



Key Issues Dialogue: Rare Diseases

Making rare diseases a global public health priority—what can the United States and Europe learn from each other?



Thought leaders participating in the Key Issues Dialogue from Paris (foreground) discuss critical issues facing patients with rare diseases with Dr. Stephen Groft, Pharm.D., National Institutes of Health, US in Bethesda (background) via videoconference.

Key Issues Dialogue: Rare Diseases

Making rare diseases a global public health priority—what can the United States and Europe learn from each other?

Dialogue participants: Dr. Stephen Groft, Pharm.D., Dr. Lennart Hammarström, M.D., Ph.D., Yann Le Cam, Peter Saltonstall, Dennis Jackman and Peter Turner

This Key Issues Dialogue is sponsored by CSL Behring to explore issues of importance to patients, caregivers and healthcare providers.

Leaders in the rare diseases community recently gathered in Paris and Bethesda, Maryland to examine some of the critical issues facing people with rare diseases. Improving diagnosis, facilitating research and development of rare disease therapies and improving access to those therapies were among the main topics discussed.

Rare Disease Priorities

DENNIS JACKMAN: *This Dialogue is being held in preparation for Rare Disease Day to draw attention to some of the more critical issues facing people with rare diseases. Let's start with a big question: what are the most important things that should be done to address rare diseases right now?*

DR. LENNART HAMMARSTRÖM: Awareness, finding the patients and treating them appropriately.

JACKMAN: *What are the challenges in doing that?*

HAMMARSTRÖM: In my area of expertise, primary immune deficiency diseases (PIDD), although we shortened the span from debut of disease to diagnosis and treatment, there is still a considerable time lapse. We need to press this point. What about neonatal screening? In this challenge the US has taken the lead, and Europe is lagging behind. But we shouldn't be because we have the expertise and we have the centers for disease screening. We have been discussing it at the EU Parliament.

PETER SALTONSTALL: It's about awareness and also making connections. I am trying to connect patient communities on a global basis so we can share knowledge and learning. As a global community we should put programs together jointly that allow patients to have better access more quickly.

PETER TURNER: One of the big challenges with rare disease is diagnosis. Alpha₁-antitrypsin deficiency, for example, is commonly confused with COPD from smoking or industrial causes. The patient has to be tested for the gene deletion, but that is not common practice amongst pulmonologists. Unfortunately, only a small percentage

of people with the disease are on therapy. We are making some gains in having patients tested, and need to continue to focus in this area.

Misperceptions About Rare Disease and Information

DR. STEPHEN GROFT: In addition to research there are concerning misperceptions about rare disorders. We are finding that there are many more patients that have rare diseases than most people thought. A published article may say that a study came up with ten or twenty patients with a rare disease. Many individuals will quote that and mistakenly say, "There are only ten people with this disease in the country."

Another misperception is that there is little or no information available to patients. The work of NORD, EURORDIS, the Genetic Alliance, Orphanet, the National Institutes of Health (NIH) and our Office of Rare Diseases Research are providing a tremendous amount of information. It is a matter of how we coordinate the information that really makes it useful to patients.

Contrary to some people's thinking that there is little or no research interest, we are finding there is considerable research interest; it is a matter of whether funds are available to support that interest. The more money that is made available for research on rare diseases, the more researchers will be willing to devote their lives to that research.

Yet another misperception is that there aren't enough patients willing to participate in research studies. However, working with the patient organizations we find there are a sufficient number of patients available to participate in clinical studies.

We need to inform the rare diseases community about clinical studies and the location of experts. The European Union countries are ahead of us in establishing their centers of excellence. Patients need to know where to go if they have a rare disease.

We have taken steps to expand newborn screening programs for about 29 different diseases. There is discussion about expanding it to approximately 54 disorders. One concern is what to do with the diagnosed patients. Do we have the infrastructure to transfer them into research or treatment centers for the individual rare diseases?

Creating a More Favorable Environment

YANN LE CAM: We need to keep in mind that we are facing 5,000 to 7,000 rare diseases on an international scale. For me, the first priority is to further promote rare diseases a long-term priority both for research and public health in America and Europe. That is the basis to create a more favorable environment and work on the specifics of drug development, creation of centers of care, provision of information and registries, and have the funding for the long-term approach.

In the last ten years there has been a lot of discussion both in Europe and the US to shape vision and strategies. The question now is to move from that vision into



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Once we start to get the patients' voices together, then it is up to us to develop policies and heighten awareness with governments about rare diseases and what we need to do moving forward.

PETER SALTONSTALL

implementation, which requires proper strategy, organization, infrastructure and long-term funding. I'd like to see more of how we build the long-term sustainability of the clinical research networks or the registries, of the information services and of the patient groups.

SALTONSTALL: The public policy issue is major in the US. Rare diseases are not well known. The people controlling funding and regulation are not as well informed as they need to be.

I also want to comment on leveraging technology. The marketplace is changing dramatically and technology enables us to bring these groups together. Once we start to get the patients' voices together, then it is up to us to develop policies and heighten awareness with governments about rare diseases and what we need to do moving forward.

