Rare Diseases Forum 1
Post Forum Summary Report

Executive Summary

The Rare Diseases Forum 1 was held on October 17, 2018 at the Carnegie Endowment for International Peace in Washington, DC. The event convened leaders and key representatives from patients and advocacy organizations and communities, academia, federal agencies, industry, professional societies and other relevant entities. The Rare Diseases Forum was initiated at the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP) and several patient advocacy and state funded networks. 115 people attended the Forum 1. Of those, 99 attended in person, and 16 people registered for the webcast.

The forum began with opening remarks by Janet Woodcock representing the FDA and other key steering committee members and continued with presentations and interactive panel discussions on current regulatory contexts and real-world cases, identifying what has worked and not in the rare diseases field. Experiences were exchanged to identify current challenges and discuss practical approaches to overcome relevant barriers. It concluded by summarizing discussions and proposing the forum's next steps. Based on those deliberations the forum will now work on addressing the following workstreams: (i) innovation in trial design, including seamless/adaptive designs and platform approaches; (ii) best practices and uses of natural history, registries and other sources of evidence; (iii) use of the totality of evidence and multi domain responder index/ every patient count: developing multi-component endpoints; (iv) biomarkers and disease intermediates; and (v) innovation in biostatics.

Introductions & Project Overview

Veronica Miller (The Forum for Collaborative Research) provided a brief introduction about The Forum for Collaborative Research and reviewed the Rare Diseases Forum key operating principles. Dr. Miller explained that once a new drug candidate has been identified, the only ethical way to move forward is to be as efficient as possible. The forum brings together all stakeholders with the purpose to advance the development of regulatory strategies by maximizing efficiency through collaboration and innovation in key aspects, including clinical trials designs and endpoints data, analytics and data use, gene therapy approaches, and diagnostic platforms. Rare Diseases is the 7th disease area addressed by the Forum for Collaborative Research.

The Forum was opened by Janet Woodcock (FDA/CDER). Dr. Woodcock highlighted the current lack of standards, adherence, common definitions, and common controls particularly regarding clinical research and clinical studies in rare diseases and noted the importance of establishing a common framework and a common ground on key areas, such as definitions, control groups and other standards. Dr. Woodcock challenged the Rare Diseases Forum members to consider a paradigm shift: rather than individual trials for each new entity in each rare disease area, we need to think about trials for a specific disease for which new entities are tested.

Dr. Woodcock emphasized that the current model of drug development – one sponsor's back and forth with the FDA in confidential meetings, does not allow for collective learning and collective understanding in advancement of science. As described in the Critical Path Initiative, we need more collaboration and open dialogue to solve the significant problems, one thing the Forum for Collaborative Research has done over the years in several disease areas. The Rare Diseases Forum is perfectly situated to operate in the technical space between the high-level policy discussion involving Congress and the detailed development plans of drug and diagnostic sponsors. The more defined the parameters are, the more we learn as we go forth. The more we build on what has already been done, and not keep all information behind a wall of secrecy, the faster the field will advance; inferences coming out of clinical research will be more reliable. Bringing together the technical, advocacy, patient, regulator and industry sides – all working towards solving problems, rather than re-invent the wheel each time, allows us to define a problem and search for pragmatic solutions.

Could natural history studies in which people are followed, biomarkers and interventions tested, in the context of all the information/knowledge we already have, be the way to better understand the effect of an intervention? It is very different from current practice and appears counterintuitive. Some groups that are starting to set up these types of projects and the Rare Diseases Forum could provide an outstanding contribution by focusing on identifying and defining standards and techniques, and best mechanisms of implementation of such studies. This would be a significant contribution to the rare disease field, because of the scarcity of patients and their geographic distribution. Let us take this tremendous opportunity to improve evaluation, learn about these diseases, and be able to evaluate interventions as soon as they emerge from the laboratory and tell whether they would work or not for patients and, if they do, move them right into patients.

