier for many rare disease patients.

How has the role of patient organisations evolved over the years?

MD The role of patient organisations has always been tremendously important in this process. I do think it has evolved as the needs and situations have changed. I think initially the patients were so isolated and so in need of coming together and learning how to work together that the early patient organisations were really focused more on just connecting patients and families. They helped them to not feel so alone and to understand that they could support each other, while also providing some basic patient-family services such as helping people find a physician. What I have really seen in recent years is a more active, more proactive involvement in both research and the regulatory process. Some of the ways that we see that happening in the USA are through the NIH Rare Diseases Clinical Research Network, which has just announced a new round of funding this week. Through this, they will be funding research on more than 200 rare diseases and working with 90 patient organisations. One of the things that is really wonderful and unique about this Rare Disease Clinical Research Network is that it requires the researchers to involve the disease-specific patient organisations in the process and to work very closely with them in designing protocols and really listening to them to understand the patient needs throughout the process. We see this happening on many fronts; we're very happy that NIH is encouraging this and we are seeing the patient organisations stepping forward and

finding ways to become more involved in the process. On the regulatory front, FDA has opened its doors to patients in recent years. There is currently an initiative called Patient-Focused Drug Development at FDA, which grew out of legislation enacted in 2012. It involves a series of public meetings and NORD helps to prepare the patient groups to assure that their voices are heard. This helps the FDA to better understand the patient needs and patient thoughts regarding topics such as benefit-risk. I think particularly in those two areas – research and regulatory – I see the patient organisations taking a very proactive role now. I also think they're more connected internationally. We have been creating a membership guide, which provides brief summaries of our member organisations, their diseases, their particular challenges and their program offerings; as I've been reading this I have been struck by how many of them mention working with international disease-specific partner organisations. I think that that is a wonderful thing for patients to minimize, as Maria has mentioned, the geographic isolation of these patients. To be thinking globally is so important for all of us.

MM I can only really echo the same things. The traditional definition of patient organisations is exactly that sort of support group, identifying and understanding more about the disease. I think there is always a place for those roles and they are still extremely important. It then depends on the type of group that EURORDIS and NORD are. We have more of a political role of raising awareness, advocating at the EU level, in the USA and now internationally. As Mary also said, patient groups have become more involved in research. We completed a survey, now 4 years old (http://www.eurordis.org/content/survey-patient-groups-research), showing how patients were involved in research by collecting funds and funding specific things such as post-doctoral scientists, equipment, thus involving them in directing the area of research both fundamental and more importantly the clinical arena. Patients are involved in regulation at the European level through participation on several committees. They are consulted and included on many guideline documents at the EMA. This really points to a growing awareness and willingness to be involved and involve them. All of this has resulted in the empowerment of the patient organisation.

We have touched on this already, but in what ways does each of your individual groups support these patient organisations?

MD In advocacy and public policy we are their representative in Washington DC. For example, tomorrow we are hosting a briefing in the House of Representatives on the topic of expanded access to investigational therapies. Several of our member organisations will be there and will participate. We also work with them in providing education and resources for patients and families. We are becoming increasingly involved in physician & health professional education – partly because it has become apparent in recent years that getting an accurate diagnosis remains a problem for patients. We help in research – NORD has a research program that is made possible by our medical advisory committee, a wonderful group of rare disease medical experts, mostly from medical schools around the country who volunteer their time and expertise to help us. We are able to do this as a service to small patient organisations that fundraise but cannot administer a grant. Also, we provide patient assistance programs to help patients access medication that their insurance would not cover or that they cannot afford.

MM In EURORDIS we have conducted surveys of patients in Europe, which can be used as advocacy tools to assist them when they go to their member state level to advocate for better diagnosis, better research, better access to care (http://www.eurordis.org/publication/voice-12000-patients). EURORDIS consults its members and submits comments whenever there is a consultation, for example the latest was the Regulation on Clinical Trials; we consulted with all of our members and brought their comments up to that level in Brussels for discussion in this revision. Similarly we offer training as well – the EURORDIS Summer School. This is an excellent training program where we introduce patients to the concepts behind medicines development and the EU regulatory processes. We are also involved in another training program for patients, not only for rare disease patients, in this case which is the European Patients' Academy on Therapeutic Innovation (EUPATI). We also bring the patient groups together, support them through membership and newsletters to keep them informed of what's going on in rare diseases globally; support and information of our members is a key role.

Moving onto the patients themselves, what are some of the biggest current challenges of living with a rare disease?

MD Certainly diagnosis, getting a timely accurate diagnosis. This is by no means a scientific study but we have posted questions related to this a few times over the past few years on our social media and we are just struck by the intensity and number of responses about the length of time it is still taking for many people to be correctly diagnosed. We are looking for ways to get more involved in awareness and physician education. Too few treatments, too little research although that is certainly improving are also issues, with much of the research funding for the very rare diseases still coming from patient organisations. Difficulty finding a medical expert and I think even though the communication tools of today have made a huge difference in this, there is still a feeling of isolation when you have a disease that other people are not familiar with and do not understand.

MM That's right, from our perspective as well, the big surveys that we completed have been published under the title 'The Voice of 12,000 Patients' focused on diagnosis, treatment and access to care and as Mary said, sometimes it will

take up 10 or 15 years to get the right diagnosis for a disease. I think you will see this in the patient stories; they are diagnosed with some sort of psychiatric disorders first because it is thought that their symptoms are 'imagined' and the consequences are extremely difficult; unfortunately this is still ongoing. People who are newly diagnosed might have gone through something like this, a long process without access to expertise. Once you are diagnosed, it is not necessarily the case there is going to be a product available for you. Even if something available that works for your disease in general it might not work specifically for you as rare diseases are also quite heterogeneous. Access to that product if it does exist – having reimbursement and timely access – all of these issues are still ongoing and we are still addressing them. We are working with the European Union on ways of earlier access, such as through adaptive licensing trying to get the product to the patient. I think the challenges are still there with a lot of work left to do.

As we move forward, are there any particular trends that you see coming in rare disease research and across the rare disease community?

MM For me, an overarching thing that I see and hope for is a more of an international profile and more awareness on a global level with respect to all aspects; whether it is fundamental research or the development of more Centres of Expertise in order for patients to get the care, treatment and diagnosis that they need. I think again, the growing awareness of rare diseases on an international level is positive.

MD I completely agree with that. When you think about some of these terribly rare diseases where there may be just hundreds or a few thousand patients around the world, it is so important to work on behalf of those people together as a group. In general it is a very exciting and hopeful time to be working in this field. Looking back over my 15 years with NORD; this period in time feels very different from the earlier years. The science of rare diseases is advancing very rapidly, and there are many more academic institutions and companies involved in research on these diseases now. It is exciting to see this awakening of interest, and we all hope that it leads to important advances for patients.

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