Right now in the US we have established a rare and neglected disease bipartisan caucus within the government to heighten awareness about rare diseases and about funding needs.

Role of Patient Registries

HAMMARSTRÖM: I started the European registry for PIDD, which is still alive and strong. But many of us are now getting into registry fatigue because we have been running on enthusiasm and little money. Registries founded five to ten years ago have to be updated. What happened to the patients? Did they get treated? Did they move away? Did they get new kinds of therapy? The money is drying up, and now we are supposed to be on our own and continue to update the registries.

LE CAM: We need resources. We also need a coordinated approach on registry good governance including who owns the registry, who owns the data, who can use it and the right infrastructure for long-term sustainability. I am hopeful about the recent EU initiative to team up with the US NIH to join forces on rare disease research policy and funding.

GROFT: We see a tremendous opportunity to utilize patient registries. In fact, we feel it is a significant early step on which the patient advocacy groups could begin to work. That is, they could establish a patient registry that will develop natural history studies, then generate research hypotheses that can move into clinical trials. Hopefully, we can then get an adequate reading and review at the regulatory level.

In that sense we are seeing more and more products having studies as requirements of proposed approval, or conditional approval with phase four studies required. Patient registries are collecting useful information on patients that starts several years before a product is on the horizon.



There are three drivers for drug development research in rare diseases: the existence of active patient organizations, European or international registries or organizations to collect information, and research networks.

YANN LE CAM

Last year, approximately \$460 million were allocated to orphan products research by NIH. There are thousands of active projects. We are trying to get a better understanding and description of the research NIH conducts.

There was a recent NIH announcement that we are considering forming a new center for translational therapeutics. The center's mission would be to coalesce many of the activities that are going to lead towards therapeutics development, including the new TRND program, Therapeutics for Rare and Neglected Diseases. The program is led by the National Human Genome Research Institute and Dr. Christopher P. Austin, M.D. We are initiating many programs, having collaborative meetings and avoiding duplication.

We are finding that when treatments become available, we are pretty well set if we have a commercial sponsor from a company. But a major problem occurs when there is no commercial interest in sponsorship of individual products.

LE CAM: There are three drivers for drug development research in rare diseases: the existence of active patient organizations, European or international registries or organizations to collect information, and research networks. Now, when we discuss the drivers for orphan drug development, clearly it is the wealth of scientific publications. The rare disease for which there are between 200-600 scientific publications has much better chances of a therapy being developed and marketed.

International Cooperation

JACKMAN: *Do we see potential in the area of international cooperation?*

SALTONSTALL: Recently, there was a meeting in Iceland that included the EU and the US. One of the major topics was registries. Out of that has come a joint task force that is being co-chaired by people in both regions.

LE CAM: We need to look at collaboration, coordination, and competition. Competition is generally a good driver. The approach we are taking between NORD and EURORDIS in these strategic partnerships is to send the message that we are serious about international collaboration. We developed an online, global patient community and try to communicate in several languages.

GROFT: We do support a tremendous amount of international research here through the grant mechanism and contracts as well. Approximately 5,000 of our research grants are global and include an international component.

Ten to fifteen years ago at scientific conferences, if we had three or four investigators from around the world, it truly was an international meeting. Now the conferences draw around 150 people from many different countries. The research community realizes that you need multidisciplinary teams and a global approach to research. You need co-investigators in various parts of the world that can bring patients into the studies.



Some of the necessary clinical trials will never be done because they are too costly. This means that certain types of therapies will be unavailable on both sides of the Atlantic.

DR. LENNART HAMMARSTRÖM

We should make greater use of the telecommunication technology so we can get the best collaborative efforts.

Harmonization

JACKMAN: *What is the potential for international harmonization? Most importantly, how might that help with drug development and availability for patients?*

HAMMARSTRÖM: Some of the necessary clinical trials will never be done because they are too costly. This means that certain types of therapies will be unavailable on both sides of the Atlantic.

TURNER: One of the issues in regulation is sovereignty. All nations will say they have the right to have their laws in their country. The good news is we don't have to obtain registration in different European countries anymore. We can get a central registration. The bad news is that Europe and the US are seldom aligned on clinical trial design. Quite often we have to design a European trial and then a US trial because of requirements differing across the Atlantic. I would encourage you as sponsors of rare diseases, both NORD and EURORDIS, to try and work with the agencies to get one common design. This is a waste of resources. It will certainly cost significantly more to run a second clinical trial or trials because of local or national requirements.

LE CAM: I hope that one day we will see an International Conference on Harmonization working group on orphan drugs developing common recommendations. EURORDIS teamed up with the EMA and FDA to do a retrospective analysis of orphan drug designations versus applications. There were more commonalities than differences. Ninety-two percent of the decisions were the same. Of the remaining eight percent, half were due to legislative differences and only four percent were difference of assessment. Based on that, we have been able to move to a common dossier for orphan status application, and now there are monthly conference calls among the teams at FDA's orphan drug office, the Committee of Orphan Medicinal Products and the EMA. Sometimes it is a question of taking the right approach to create dialogue and move towards the harmonization.

