The Rare Disease Gazette

Conversations with the world's experts about rare disease

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WORKING THE REGULATORY ANGLE

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Editorial

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Rare Disease Detection: Rare But Not Alone

The plight of patients with rare diseases is a critical unmet need of patients in healthcare. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public.

In 2023, these webinars focused on advocacy in rare disease. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine

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DON'T MISS!

The Conversation

Experts of the month: Erika Berg, Ph.D, hosts a conversation with world's experts about Advocacy in rare disease: Working the regulatory angle

The Conversation

Experts of the month

Simone Boselli *(Eurodis, Brussels, Belgium)*
Karin Hoelzer, D.V.M., Ph.D. *(National Organization for Rare Disorders, Washington, DC)*
Julia Jenkins *(EveryLifeFoundation, Washington, DC)*
Stuart Portman, M.P.H. *(U.S. Senate Committee on Finance, Washington, DC)*

Erika Gebel Berg, Ph.D. *(Science/AAAS, Washington, DC; moderator)*

Erica Berg (*host*):
Hello everyone, and welcome to the fourth webinar in our 2023 Science series on advocacy in rare disease entitled "Working the Regulatory Angle". I am Erika Berg, Director and Senior Editor for Custom Publishing at Science, and I will be the moderator for this discussion. This is our third year exploring the challenges and successes in the rare diseases field. In previous years, our panelists have discussed diagnosis and detection, testing, research hurdles and opportunities, and mental health challenges. This year we have shifted our focus to advocacy. We have learned from advocacy experts from inside and outside the rare disease space covering such topics as crafting a compelling public narrative and securing funding. Today we will be having a conversation about how advocates can influence regulation. Across the globe, regulatory landscapes are notoriously complex and difficult to navigate. Yet laws regarding human health can literally be a matter of life and death.

Diagnosis and treatment remain challenging for the more than 7000 rare diseases impacting 350 million people worldwide. Policy makers set research funding agendas and make laws that can tip the balance on whether drug makers will pursue treatments for rare disease and make them accessible. Advocates play a critical role in getting the attention of lawmakers and making the case that regulations shape healthcare outcomes for people with rare disease. I would now like to take the opportunity to welcome a star-studded panel today. I will give each of them a chance to say hello and to introduce themselves.

Karin Hoelzer:
Hello, everyone. I am Karin Hoelzer and by training I am an infectious disease epidemiologist and a veterinarian. Earlier in my career, I spent a fair amount of time at the US Food and Drug Administration (FDA) and then in various health policy roles in Washington DC. Currently, I serve as the Director of Policy and Regulatory Affairs for the National Organization for Rare Disorders (NORD), where my job is to make sure that we elevate the patient's voice in government at every level. I am very excited to be here today.

Julia Jenkins:
My name is Julia Jenkins. I am the Executive Director at the EveryLife Foundation for Rare Diseases. My background is in grassroots organizing and government relations. At the EveryLife Foundation, we are a policy and advocacy organization. Much of what we do is helping patients navigate the regulatory challenges, both through the FDA and through the access environment.

Simone Boselli:
My name is Simone Boselli. I am the Public Affairs Director at EURORDIS-Rare Diseases Europe, which is the largest umbrella organization of patient organizations working to promote the rights of people living with rare diseases with the aspiration of improving their lives across borders. We are an organization working in over 70 countries with over 2500 members spanning across the globe. My role here is to work in advocacy and policy building, specifically with the European institutions and focusing primarily on research, development, authorization and accessibility of therapies for people living with rare diseases.

Stuart Portman:
My name is Stuart Portman. I serve as Senior Health Policy Advisor on the Senate Finance Committee for ranking member Mike Crapo. Previously, I worked on the Senate Finance Committee for Senator Chuck Grassley, and before that for Senator Orrin Hatch, who I had the pleasure of serving as his health advisor on all issues related to the FDA and rare diseases. Since 2017, I have handled all issues related to Medicaid and the Children's Health Insurance Program, which has provided a window into many of the payer discussions as it relates to rare diseases.

Erica Berg (*host*):
Thank you. I am going to put my first question to Karin. What are the rare disease issues that are impacted by regulation?