Other welcoming remarks were provided by Marshall L. Summar (Academic Co-Chair); John F. Crowley (Industry Co-Chair); Frank J. Sasinowski (EveryLife Foundation for Rare Diseases); and Dragos Roman (FDA/ CDER). Dr. Summar commented that even though we have currently 8,000 plus rare diseases conditions, each one with different needs, there are some commonalities that we could address, including how we design our studies so we can carry them out without exhausting patient populations. Mr. Crowley emphasized the need for modernization of clinical studies, and the consistency in applying a regulatory framework and best practices. The opportunities before in this new golden age in medicine (approval of a gene therapy product, precision medicine, CAR T cells) imply vastly different promises for people with rare diseases. Our guiding principles should be: (i) not lowering regulatory standards but elevating clinical science prioritizing safety and efficacy; (ii) a flexible regulatory framework and a custom-tailored approach for every new therapeutic agent in every disease, applying a risk-benefit assessment for each molecule in each disease; (iii) aiming not to create new laws and new statutory frameworks, but to use and optimize existing statutory frameworks to advance these therapies, particularly the 21st Century Cures Act. Lastly, we must always remember that the patient with a rare disease is at the core of all our discussions and deliberations.

Dr. Sasinoswski noted that instead of seeing each case as an "ad hoc one-off" we could instead draw from each of these experiences so we can move forward collectively as a community and look for the commonalities and the ways that we can all advance. Dr. Roman added that another

goal for the forum is to have a data-driven and science-based discussion on issues with a bottom-up approach, looking at very specific issues to create a common connection and vocabulary to figure out a common approach. The need for the Forum space for conversations with industry and other stakeholders; to comprehend and leverage models for clinical programs; dose selections, including direct administration of enzymes therapies into cerebral spinal fluid; and to understand novel trial designs and novel approaches to statistical analysis. Lastly, the need for new approaches since traditional models do not work for rare diseases.

Regulatory Considerations

Please note: All PowerPoint presentations from the forum are available at this link: http://forumresearch.org/projects/rare-diseases-forum/rare-diseases-forum-meetings

The second session provided relevant regulatory considerations for rare diseases. Erica Lyons (FDA/CDER) outlined the FDA/DGIEP mission, commitments, and key drug development considerations, including current challenges, what is mandated and what can be flexible, the Orphan Drug Act, the pediatric rare disease program, and the aim to better incorporate the voice of the patient into drug development. DGIEP's mission is to get safe and effective drugs for rare diseases with serious unmet medical needs to the market in as expeditious a manner as possible. The Division supports innovative, science-based trial designs and recognized the need for enhanced understanding of disease and the patient's experience in advancing the field.

Quoting from Henry Ford: "Coming together is the beginning, keeping together is progress, but working together is success".

We have about 500 approved therapies, representing about 7% of the total population in need. The lack of regulatory precedent is challenging for all stakeholders. This is compounded by the scarcity of patients for individual diseases; the diversity in phenotypes, complicating diagnosis and standardization; the diversity in needs, consequently endpoints, among the diseases; and frequent lack of well-defined endpoints, outcome assessment and biomarkers. The traditional clearly demarcated pre-clinical, phase 1-3 development path is rarely feasible in the rare diseases space, yet the statutory and ethical standards for approval of effective, safe and quality treatments apply. Rare diseases patients deserve the same protection as all other patients.