Regulatory Approaches and Alternative Methodologies

JACKMAN: *I understand NORD is asking for a policy statement about regulatory flexibility to help reviewers understand this should be embraced to foster rare disease therapy development. Does that happen on the European side as well?*

LE CAM: Of the 60 orphan drugs now on the market, 50 percent were approved at the end of phase two by the European Medicines Agency (EMA). The majority of them were based on clinical trials that were non-randomized and non-placebo.



Recovery of investment becomes an interesting challenge for the developer of therapies. That leads to the next problem, which is the affordability of the therapy given the restraint in health care budgets with all the global economic issues.

PETER TURNER

The EMA has published a guideline on alternative methodologies in clinical trials and statistical methods. The right moment to discuss that is at the beginning of the clinical trials, in phase one. That is the right time to ask regulators: how can I do that?

For rare diseases and orphan drugs the approach we need is more about collecting data on safety, efficacy and effectiveness before and after marketing authorization. That means using tools like the registries to collect data, which we can then use for the clinical trial and submission of application for marketing authorization and for the early access program.

Other areas to look are patients' reported outcomes during clinical trials or after marketing authorization as well as the surveys of patients' preferred treatment options, in which patients declared their perceived risk and benefits.

SALTONSTALL: I respect that every country and regulatory agency has its own set of rules and criteria. I also understand that if a therapy has been used on patients for a period of time in Europe, and the European safety and efficacy standards and tests have been demonstrated, we need to find a way to apply that information within the US market. There needs to be a way for patients to get the drugs and therapies more quickly. I am working with EURORDIS, and there are monthly meetings between agencies across the ocean that are looking at exactly that issue.

TURNER: If you develop a drug or a therapy, you want to know the mode of action. So clearly research is quite important in determining that. However, in rare diseases it is not always known. There has been medical experimentation, usually non-labeled use of products, and in some cases, physicians find a clinical benefit. But we don't always know why. That is the nature of rare disease.

From our point of view, one of the issues in rare disease is recruiting patients for clinical trials. By definition there are not that many of them. For instance, when we are trying to get 100 patients, it might take 50 centers recruiting people for trials.

Financially, it is exciting working in rare disease. Sometimes it works out, and sometimes you are in for a surprise. What regulators could do is try and be clearer in terms of their needs, particularly in terms of clinical evidence when you are trying to develop these products. Post-marketing commitments can effectively lead you into three or four clinical trials for one rare disease therapy. Recovery of investment becomes an interesting challenge for the developer of therapies. That leads to the next problem, which is the affordability of the therapy given the restraint in health care budgets with all the global economic issues.

SALTONSTALL: Patients are concerned about the price of bringing drugs to market and the time it takes. Our patient groups pushed us to do market research. We spoke to investor groups, to the government and others. We found a very strong indication

to look at the regulatory side for a way to smooth it out. As we dug in we found inconsistencies prolonging the process.

TURNER: I think regulators have done a great job of trying to work in rare diseases because it is very different from working with drugs for large patient populations such as in cardiovascular health or kidney disease. An issue that often comes up is placebo-controlled trials. In many cases a treatment has evolved medically but is off-label or considered experimental. Yet it seems unethical not to treat these patients.

One example is Guillain-Barré syndrome (GBS): we have heard about physicians using immunoglobulins to treat GBS for some time. But a prospective double-blind controlled study has never been done. It is very hard to do given the ethics of that particular situation. Each day that patients with the condition do not receive treatment, they become more impaired in their movement. One of the problems that stems from not having the approved indication is reimbursement. Particularly in the US, patients can get turned away on insurance and other elements of their treatment because it is not an approved indication.

Coordinated Approach Toward Rare Diseases

JACKMAN: *Let's turn to the holistic view of addressing rare diseases. On the one hand, a number of entities are trying to support rare disease development, research, etc. Then there are reimbursement policies that exist, some of which foster access to rare disease therapy and some of which can delay or alter access. How can we get a more coordinated approach toward rare diseases along the entire continuum? An example would be the European Council recommendation on developing national plans.*

LE CAM: We have been trying to establish rare diseases as a priority across the European Union, and first on the European Commission level. The Commission Communication on Rare Diseases in 2008 made rare diseases research a priority in addition to public health, legislation and drug development. Six months later the Council adopted a Recommendation on Rare Diseases. The Council Recommendation means there is a commitment from the 27 Member States to develop national strategies or plans before the end of 2013 based on six common priorities. They are research, drug development and access, information, centers of expertise and patient empowerment.

Now we are trying to turn this policy framework into reality to build integrated policies between EU and member states as well as across member states. They will be among the most integrated policies in the European Union health area. The only possible approach on rare diseases for a continent like Europe, which is fragmented in so many countries, is to gather expertise on the European level.



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DENNIS JACKMAN



In Europe, you have very strong and excellent teams on the national level, and if you bring them together you have even stronger potential. We need a synergy of that potential with a good strategy and funding on a European level.

YANN LE CAM

JACKMAN: *Is there an integrated or coordinated approach like that in the US?*

GROFT: The Institute of Medicine report recognized the need for a national strategy to foster collaborative efforts. The nature of rare diseases is such that there are multiple organs and multiple systems involved in individual diseases. Until we are able to bring all the partners together, not only the academic researchers, but also the industry, the patient advocacy groups, and government research and regulatory groups, the lack of coordination will harm any possibility of rapid product development. We have to become more proactive, identify the opportunities and then make the resources available.