Karin Hoelzer:
In a nutshell, regulation impacts pretty much everything that we do in the rare disease space. The National Organization for Rare Disorders (NORD) was actually founded 40 years ago because a rare disease mom would not take no for an answer. The drug company that was making the drug that helped her son navigate his Tourette syndrome stopped making the drug because it was not economically feasible. As she was trying to find a way to change that, she started to realize that this was true for too many patients and families. The rare disease community came together and worked with Congress to pass a law to really change that and create more incentives to bring orphan drugs to market. We still have a huge unmet need, but we have been quite successful. Today, about half of all FDA-approved drugs are for orphan diseases. Now that we have more orphan products available, we see that coverage and reimbursement are becoming a bigger issue. We probably spend about half of our time advocating for appropriate access to these therapies. We have also started to realize that many of our patient groups want to be engaged in research but there are numerous regulations related to research funding and the conduct of research. So we work, for instance, through an FDA-funded research grant with the Critical Path Institute to help our community navigate this regulatory landscape and really bring the patient voice and the patient experience into research and to help create data. Ultimately, we hope to bring therapies to the more than 7000 rare diseases, many of whom currently do not have any treatments.

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see that coverage and reimbursement are becoming a bigger issue."

Erica Berg (*host*):
Julia, what are some of the unique challenges that advocates face when working with regulatory agencies in the context of rare diseases?

Julia Jenkins:
One of the biggest challenges for rare disease patients is that everything falls in the backpack of patients. NORD was founded by a parent advocate. Every drug that has been developed and approved in the rare disease space is likely due to a patient or their family doing the work in the very beginning; by de-risking it, finding the scientists and funding the scientists. When you get diagnosed with cancer, there are a ton of cancer organizations that can support you. Whereas in the rare disease space, if you are lucky enough to get your rare disease diagnosis, it usually falls on the individual patient to find their community, to start their own organization and to fund their research. That translates into these really small organizations that have to fundraise and navigate these really complex regulatory pathways and work with companies to bring patients to the trial and to design trials. A lot of this falls on the patients to become experts in their diseases and they have done so. Our patient community is amazing. To address the question of how they navigate the regulatory process, I think the FDA has really done an amazing job at working to improve patient engagement and patient-focused drug development at the FDA. On the access side, I think we are still in the beginning steps of that. When we started the foundation 15 years ago, we were not really working on access issues because there were not a lot of treatments to get access to. It has been a really exciting time to see so many drugs being developed for rare diseases that now these access barriers are becoming such an issue for our community, so it is going to take another big patient movement to help navigate the access environment. Back in 2012 it was the advocacy efforts around patient-focused drug development that became law in Prescription Drug User Fee Act (PDUFA) V, of the Food and Drug Administration Safety and Innovation Act (FDASIA) legislation, which I think Stuart worked on. That was really codifying in the statute that the patients could work on patient-focused drug development and requiring companies and the FDA to include them. We are probably going to need something like that in the future to help navigate the access environment.

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Karin Hoelzer:
I think one other challenge that Julia has already alluded to, is that regulatory issues are complex and they take a long time. So one of the things that we at NORD have really prioritized from the beginning is to provide the education and training and the background that patients need to navigate the regulatory process. We currently have, for instance, an FDA grant to develop advanced educational materials related to FDA regulatory issues for patients so that patients can be better informed and can more easily participate in the complex regulatory process. Bringing a drug to market is a very complex issue that takes many years and many stakeholders, and it is usually very difficult for patients who are new to this space to understand how to effectively engage and be part of this process. So we are trying our best to help.

Erica Berg (*host*):
Stuart, maybe you could shed a little light on how rare disease issues are regulated in the United States? There are federal regulations and there are state regulations and I can imagine they span across everything from diagnosis to treatment. So maybe you could give us a little insight about how this happens.