What constitutes "substantial evidence of effectiveness/clinical benefit" for approval of investigational agents to treat rare diseases? Are two trials, each independently affirming and confirming benefit always required? Essentially, we need to be able to "distinguish the effect of a drug form other influences, such as spontaneous change…. placebo effect, or biased observation", which requires comparison of an active treatment to a control arm (which may be a concurrent placebo, dose-comparison concurrent, no-treatment concurrent, active treatment concurrent, or a historical control). The 1997 FDA Modernization Act allowed more flexibility in determining whether the "substantial evidence" threshold is met: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence". The impact that this new flexibility allowed is seen when looking at approvals for orphan drugs and non-orphan drugs. Among the 423 novel drugs approved between 2006 and 2017, 35% of

orphan drug versus 74% of non-orphan drug approvals were based on 2 or more adequate and well-controlled studies. Conversely, 60% of orphan drug versus 25% of non-orphan drug approvals were based on 1 adequate and well-controlled study plus supporting evidence. Three examples of the flexible approval approach for orphan drugs are Palynziq (approved in 2018), Brineura (2017) and Mepsevii (2017). These cases will be presented in more detail later in the program.

The concept of patient-focused drug development is paramount for rare diseases. The 21st Century Cures Act of 2016 and the 2017 FDA Reauthorization Act (FDARA) have special provisions for incorporating relevant patient experience data and related information into the structured benefit-risk assessment framework in regulatory decision making. The paths to achieve the goal include collecting and utilizing patient/caregiver input; facilitating enrollment and minimizing patient burden; capturing information on patient preferences and acceptability of tradeoffs between benefit and risk; and identifying what information is most important to patients. The rare disease community recognizes the challenges involved in validating patient/observer reported outcomes, especially in small populations across multi-national trials. This is an important challenge for the community of experts to address. Finally, the Orphan Drug Act and the Rare Pediatric Disease Priority Review Voucher Program provide incentives to make the development of drugs for small populations financially viable.

Rachel Witten (FDA/CBER) reviewed the regulatory context for gene therapy, challenges in development, and the assistance that CBER can provide to develop faster and more efficient products. The Office of Tissues and Advanced Therapies (OTAT) has seen a significant rise in new gene therapy IND applications (over 120 applications in 2017). Luxturna was the first approved gene therapy product for an inherited rare disease – retinal dystrophy. The challenges in gene therapy in part mirror those for other drugs, e.g. clinical trial design and endpoints. Additional challenges inherent in the development of gene therapy are quality and consistency of the product, impact of cost and manufacturing capability on dose exploration, pre-existing antibody to the gene therapy product, delivery routes (may need to be invasive), and the co-development of delivery devices (resulting in a combination product).

In terms of safety, the field has less experience with pharmacokinetics of gene therapy products, whereas the concern for drug-drug interactions is relatively low, compared to small-molecule drugs. But insertional mutagenesis, viral vector shedding, immunological reactions to vector or protein products, unknown duration of action, and off-target effects present novel safety concerns. Inherent in the rare disease space is increased uncertainty for safety assessment because of small study populations. Gene therapy research faces unique ethical issues. For example, it is not ethical to expose health volunteers to gene therapy products.

CBER has put in place the INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER producTs) program to allow early engagement of the sponsor to discuss clinical models and trial options. The RMAT (Regenerative Medicine Advanced Therapy) designation, as described in Section 3033 of the 21st Century Cures Act -- for products intended to treat serious or life-threatening diseases, RMAT designation requires that preliminary clinical evidence shows that the product has the potential to addresses an unmet medical need. Following an RMAT designation, sponsors may start interacting with the agency as early as phase ½ and qualify for

a full priority review and accelerated approval. RMAT adds flexibility to the development path in that registry or real-world evidence could contribute to phase 4 confirmatory studies. Like CDER, CBER has been busy publishing clinical guidance documents (hemophilia, retinal disorder, and treatment of rare diseases). In summary, the genetic basis of human disease is complex, and we continue to gain

What has worked, what has not?

Three case studies - 1) Palynziq; 2) Brineura; and 3) Mepsevii – were discussed to illustrate specific challenges and solutions in the rare disease drug development/regulatory path.

The Palynziq Case Study: presented by Holly Weng (BioMarin) and Patroula Smpokou (FDA).