In many respects, I think the European Union, because of having multiple countries, is forced into collaboration. We realize and recognize that need. I think it is slowly starting to evolve.

SALTONSTALL: With the publication of an Institute of Medicine report, for the first time there is a federal document from an organization perceived as one people listen to. There are seven steps of action, including a major task force set up by Health and Human Services to monitor on-going actions in the US. NORD and some of the other patient organizations in the country are taking a leadership role, and we hope the Rare and Neglected Disease Caucus will be an important part of this, to heighten awareness and hopefully to drive a process very similar to what has been done in Europe.

LE CAM: Europe started 15 years after the US, so we had to bridge a gap, starting with shaping regulations and policy to create a favorable environment for rare disease. Putting Europe in motion is not only about the European institutions, it is also about the member states and the different stakeholders. In Europe, you have very strong and excellent teams on the national level, and if you bring them together you have even stronger potential. We need a synergy of that potential with a good strategy and funding on a European level.

We held a workshop last year in Barcelona on whether we should revise the EU orphan regulation and US Orphan Drug Act. Clearly the conclusion was no. It is better to favor a stable regulatory environment until we have something better to propose. There is plenty of progress to implement within the current legislative framework. We need to stick to the spirit of the regulations while applying them with flexibility. We also need to link the regulatory steps in the orphan drug development process.

The two key bridges for that link are protocol assistance and the concept of clinical added value of orphan drugs. Protocol assistance needs to be better used at an early stage and on an ongoing basis to support successful drug development.

For the clinical added value of orphan drugs after marketing authorization, we would bring together regulators, health sector agencies and payers, along with medical experts and patient groups and discuss the value of the drug at the moment of marketing

authorization, and a European coordinated plan for post-marketing research activities called risk-benefit-effectiveness management plan.

Reducing Risk in R&D

JACKMAN: *What is the role of regulatory predictability in therapy development and what are some ideas on accomplishing that?*

TURNER: It takes some of the usual uncertainty out of the process. All drug discovery and development is risk-based. The more regulators can define the hurdles to be met to get a registration, the better. Sometimes it appears those hurdles have developed along the path of bringing a drug to market. Depending on the clinical reviewer, the process can be completely different. The individual can have a huge impact on the drug approval process.

SALTONSTALL: We need to eliminate as much risk in the process as possible. As a patient organization, we put together a task force to work with the NIH and the FDA to develop a handbook to lower risk in the drug approval process and establish consistent policies.

GROFT: Reducing the risk of failure is a major task. Collaboration and discussions with industry are surely needed to help us understand how to reduce risks of failure. How do you approach products and make a judgment call? Which one will be successful and which one will not? When do you actually stop studies? We will be grappling with these issues at the NIH.

There is the perception that there are a number of products on industry shelves that are either compounds or in chemical libraries that would be available to develop for rare diseases. I wish we had a good survey of possible compounds that could be useful. In the late 1970s, surveys were done, and we only found 42 compounds that could be used for rare diseases. We have the capability now, using informatics tools, to look at compounds. I know FDA and the Office of Orphan Products Development are considering ways, along with our TRND program, to look at the compounds that are already in humans. How do we match those with the literature and with the experiences of industry to identify more compounds and then bring them into the system by priority? We could then begin to foster collaboration and the coordinated efforts that we need.

Orphan Drug Status

JACKMAN: *An issue is the number of orphan designated products that never wind up as licensed orphan products. Why do people think that happens?*

SALTONSTALL: Out of 2,252 designated products there are 361 approved orphan drugs for about 200 different diseases. That is a fairly large delta. I don't have a good answer other than the fact that in trying to ensure safety and efficacy, the process



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takes a long time. We need to take a careful look at the process to see if there is a way to shorten it.

TURNER: The degree of difficulty in some of these diseases could be another complicating factor. We don't necessarily know the actual mechanism, the course of the disease itself. There are a lot of unknowns in rare diseases.

LE CAM: I would like to see a stronger, passionate commitment to that from the regulatory agencies, the public funding research bodies, and also from some of the companies to really make things move. Designated orphan drugs are the best candidate drugs for new rare disease therapies and the best hope for patients. The FDA Office of Orphan Product Development and the EMA do receive annual reports after designation from all companies having designating products, but they are not analyzed. After 10 years of EU regulation and 25 years of US regulation, that is not acceptable. I am concerned that in Europe there is, on the one hand, a strong political momentum to develop the rare disease research policy with more funding, yet, in the Commission's DG Research Office of Rare Disease, there are only two staff people. These are the kinds of issues to be addressed very quickly in both Europe and the US.

Off-Label Treatment

HAMMARSTRÖM: In Sweden, you can treat patients off-label. But you can only do that in your clinic on maybe one patient. The Läkemedelsverket, the medical products agency, may say you have to have a clinical trial, but if you don't have enough patients you cannot. This type of bottleneck stopped a therapy treatment for one of our patients.