Stuart Portman:
I will focus more on the FDA and the Centers for Medicare and Medicaid services (CMS) side of this. Obviously, there are the mixed emotions of having the ability to receive a diagnosis where you are excited that you have something that you can work forward from. The National Institutes of Health (NIH) play a role in this aspect as do a lot of other funders of research in regards to the points that were previously made. When talking about the federal role in the US, the conversations usually start when it comes to the FDA and the different approaches to how we treat orphan products. Whether we are talking about small molecule drugs, cell therapies, gene therapies or, in some cases, generic treatments that work for certain additional indications or for certain symptoms, the regulatory frameworks are different. Even within FDA, if you are going through the Center for Drug Evaluation and Research (CDER), on the drug side, or, the Center for Biologics Evaluation and Research (CBER), on the biologic side, it is important that the expertise is aligned within the agency and to make sure that there is a shared vision. Those regulatory actions take place within the FDA, however a lot of the direction can also come from the Department of Health and Human Services and from the White House. In the rare disease space, we have seen successes occasionally when there is that broader leadership as it relates to these issues. I think it is also important to note that when speaking about the regulatory differences at the FDA, there are traditional approvals and there are times when accelerated approval will be granted. I think that you also create additional incentives for innovators in this space with priority review vouchers, for some of the rare diseases for children or some of the pediatric review vouchers, just some of the ways to make sure that the incentives exist to enter this space when there are so many competing interests.

One must also make sure that the FDA has what they need in order to make the right judgment call. There has been a lot that has gone through, and you do not want situations where rare disease products only make it through because of leadership. You want the reviewers to also have the expertise to make these decisions that are informed by science and data so that they are based on safety and efficacy. I would also say that when you shift from the FDA side to the Centers for Medicare and Medicaid services (CMS), which would be the largest payer as the combination of Medicare, Medicaid, and the Children's Health Insurance Program, as well as marketplace coverage, those discussions, primarily Medicare and Medicaid, guide a lot of discussions. Too frequently in the rare disease space, the

focus has been on the FDA because of the journey and the odyssey to get there, and we have lost the ability to bring along some of our coverage experts into the mix. That has led to these delays where there is a lack of understanding. Where you have people that are confusing accelerated approval in the United States and conditional approval from Europe, which are different things, but they are frequently conflated. For those of us in the space, it is always very frustrating because you want to make sure that when you are talking about coverage, you are talking about is there a guarantee of coverage and can there be a rebate? Is it federally authorized? Is it state-based? Is it something supplemental that is determined by the manufacturer to work with a state or a payer of some kind? What kind of utilization management controls are going to be there? Some of these can be federal and some of them can be state. Are we talking about prior authorizations? The use of step therapies? Sometimes there is an additional fail first policy that could be included. Those all play a role in access to a treatment and the regulations that flow from CMS oftentimes could use a little more connectivity to the decisions and approvals that come out of the FDA. I think that we see a lot of growing interest with, as Julia mentioned, patient-focused drug development. It is still novel to talk about surrogate endpoints for those that are on the payer side, while for those on the FDA side, this is a very well discussed area. The people understand, especially when talking about rare diseases, that your clinical trial design is inherently different. That is not always understood by those that live their lives solely in the coverage realm and understanding how you can have an endpoint that is not solely clinical in nature is something that stands out. Additional education could be helpful there. So there is a lot in the federal space within the United States, but there are also some state-based decisions on the public health side, particularly around newborn screening and a lot of the decisions that take place related to public health.

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When you are speaking about coverage, Medicaid is the largest payer in this space, currently serving about 92 million people, which is a very large population. Prior to the pandemic, it was closer to about 74 million or so, which is still a very large population and the largest payer for rare diseases. So when we have these discussions and need to figure out how a program that is operated state by state plays a role, it creates both opportunities for rare disease advocacy at the state level to enhance what has happened federally, but there are challenges with making sure that there is access to treatments and that no unnecessary utilization controls are put forward because of unrelated access concerns that deal with price. When speaking to the nature of how these coverage discussions play out, including the role of pharmacy and therapeutics committees within a state and the use of additional managed care entities to make some decisions versus the state making all decisions, things get very complex very quickly. There should be the shared vision and goal of making sure that patients with rare diseases have access to the treatments that can actually help them improve their lives and, with the emergence of the science that we are seeing today, in some cases, potentially cure them.

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Erica Berg (*host*):
Maybe we can clear up some of the European Medicine Agency (EMA) and FDA confusion happening. Simone, what can you tell us about how things are done in Europe and elsewhere?