Phenylketonuria, PKU, is a rare, serious genetic disorder, caused by mutations in the phenylalanine hydroxylase (PAH) gene resulting in an inability to break down phenylalanine (Phe). Untreated patients with PKU typically exhibit blood Phe blood levels >600 umol/L. The overall treatment goal in PKU is metabolic control reflected in reduced blood Phe levels which is generally accomplished through strict protein and Phe intake restriction. The main clinical symptoms of PKU in adults include executive dysfunction, inattention, anxiety, and depression. Dietary management requires a severely restricted and difficult to maintain diet. Kuvan (sapropterin), a previously approved BioMarin product for PKU, received traditional approval based on reduction of blood Phe levels. PKU patients still face an unmet medical need as only a small proportion of them (30%) are Kuvan-responsive. BioMarin developed Palynziq (pegvaliase-pqpz), an injectable phenylalanine ammonia lyase (PAL) enzyme, which breaks down Phe into ammonia and trans-cinnamic acid, both excreted in the urine. In that way, PAL substitutes for the deficient PAH activity to reduce blood Phe concentrations. It is a first-in-class product.

The major development/regulatory path challenge was the complicated safety review of the application which included high incidence of hypersensitivity adverse events (HAE), occurring more frequently during the initial induction/titration phase than in the later maintenance phase of treatment phase. 9% of patients had at least one episode of anaphylaxis. FDA and the sponsor agreed on a REMS with ETASU plan, which included education and the requirement to always have injectable epinephrine available. Pharmacies and other dispensing facilities need to be specially certified, drug may only be dispensed with evidence of safe-use conditions, and each patient is monitored and enrolled in a registry.

The justification of accepting reduction in blood Phe concentration (> 20%) as a biomarker predicting clinical benefit were based on the PKU disease definition accepted by the clinical field and the fact that Phe elevation is the fundamental pathophysiologic disturbance causing PKU. Direct studies correlating blood Phe levels with clinical outcome were difficult to carry out within the confines of the study: self-reported patient outcomes would not be appropriate for this patient population and optimized tools for neuropsychological evaluation for PKU were not available.

Patients and clinicians contributed significantly to the regulatory decision-making process. FDA met with NPKUA representative, PKU patients before BLA submission and then also met with PKU adults who were treated with Palynziq in the trials during the review process and solicited their input regarding what matters most to the patient; what constitutes acceptable versus

unacceptable risk; and what information is missing. Questions remain, including how the benefit and risk of Palynziq treatment relates to age (treating children versus adults); how to quantitate the clinical benefit in PKU patients; and how to interpret the pre-clinical embryo-fetal toxicity signal seen with Palynziq. Required post-marketing studies include studies to assess and characterize long-term safety and immunogenicity, observational studies to assess pregnancy outcomes and animal studies to better characterize the embryo-fetal risk.

In conclusion, what worked in the Palynziq case: (i) frequent and open communication among main parties (patients, treating physicians/investigators, company, FDA, etc.) led to a better and mutual understanding of critical issues; (ii) commitment to collaboration and ability to partner together to find solutions shape a program tailored product; (iii) flexibility on the part of all stakeholders, (iv) and incorporation of patient's perspectives into the regulatory decision making.

The Brineura Case Study: presented by David Jacoby (BioMarin) and Elizabeth Hart (FDA).

CLN2 Battens Disease (late infantile neuronal steroid like lipofuscinosis type 2) is a very rare, rapidly progressive, lysosomal storage degenerative disease manifesting as a neurologic dementia, progressing to a vegetative state and death. The field has little clinical experience and no guidelines. Brineura (cerliponase alfa), an enzyme replacement therapy, was approved in April 2017 "to slow loss of ambulation in symptomatic pediatric patients 3 years of age or older with late infantile CLN2 disease". The drug is administered via intracerebroventricular infusion every two weeks, requiring neurosurgical placement of a chronically indwelling reservoir and catheter. Natural history data existed at the time of the pivotal trials, although data was not extensive and lacked standardization. The disease has significant allelic heterogeneity (135 different disease alleles described). However, the clinical course, especially after the onset of symptoms, is predictable and measurable with no identified biomarkers to relate alleles to residual activity and phenotype.