JACKMAN: *So is there concern with maintaining physicians' prerogative on how to treat patients?*

LE CAM: We know that 80-85% of people with rare disease are treated today with drugs off-label. At the moment payers are looking more closely at that. We have a common issue for industry, regulators, payers and for patient organizations. I would like the industry to collectively explain the importance and usefulness of off-label drugs.

From the patient perspective it is a huge waste of knowledge and of financial resources. We should encourage the collection of data during off-label use, both on safety and efficacy. This would be good medical practice, better care for patients and also a better allocation of resources.

TURNER: On a global basis, intravenous immunoglobulin products total about ten indications, but through scientific and medical publications and conferences, we can identify about 200 off-label uses. Many involve rare diseases where treatment is quite difficult and complex. Patients with rare diseases often receive multiple therapies. We don't know the course of the disease. Everyone saved is a benefit, but they will need multiple treatments that can include immunosuppressants, steroids and immunoglobulin.



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PETER SALTONSTALL

It is very difficult, as a provider of immunoglobulin, to see how every physician-chosen use for patient treatment could be labeled.

GROFT: Physicians are treating people with a number of off-label uses, but we are not capturing that data. We are also not capturing the information from the literature. If phase two studies have been done or even phase three, we still haven't taken the names of the diseases, searched for them in the literature to find out which compounds are being used and being reported in the literature. Then we should go back and see the strengths of those reports. This requires a tremendous amount of effort and resources. It could be \$20-50 million, but that is not a lot of money compared to the cost of product development.

We have the capabilities, but the resources are lacking. It really goes back to whether governments are willing to make rare disease research and development priorities within our own organizations throughout the world. There is a tremendous groundswell of interest and willingness to participate and develop products. We have to take advantage of that and utilize resources on a global basis to develop the knowledge base and priorities, identify products, get them tested and get them to patients.

Rising Patient Costs

SALTONSTALL: Tough economics are going to challenge us this year. Because of the recession, we are seeing a huge pushback, because it is easy to push back in the US. If it is off-label, the insurance provider might not have to pay for it. Historically, we have seen trends where major insurance providers have covered off-label therapies for rare diseases because they were a small segment of their population and it was the right thing to do. We are seeing a reversal of that trend because of the tight economic times. In 2011 we are going to see, at least in the US, a number of people who will not get their drug off-label anymore. We are going to see more disappointed people unable to meet their co-pay. Talking about it, as we are doing right now, with major insurance companies is an important next step.

HAMMARSTRÖM: The economic recession is hitting affluent countries and even approved indications are starting to be questioned. We need to get the true costs for the diseases to show to politicians and other stakeholders. We have been trying to do that retrospectively but we cannot. This means we have to start from scratch again and do prospective studies to see the true costs of different diseases.

Patients and Patient Organizations Play Key Role

TURNER: The individual patient organizations are also very important in this situation.

LE CAM: A lot of what we are saying is about raising awareness among key stakeholders and also the public at large. A few years ago EURORDIS initiated Rare Disease



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PETER TURNER

Day partnering with the 22 national alliances in Europe, with NORD in the US, CORD in Canada and other organizations including in New Zealand and on five continents.

The focus of Rare Disease Day 2011 is health inequalities. Lots of the issues we have been discussing have to do with health inequalities. That is, how we try to bridge the gap between the rare diseases population, which is more vulnerable and less served than other parts of the population and how we try to bridge the knowledge gap and the drug and services gaps. For Rare Disease Day 2012, we are considering focusing on innovation including an innovative health agenda, and innovation in medicine and research. I encourage patients, families and health care professionals to use YouTube and Facebook to tell their stories. They should not underestimate the power of telling their stories with text and video to raise awareness.

TURNER: A lot of treatments keep people out of the hospital and out of institutionalized care. Yet, for political reasons, governments don't move to provide more treatments. Politicians will listen to patients, caregivers and patient groups much more than they will listen to a manufacturer or a scientist.

HAMMARSTRÖM: We have had much help from patient organizations because they can tell the real stories. We bring patient organizations onboard for all activities. They serve as sounding boards for suggestions we make. They have input early in the process.

TURNER: As CSL Behring works with many patient groups, we have a clear role of keeping them informed of issues that can impact product supply and development. We are also committed to helping ensure they have a voice with policymakers, because negative impacts on small rare disease groups can be an unintended consequence of major legislation. There are times we see that, when reimbursement models have changed, and there is a disproportionate impact on a rare disease category, as distinct from a major category like cardiovascular. It is about awareness, knowing how the system works and making sure patient groups are informed of movements and changes.

Patient Empowerment

JACKMAN: *How can patient organizations be empowered and most effective?*

LE CAM: The empowerment of patient organizations starts with the collection and dissemination of information. It is a lot about identifying leaders, building their strengths and supporting them to work together across rare diseases and across countries. The way that patient organizations, academics, healthcare professionals, policymakers, and industry are working together is unique to the field of rare diseases. Without funds we cannot empower the patient representatives. We can use the virtual new information technology, but that has a cost.