Simone Boselli:
I will focus on Europe, which is where I know best, along with the UK. I recognize a lot of the issues that Stuart has just outlined in the European context, which are probably aggravated by the dichotomy between the regulatory approvals that, particularly for innovative therapies, are centralized at the European level with the European Medicine Agency. The EMA was created in 1995 to harmonize the work of the existing national medicine regulatory bodies, particularly for the quality, efficacy and safety of the medicine that came into the European market. This is an issue that dates almost as far back as the birth of the European project itself in 1965, when the first common decision on the approximation of national laws regarding medicine came about following the thalidomide crisis.

Since 1995, the European agencies remit has expanded, and the agency has been responsible for products related to the specialized area of rare diseases. I think here a parenthesis should be made as EURORDIS was effectively created to bring to Europe that efficient environment of incentives created in the US. And if anything, we succeeded in the first step to create a much broader set of policies on rare diseases that stem through that landmark legislation of 2000 and also for medicine specifically for children through the pediatric regulation of 2006, and a regulation on advanced therapy medicine, often called Advanced Therapy Medicinal Products (ATMPs), since 2007. Another characteristic of the 2000 orphan medicinal product regulation is that it opened up the official involvement of patients and their representatives as well as healthcare professionals at the EMA. It is in this structure made up of committees that patients can represent their voice both through the appointed members, of which EURORDIS has a few in both the Committee for Orphan Medicinal Products (COMP) and the Committee for Advanced Therapies (CAT), as well as in the scientific advice group that supports the work of the agency towards authorization at the European level. We have an agency that represents and authorizes therapies, but things get a little bit more complicated when it comes to the access part, as there is a product that for rare diseases is solely decided at a central level, that goes to an access system that is fragmented in at least 27 different markets because of the fundamental idiosyncrasy of the European project in health. The products are regulated at the European level. The public health systems are regulated at national and also the regional and hospital levels. Therefore, all of the issues that Stuart and the other panelists mentioned in relation to access are exacerbated by these differences at the country level. To the point that in some countries therapies

are not even reaching the patients. In some countries there are delays of 3 to 4 years, while in others, namely Germany and to some extent Italy and France, things are much better. From the perspective of an umbrella organization, this inequity is not sustainable, particularly as the science that we are seeing at the moment is phenomenal and potentially represents a hope for a cure that only a few years back we could not have dreamed of.

Erica Berg (*host*):

As a follow up question, Simone, are there any current laws that are being debated that would impact rare diseases? What is going on right now that we should be aware of?

Simone Boselli:

A lot! It is exciting and yet challenging at the same time. The European Commission has embarked in a proposed reform of the entire pharmaceutical legislation framework, which included the general pharmaceutical legislation, as well as the specific regulations for orphan medicinal products and therapies for children. These regulations have been very successful but there is a recognition that some issues need to be addressed if Europe wants to stay competitive and provide access to innovative therapies to the largest possible number of people in Europe. These are not only questions related to affordability but are also questions related to the speed of regulatory approval, which is currently still a little bit behind when compared to the US.

There is recognition that some of the incentives that have been provided to the industry have not yielded the outcomes that we have expected and therefore a recalibration might be needed. On the other hand, talks of such sweeping changes, which include for the first time an emphasis on access issues, have already frightened a lot of people, particularly in the R&D based industry and, to be honest, us as well, because we need a thriving European ecosystem that is not solely based on the research that comes out of the US. Furthermore, at a national level, we have a number of countries that are looking once again at introducing or improving their existing frameworks of national plans for rare diseases. Sweden, for example, has announced that they will be starting work on their first national plan in October. France, on the other hand, is already on their fourth national plan. We at EURORDIS need to continue to advocate for a comprehensive view and therefore a European action plan that brings together all of these parts.

Erica Berg (*host*):

Thank you. Stuart, what is going on in the US?

Stuart Portman:

There are always many different bills in Congress and regulatory actions that are under consideration. I know others can speak to this as well, but I would say that there are many things that stand out right now where there is a growing interest. Medicaid payment policy is rather complex but allowing payment for value and whether that means the ability to have a non-payment or a reduced payment or a payment over time and a sort of mortgage model, those conversations, while there is a lot of support for any sort of outcome-based arrangement, require legislative changes to be as effective as they could be. There are conversations that have been going on for a while, but that have become recently vocally bipartisan. There is a potential for change to happen there, just to open up access. I am not one who thinks it is going to happen tomorrow, but I think it could happen in the near future as a way to make sure that the largest payer for individuals with rare diseases actually can cover those products, especially with the increasing innovation and novelty of the treatments that are coming down the pipeline right now.

We want to make sure that the system is able to handle those products and the potential cost implications of those products. You have budget operators that are alarmed, even though they are excited, and it is important that any legislative regulatory approaches can try to manage all of those different interests. There are also conversations related to how do we ensure access to centers of excellence for treatment across state lines. While obviously it is a different conversation, making sure that providers with expertise in some states are able to treat individuals more seamlessly is important. A lot of the work of NORD and EveryLife, goes into helping make sure that patients can actually get to the treatment and legislatively there are efforts to try to make that easier and less burdensome.

There is also a lot of focus on implementation of the recent changes to the Medicare program. I do not want to go too far into the weeds, but there were potential areas that could have unintended consequences. I am sure there is going to be a focus on whether or not those unintended consequences bear out because anything that reduces innovation in this space is detrimental to patient access and their future care. Similarly there is regulatory work going on that, especially in the Medicaid program, could create some sort of disincentives for investment in this space because of rebate obligations that would be put onto manufacturers. So those are just a few things that folks are keeping an eye on here while also working on some of these other legislative efforts.

Julia Jenkins:

Can I just paint a picture for the audience too? When we talk about global perspective and why what is happening in Europe and in the US and globally is really important, it is because when we talk about a rare disease, and especially an ultra rare disease, a company is needing to ensure access to as many of those rare disease patients as possible for them to get investors to invest in their drug. If access is being blocked in some of the European countries or some of the US states or is not going to be reimbursed, they will not develop the drug. We would therefore love to see a more global action happening. To think about rare diseases and only being able to treat the patients in Europe and the US also really limits the scope. We know there are so many other rare disease families out there in the world that are not even going to have an opportunity to access treatment in their lifetime. If we really want to be successful, we have to look at a global model for these drug companies to really try to invest in these ultra rare diseases. That is why it matters whether or not the US pay organizations care about what is happening in Europe. We have to, as it is a global drug development ecosystem. So to have that perspective is really important as we move through the different countries and as they navigate the regulations, we also need to be looking at what is happening elsewhere.

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Karin Hoelzer:
To maybe briefly dovetail with what Julia said there has been a growing recognition even in the US that there are large parts of the patient population that have a much harder time to participate in clinical trials and to benefit from the treatments. So there has really been a lot of emphasis both on the regulatory side and on the congressional side to improve access to these life-saving therapies. That may include, for instance, telehealth, as Stuart mentioned, and bringing trials into the patient's home. Many of our rare disease patients have a hard time traveling, but we know that many of them have to travel 60 miles or more to seek care and oftentimes fly across state lines to participate in clinical trials, which puts a tremendous burden on our patients and our families. Leveraging the learnings from the COVID pandemic and new technologies to really break down these barriers to encourage equitable access and participation in research so that patients can benefit from these therapies is tremendously important for our community. We see a lot of proposals and a lot of emphasis luckily in that area at the federal and state level.

Erica Berg (*host*):
So we have heard a lot of complexity and challenges. Let us turn our attention to the patient advocate. Julia, with all of these complexities, how can advocates stay informed about regulations and where should they be placing their energy in terms of advocacy efforts to get these changes that will help them?

Julia Jenkins:
I talked earlier about really small patient organizations and how this creates another burden on these tiny patient organizations. I think that is why it is so important that there are organizations like NORD and EURORDIS and EveryLife Foundation to help track all of those regulations. The National Health Council as well will do draft guidance comments. NORD and the EveryLife Foundation do comments. We have a community congress where we work with hundreds of patient organizations and industry partners to inform our comments so that there is collaboration between the different stakeholders. Because it is a lot of work to track the regulations and to provide comments and feedbacks in the hopes of getting regulators to really understand the patient experience and perspective. It is not always successful. In that case you have to take action and go back to the hill and lobby Stuart, who is an amazing rare disease advocate in his role, to really get other members of Congress to understand how the drug development system is impacted by legislation.