SALTONSTALL: Patient groups do have power to a large extent. When you bring patient groups to the United States Congress, it changes the dynamic in how decisions

are made because policymakers and lawmakers see patients as real people and not just statistics. For us it is important as the lead voice of patients with rare diseases in the US. Earlier we talked about somewhere in the range of 6,000-7,000 rare diseases. We have a membership that is much smaller than that; it is under 250. We need to communicate to disease-specific patient organizations the value and importance of working together on problems and issues that affect all. We are reaching out to try to double our membership in the next couple of years, and using technology to help internationally.

GROFT: The success of many advocacy initiatives for specific diseases depends on strong leadership of the patient advocacy groups. We may have 1,000 or more patient advocacy groups we are aware of in the US, but a serious concern is those patients who don't have an advocacy group relating to them to move their research agenda forward and meet their needs. We are looking at developing a common interface, a web-based patient registry accessible to everyone.

HAMMARSTRÖM: About 20 years ago we started the European Society for Immunodeficiency where people collaborated very well. Another example is the Jeffrey Modell Foundation that has been instrumental in raising awareness. They now have collaborating centers in every part of the world. We are all working together and that is pretty amazing. They understand the importance of awareness of rare diseases and have raised European medical professionals' interest. The Jeffrey Modell Foundation is the driving force. They gathered us in Brussels and this was an excellent example of how we can share across the Atlantic. They are a marvelous catalyst for PIDD that is reflected by the skyrocketing number of patients diagnosed.

LE CAM: One of our major concerns is that we not leave any patients behind. That is pretty ambitious with all the different diseases. We focus too much on some rare diseases and don't think about the very rare one or the ones for which there is no current research or drug development. I will never accept that there is nothing that can be done for a patient.

We need to provide the tools for all patients, regardless of the size of their rare disease population, to be organized, to exchange information, to support each other and to speak with one voice. It can be patient groups or it can be umbrella groups like NORD and EURORDIS providing the framework, but it can also be online patient communities and different ways that will evolve in the years to come.

SALTONSTALL: Everything we have talked about here requires money to heighten awareness. In the US right now, the key for us is to do all the things we talked about, which includes identifying and helping to coordinate the small patient groups so they are organized and communicating more effectively.



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YANN LE CAM



Comparative effectiveness research and health technology assessment will impact rare disease therapies.

DENNIS JACKMAN

A second issue is working with policy leaders to help them better understand the size and scope of rare diseases and what that means. We are really helping to educate people on the cost-shifting issue. When we fail to take care of these patients the cost shifts to another part of the system. This doesn't solve the problem. There are some cutting-edge ideas that, when brought to the policy makers who control the purse strings, can heighten awareness and bring some meaningful solutions to the forefront.

Reimbursement Strategies

JACKMAN: *We touched on payment, and that is an issue, because we could do all these things for regulatory pathways, accelerating development and licensing, but if the drug cannot be paid for and the patient cannot access the drug, those efforts could be for naught. What are the strategies around that? How are you going about differentiating these rare disease therapies for payment purposes?*

SALTONSTALL: We are in the early stages right now, talking to all the payers. We are also talking to regulators, trying to determine the best touch point to get their attention on the issue. Unfortunately we are not having success. I think it is because we are early in this process. We didn't see the payment and the off-label issues coming at us as quickly as they did.

JACKMAN: *On the physician service side, payment for treating rare conditions becomes an issue too. In other words, how the physician does or doesn't get paid. For instance, Germany has a somewhat "capitated" approach. General physicians are almost discouraged from treating "expensive" conditions because there often is no additional payment for the additional therapy, only the base payment. Any thought as to what happens with physicians and payment?*

HAMMARSTRÖM: That is just unacceptable. Patient need is what is important. We have been lucky in Sweden to be able to treat the patients we want to treat. This is now starting to be challenged, and we have to come up with hard data as to why we are treating the patients we are treating.

TURNER: *Is health economics important here?*

HAMMARSTRÖM: It hasn't been in the past, but I think it will be in the future. I am not sure that health economics will actually give you the right figures, but they will be figures we need to show.

Comparative Effectiveness

JACKMAN: *Comparative effectiveness research and health technology assessment will impact rare disease therapies. What are the potential benefits and risks for rare disease patients under these regimes? What are you trying to do about it?*

LE CAM: Today there are 60 orphan drugs approved with marketing organizations in Europe. We have looked at the situation in 10 countries, which means a potential 2.2



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DR. STEPHEN GROFT

million patients affected. Of this number, we showed that 200,000 patients—about 8-10%—don't have access to the medicines for sure. Another 500,000 of them probably don't have access. That is about one-third of the patients. It is not acceptable that while we have policy, regulation and investments in the development of these drugs, in the end, they are not accessible to all patients.

We are working to overcome that by focusing on the underlying issue, which is the collective cost for society of these medicines. The approach in Europe is that people should have access to medicines and to achieve this we need better pricing based on value. First we need to work on clinical added value of orphan drugs through collaboration in Europe. In the context of national plans, we are pushing to have a clear reference to this approach on pricing based on value, using the European common assessment report of clinical added value and also using a conditional pricing scheme and a revised pricing scheme based on the data generated years later. The health economics and Health Technology Assessment requirements will probably continue to increase across Europe, including for rare diseases.