People in Congress and people at home do not realize that it is laws and regulations that are impacting their ability to get a therapy. Once that light bulb turns on and they realize that they need to be a policy advocate, it is a really exciting transformation and it gives the individual patient that power to be able to have a voice and to contact their member of Congress and advocate for needed changes. We host Rare Disease Week on Capitol Hill, which brings nearly a thousand advocates together to fly in and meet with their members in person. We were happy to partner with EURORDIS earlier this year to help bring patients to Parliament for the very first time. So it is really a great opportunity to make sure that patients have the chance to be heard by their policy makers.

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Erica Berg (*host*):
Thank you. Anything to add for Europe as far as ways that patient advocates can stay informed of regulatory changes and things that are happening right now that they should make a statement about?

Simone Boselli:
Well, we definitely do try to maintain a regular conversation with all of our members. We primarily work with national alliances because you have to remember that we do not all speak the same language and therefore there are issues related to that specifically, although many make the efforts to do so. That is why we brought over 40 different rare disease advocates of 10 to 15 different nationalities to Brussels, because the geographical providence is also very important here and the language is as well. The main way that we are trying to do it is through our empowerment programs such as the EURORDIS Open Academy, and particularly what we used to call summer school, which has dealt with the topic of regulatory development. Since 2009/2010, in cooperation with the European Medicine Agency, we have trained over 500 patient experts that, in some cases, have continued their own education. Those that have continued have become members of committees at the European Medicines Agency (EMA) and they are now advocating for regulatory changes in their own disease area or in other disease areas, in the agency but also at a national level. So that is what we are trying to do, in addition to communication, plus the work that we do around Rare Disease Day and on an individual basis.

Erica Berg (*host*):
Stuart, so how can an advocate reach out to their elected representative? They could go through one of these organizations and work through there, but can patient advocates reach out directly and what are some best practices?

Stuart Portman:
Of course going through an organization is always helpful, but it is not necessary in the sense that there are many members that will take meetings or have their staff take meetings. Especially today, there are opportunities as a rare disease advocate to educate, which feels like such a innate part of any rare disease advocate as they are used to doing it all the time, but there are a lot of staff that help advise their bosses (the members) that all could use a refresher in understanding what it means to live with a rare disease. Understanding the various types of care and providers that are needed and all the different appointments. The impact on day-to-day life. The fact that a current treatment regimen may not be some oral therapy. It might involve infusions, it might involve hospital stays or it might involve additional use of durable medical equipment. Understanding what that looks like is

something that is very hard to put into a letter or an email, even if it is heartfelt. It is best shared when it can be verbalized and ideally verbalized in person because it opens up a lot of doors to making sure that someone has empathy and understanding and can really start to see that this is not something that you can just wave a magic wand and legislatively everyone will agree to solve it. There is complexity here and you want to make sure that you help as many people as possible. Advocates that ask for meetings tend to get those meetings. Most offices are not looking to turn away a rare disease patient from being able to express what their lived experience is and how they envision a difference in the future. I would say organizations tend to be better equipped to talk about how to fix something through regulation or legislation, but to understand the human voice that goes behind a lot of those pieces, individuals have the ability to ask for those meetings and it is really as simple as writing in to ask for a meeting or calling or organizing through an association or organization. I know of very few instances that someone ever said no, when someone wanted to share that experience with them. One thing to keep in mind is that a lot of times people want to talk to the member, and frequently that happens, but sometimes they feel let down if they end up talking to the staff. I am not just saying that as a staff member. I would say that there are actual benefits to educating the staff because frequently they are in the room developing the legislative text based on a broader directive from the member of Congress and then they go back with that approach to the member of Congress for approval. Sometimes members are deeply involved and sometimes they are less involved, and they hand off a lot of the responsibility to their staff. So never look at a staff-based conversation as a negative because you never know where someone is going to be five or ten years down the road and could be of assistance. Building allies on this journey is a goal across the board.

Karin Hoelzer:
There are a variety of different ways for advocates to have their voice heard. Obviously meetings with Congress and providing testimony are great opportunities to tell your story. But I know that for many patients this may be overwhelming at first or it may not be physically feasible. So they have a variety of other ways, such as writing letters. We regularly help our community to write letters to their Congressmen on legislation. You can also tell your story through social media or through blogs or provide comments on dockets. There are a variety of different ways that are more or less involved and more or less time consuming. I really want to make sure that everybody feels that there is a path for you to have your story heard regardless of what is feasible or what is comfortable in your life. It does not have to be a meeting with congress, even though that is a great opportunity.

Erica Berg (*host*):
Karin, could you share a success story where advocacy efforts led to a positive regulatory outcome?

Karin Hoelzer:
Absolutely! Julia already mentioned the history of patient-focused drug development starting with the 2012 User Fee Act, where the FDA committed to bringing the patient voice as an integral part of the drug development process. It is really important to make sure that what is measured in a clinical trial actually matters to patients. That the risks and benefits that a patient has to consider and whether a patient wants to take a drug is appropriately captured in the drug development process. This was really revolutionary and required a lot of engagement from the patient community to make this happen. Then there was working with Congress to make patient-focused drug development a more integral part and a more standard part of the drug development process. We have come a tremendous way. We have seen the FDA not only hold a lot of patient-focused drug development meetings, but also develop tools and provide guidance for the community for how to bring the patient voice more effectively into these meetings. We have seen the creation of patient listening sessions, which are somewhat smaller, more intimate and in some instances a different way for patients to share their story with the FDA reviewers who will be reviewing the application. So, we have seen a tremendous trajectory over the last 10 or more years in bringing the patient voice and the patient experience into the drug development process. On the coverage and reimbursement side, we, at NORD and others, have worked very closely with the Centers for Medicaid and Medicare (CMS) to make sure that patient experience data is incorporated. For the first time this fall, the price of some prescription drugs will be negotiated to really capture what the value of these therapies is in particular for rare disease patients. We have really seen CMS embrace that idea and just earlier this summer, CMS committed to holding patient listening sessions to really find a way to bring that vital patient voice into the negotiation process. I think that is a really great example of how continuous interaction with a regulator really brings value, but it also demonstrates how many years it takes to bring about that change.

"We have seen the creation of patient listening sessions, which are somewhat smaller, more intimate and in some instances a different way for patients to share their story with the FDA reviewers who will be reviewing the application. So, we have seen a tremendous trajectory over the last 10 or more years in bringing the patient voice and the patient experience into the drug development process. On the coverage and reimbursement side, we, at NORD and others, have worked very closely with the Centers for Medicaid and Medicare (CMS) to make sure that patient experience data is incorporated. For the first time this fall, the price of some prescription drugs will be negotiated to really capture what the value of these therapies is in particular for rare disease patients. We have really seen CMS embrace that idea and just earlier this summer, CMS committed to holding patient listening sessions to really find a way to bring that vital patient voice into the negotiation process."

Julia Jenkins:
Just to highlight too, that this legislation impacts all diseases but it was led by the rare disease community. The work we do in the rare disease space really helps all patients everywhere. I know you said seven thousand, but I think the number of rare diseases is now estimated to be closer to 10,000 different rare diseases.

Therefore, the work that we are doing in drug development and regulations is really impacting the entire world with getting access to innovative therapies.

Erica Berg (*host*):
That is fantastic. One thing we have been trying to do this year is to get insights from outside the rare disease space, in order to understand what advocacy strategies work. Stuart, I was wondering if you have an example of a successful advocacy strategy that worked for the passage of legislation in Congress that we could learn from?