TURNER: The way health economics is applied in certain countries does not favor the innovative drugs and therapies. The economics become a cost-cutting process. This is unfortunate because we have seen products disappear when taken too far.

JACKMAN: *It's challenging for small disease populations to get sufficient data to be convincing for comparative effectiveness research. Yet, the consequence of not having access presents many problems as well. Any thoughts on how comparative effectiveness research will develop for rare diseases?*

SALTONSTALL: On the comparative effectiveness issue, we need to make sure it doesn't become comparative cost effectiveness. The data will help drive this. My concern is that we are trying to implement a new program without having all the facts. That may ultimately hurt patients. So, while I recognize that we are trying to understand how and what we can pay for, we need to make sure we understand the risks before we implement programs.

GROFT: We have to focus on available interventions and show the benefits. Living with a rare disorder is extremely costly, not only for the family but also to society. We need good prevalence studies with many diseases. There is excitement and enthusiasm for expanding the whole codification system from the ICD, but it is a long road.

Value Proposition and Ethics

JACKMAN: *I have heard the term value proposition referenced several times. Is that something for which a certain amount of focus is needed, to explain and develop the data and demonstrate the value?*

HAMMARSTRÖM: We need to remember that any life, even one with many disabilities and incapacities, is worth any other life. We have a moral obligation to



The priorities (for rare diseases) are awareness, finding the patients and giving them the treatments that they deserve.

DR. LENNART HAMMERSTRÖM

provide hope for the patient, the family and the next generation who will be born with the same diseases. I am very concerned about the tendency in some quarters to put a price tag on life. Is one year of life worth 40,000 pounds or 50,000 euros?

JACKMAN: *It seems that you are saying that it is much more than just an economic proposition. There is another very important consideration—are we supporting and safeguarding the fundamental values of the society?*

HAMMARSTRÖM: What we are being told is, show me the figures. At a meeting last week the bottom line was clearly stated to me: “You asked for money, but show the data. Prove how effective this is.”

SALTONSTALL: You have to have both data and ethics to sell the story. It is going to become much more complicated this year. It comes back to the point: “a price on a life.” Ethically, we need to look inside ourselves, push some of those economic questions away and start to deal with the tough issues. It is about implementing the Institute of Medicine report and the seven priorities coming out of it. Off-label issues are one of the priorities for us as mentioned in the report. Also, a very clear goal for NORD is to reach out to many more patient organizations, mobilize them and help them have a much stronger voice.

Innovation

JACKMAN: *Let’s talk about innovation. What science do we think is coming in the future for being able to research and develop drugs, therapies and treatments for rare diseases?*

HAMMARSTRÖM: The mechanism of action is going to be important. You can only find that out through genetics or proteomics. That is why we are working to define a number of new diseases. The first disease defined based on Exome sequencing was published in *Nature* in 2010. The costs are coming down. We can see with new technologies on the horizon that full sequencing will be \$1000. We will know what kind of mutation a patient has. Compared with mistreating or not treating a patient, \$1000 is a small price to pay.

GROFT: Everyone is waiting with great anticipation for the increased capacity and ability to speed up diagnosis. Part of the problem is the interpretation of results, and then communication of those results back to the practicing physician, the patient and the family. There are some tremendous implications there. How do we change our lifestyle to adapt to what our genetic make-up is telling us? Communication will be essential to maximize the usefulness of the data.

We need translational research advances into treatments. That is very expensive. Somehow we have to find ways to reduce that cost to speed up development and



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PETER TURNER

better utilize resources. It is an exciting time. Taking advantage of all the resources that are coming and maximizing partnerships between the private and public sectors is essential.

JACKMAN: *Are there closing thoughts on your priorities for rare diseases?*

HAMMARSTRÖM: The priorities are awareness, finding the patients and giving them the treatments that they deserve.

LE CAM: For us, the priorities are to build national strategies and plans between now and the end of 2013 all over Europe. We have organized 15 national conferences in the last six months. We will continue. It is important to bring all stakeholders together across Europe. Awareness is also a part of that effort; we will further promote the Rare Disease Day and create other events in Europe and worldwide.

GROFT: We will continue to increase awareness of rare diseases here at the NIH and other government agencies. Specific projects include a global approach to a patient registry and providing access to biospecimen samples. We are in the process of developing a database of sample repositories and what is available, and how we plan to implement those recommendations from the Institute of Medicine along with effective collaboration with the EU and the US. There is also expansion into Latin American countries, the Caribbean basin and the Pacific nations. Australia is also looking again at their legislation.

I have to compliment CSL Behring for fostering this dialogue which I believe is significant to the rare disease community. The ability to bring the leaders together is just tremendous. I hope we are able to repeat this in the future and bring in others from other parts of the world. I look forward to future discussions and dialogues to really keep things moving.

TURNER: Our role is to provide treatments for rare diseases. We are really looking forward to having new and innovative products approved, and we have several in the pipeline at various stages of clinical development. That is our priority.

JACKMAN: I want to thank everybody for participating. We all see great value in conversation to identify issues and possible solutions. We will disseminate the information obtained today.