Stuart Portman:
I have been fortunate enough to see the passage of a lot of legislation and there are big ticket items that draw a lot of attention and then there are smaller pieces as well, where it is about how you build that coalition of support. I think the passage of 10 years of the Children's Health Insurance program is a good example of how a coalition came together. For the non-US based audience, the Children's Health Insurance program operates at an income threshold that is above where Medicaid is for children and some eligible adults. It is an additional way to provide coverage and while it is quite comprehensive, it is also authorized in a time-limited way as a block grant. The Children's Health Insurance program was up for reauthorization in 2017. So at the end of 2017, going into 2018, there were debates on how long it could go, and there was a desire led by my boss at the time, Senator Orrin Hatch (due to the fact that he helped create the program in 1997), to have it go for another 10 years rather than a shorter period of time. That effort required advocates in the children's health space to come together from across the more traditional advocacy groups, involving the providers and the payers and everyone had to come. We had weekly sessions where they all came together into one room and everyone could voice what was working and what was not working. We could voice areas where we thought additional reforms might be needed and people could push back. There was a weekly conversation at the committee level while those organizations had additional conversations with members of Congress throughout the week. Then we would all come back and have those follow-up discussions and figure out where people agreed, and where people could be comfortable, as we worked towards this broader strategy of how do you get to 10 years. The senator helped convince other members that it was better to go longer term, for those that were on the fence, as opposed to coming to do a check-in on the program later. The advocates bought into the fact that continuity of care in this program would be really amazing for a decade. So they could have these committee-based conversations that were happening with both parties, not usually together, but sometimes together. Just so that everyone knew that we were all working towards the same goal while still having those discussions at a more state-based level as well. It was a way to bring experts at the state government and experts in the advocacy space together with federal policy makers and it really was a successful effort as we managed to get 10 years of the Children's Health Insurance Program.

Erica Berg (*host*):
We have talked a lot about how important it is to have a global perspective for getting anything done in the rare disease space. Simone, I was wondering if you could talk about any successful examples of cross-border advocacy collaborations that have had a successful outcome?

Simone Boselli:
As part of the global work that Julia mentioned earlier, I think the work that has been done at United Nations with the resolution on people living with rare diseases just a couple of years ago, was a real pinnacle of global advocacy that required going beyond the geographical territories and bringing together a common platform to advocate for equal rights to access of healthcare across the world. Despite all of our challenges, we need to bear in mind that we are in a much more fortunate position than other people around the world. As Julia was saying earlier on, without a global mindset it is not possible to access potentially lifesaving or life transformative therapies, or even to ensure the basics of diagnosis and dignity of care, or to end discrimination and stigma. The best strategies are those that go across borders and cover all disease area while preserving the individual disease issues that are of clear importance to each patient. That is how we try to work in Europe as well, given that we have to bring a lot of people from different countries together.

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Erica Berg (*host*):
As an umbrella organization, how do you allocate resources when you are covering so many different diseases and how do you decide what regulatory issues you are going focus your efforts on?

Simone Boselli:
Fortunately, as the European Medicine Agency is currently structured with a specific committee for orphan medicinal products with committees for advanced therapy, we know where to focus our work. At EURORDIS, as I mentioned before, we have the Open Academy that trains our experts, who will then be requested by the European agency to provide insights into their daily life, what are the common patient experiences, what are the outcomes and the measurements that are needed to quantify how a treatment is safe and efficacious. We are also now entering 15 years of work in health technology

assessment, which is separate from the authorization process. It will be harmonized as of 2025, but as Karin was saying earlier how do we present that when it comes to reimbursement decisions and how can people and organizations be heard? What we try to instill, which is not always easy to do, is that if we work for the overall sake of the rare disease community, the benefit to the individual diseases will come as well.

Karin Hoelzer:
It is actually quite similar for us. Going back to our roots, we were established by uniting the voice across rare diseases. It allowed for a more compelling voice and to bring the Orphan Drug Act to pass, and that is really still our guiding star. We try to focus on issues that are cross-cutting and where speaking across different rare disease communities can really help elevate the story. We have about 330 disease-specific member organizations and we work with hundreds more communities that are in the process of developing rare disease advocacy groups. We see a lot of our job, just like Stuart said, in elevating that voice, in helping to share best practices from one community to another, and, again, in uniting so that we as a rare disease community can have a louder voice and ultimately be more successful in overcoming the barriers for our patients.

Erica Berg (*host*):
And on that note, we will unfortunately have to stop there. Many thanks to all of our panelists for being here, it has been a delight talking with you all. Thank you once again to our panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship. ■

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