The views and opinions expressed in this Key Issues Dialogue are those of the participants and do not necessarily reflect the official policy or position of CSL Behring.

About the Participants



The Dialogue spanned two continents and highlighted a number of universal issues that challenge people with rare diseases around the world.

Dr. Stephen Groft, Pharm.D.

Director, Office of Rare Diseases, National Institutes for Health (NIH)

Dr. Stephen Groft has held a number of positions that focus on rare diseases with federal agencies in the US. He began his career as a pharmacist in the US Public Health Service. From there he went on to serve in the Office of Orphan Drug Development in the Food and Drug Administration and with the Department of Health and Human Services as Executive Director of the National Commission on Orphan Diseases. As Director of NIH's Office of Rare Diseases, he has worked with patient advocacy groups in their efforts to stimulate research for their diseases. Dr. Groft established the Office of Alternative Medicine at NIH and served as Executive Director of the White House Commission on Complementary and Alternative Medicine Policy.

Dr. Lennart Hammarström, M.D., Ph.D.

Professor of Clinical Immunology, Karolinska Institute

Dr. Lennart Hammarström's clinical and research interests are in the field of immunodeficiency, regulation of antibody production and immunotherapy. He has served in a number of teaching, research and administrative positions and received the Research Career Award from the Swedish Medical Research Council for his work in autoimmunity and inflammation. Dr. Hammarström has served on

numerous professional and scientific boards and committees including the Adverse Drug Reaction Committee of the Swedish National Board for Health and Welfare, the Biotechnology Committee of the Swedish Pharmaceutical Association, the Steering Committee of ESID (European Society for Immunodeficiency) and the WHO/IUIS Committee on Primary Immunodeficiencies and has served as President of the Swedish Society for Immunology.

Yann Le Cam

Chief Executive Officer, EURORDIS (European Organization for Rare Diseases)

Yann Le Cam is a patients' association advocate who has years of experience working with health and medical research organizations in Europe and the US in the fields of cancer, HIV/AIDS and rare diseases. He served as a Special Advisor to the French Neuromuscular Association (AFM) and founded the Alliance Maladies Rares, a national umbrella organization of more than 150 patient associations in France. Mr. Le Cam was one of the founding members of EURORDIS and he contributed to the adoption of the European Regulation on Orphan Drugs and other EU legislation and policies on rare diseases. He served as Vice Chair of the Committee for Orphan Medical Products at the European Medicines Agency in London, and now serves as Vice Chair of the EU Committee of Experts on Rare Diseases.



Increasing global awareness of rare diseases among governments and government agencies is critical to ensuring patient access to life-saving therapies.

Peter Saltonstall

President and Chief Executive Officer, NORD (National Organization for Rare Disorders, US)

Peter Saltonstall has more than 30 years of healthcare experience in both for-profit and not-for-profit environments. He has held senior positions within a number of academic medical centers and organizations including Harvard's Brigham and Women's Hospital, Tufts-New England Medical Center and Harvard's Risk Management Foundation. Mr. Saltonstall also played an active role on Capitol Hill in the development of the Patient Safety Act of 2005, which has dramatically improved the reporting of events that adversely affect patients.

Dennis Jackman

Senior Vice President of Public Affairs, CSL Behring

Dennis Jackman is responsible for optimizing stakeholder impact on CSL Behring's ability to provide lifesaving therapies worldwide. Previously he served as executive director of the Plasma Protein Therapeutics Association for North America, the industry group for advocacy, quality standards and communications. He has held senior public affairs positions in the pharmaceutical and biotechnology industries since 1989.

Peter Turner

President, CSL Behring

Peter Turner has more than 40 years of experience in the biopharmaceutical industry, including more than 20 years of plasma fractionation research and development, production, engineering and business expertise. He contributed to the successful acquisition of Aventis Behring to form CSL Behring and has served as its President since the company was established. Under his leadership, the company has introduced two major global products and brought a number of existing products into other markets, expanding therapeutic access for people with rare diseases. Mr. Turner has also served on the Board of Directors of the Plasma Protein Therapeutics Association including four years as Chairman.

About CSL Behring

CSL Behring is a global leader in the plasma protein therapeutics industry. Committed to improving the quality of life for people with rare and serious diseases, the company manufactures a range of plasma-derived and recombinant therapies for the treatment of coagulation disorders, primary immune deficiencies, hereditary angioedema and inherited respiratory disease. The company's products are also used in cardiac surgery, organ transplantation, burn treatment and to prevent hemolytic diseases in the newborn. CSL Behring is a subsidiary of CSL Limited. For more information, visit www.cslbehring.com.



Key Issues Dialogue participants left to right: Peter Turner, CSL Behring; Yann Le Cam, EURORDIS; Dennis Jackman, CSL Behring; Dr. Lennart Hammarström, M.D., Ph.D., Karolinska Institute; Peter Saltonstall, NORD; and Dr. Stephen Groft, Pharm.D., National Institutes for Health (not shown).

This Key Issues Dialogue and previous dialogues are available at <http://www.cslbehring.com/knowledge-center/dialogue-series.htm>.