FDA and sponsors agreed on an open label trial design, comparing treated patients to historical controls – a non-concurrent external control. The primary objective was the responder rate of a 2-point loss on a 6-point scale describing ambulation and language. Secondary objectives were brain atrophy measured by MRI, and formation of drug specific antibodies. Ongoing exploratory studies include CSF and plasma biomarkers, QOL family outcomes and developmental assessments. This design presented significant challenges with respect to comparability between treated patients and historic controls, comparability of the rating scale to assess efficacy, bias minimization, analytic methodology and assessing durability of treatment. Treated patients were prospectively monitored every 8 weeks, whereas the historic control studies included prospective data collected at variable time intervals complemented by retrospective clinical data. Challenges in acquisition and verification of data were substantial.

A separate natural history cohort with different patients and raters was obtained independently and used to verify the characteristics of disease progression used as a treatment comparator. Further analyses of the historic control patients, grouped according to the presence of two most common alleles, demonstrated that the contribution of genotype to variation in disease progression was small. Age and baseline scores were the major predictors for disease progression. Use of natural history cohorts comes with a price in the form of conservative

statistical assumptions. The fact that the sponsor extended the study to 96 weeks permitted a clear demonstration of efficacy (in this case on the motor domain) in a Cox Proportional Hazards model.

This case study illustrates the flexibility in designing a regulatory/development path using external non-concurrent controls. Lessons learned include the importance of comparability of data between the treatment and the natural history cohorts, optimization of assessment criteria such as standardized instruments, rater training, and assessment intervals to improve data interpretability.

The Mepsevii Case Study: presented by Qai Abu Ali (Ultragenyx) and Dina Zand (FDA).

MPS VII (Sly's Disease) is an ultra-rare, chronic, progressive, and life-threatening disease caused by a deficiency in beta-the glucoronidase (GUS). The enzyme deficiency results in connective tissue accumulation of dermatan, chondroitin and heparin sulfate glycosaminoglycans. Clinical phenotypes are quite heterogeneous, including hydrops fetalis, enlarged liver and spleen, cardiac and pulmonary involvement, joint and bone abnormalities, corneal clouding, and short stature. Development delay and progressive intellectual disability are key features. Most patients die before they reach their 20's or 30's due to heart or pulmonary failure. The major challenge presented by Sly's disease is the very low prevalence of the disease, with less than 100 living patients worldwide, compounded by significant disease heterogeneity. These in turn hamper the development of a feasible clinical trial design with sufficient statistical power, and the identification of single primary endpoints. Whereas urinary GAG is accepted by EMA as a primary efficacy endpoint, no primary efficacy endpoint existed in the US. The approach agreed on was to evaluate Mepsevii in a randomized, placebo controlled, single cross-over trial, blinded at the start, and a multi-domain responder index (MDRI). The trial consisted of a 48-week double-blind phase, extending into 144 weeks of open label. Groups A-D each eventually received 4 mg/kg of vestronidase alfa IV every two weeks: Group A starting at Week 2, Group B after 8 weeks of placebo, Group C after 16 weeks, and Group D after 24 weeks of placebo.

Because of the limited number of patients available to enroll in this study and the heterogeneity of disease, a multi-domain responder index was created that encompassed six clinical domains presumed clinically relevant to the disease phenotype. These domains were: 6-minute walk test (6MWT), percent predicted forced vital capacity (% predicted FVC), shoulder flexion, visual acuity and the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) for fine and gross motor skill evaluations. Each domain was scored on a pre-specified difference that the Sponsor identified as minimally important. The MDRI as a concept is of interest because this approach offers the advantage of combining responses across different domains, thus assessing a drug's efficacy more broadly. For Mepsevii, completion of tests was impacted by each patient's ability or inability to understand and follow instructions, and many subjects were not able to complete the tests. In the final analysis, Mepsevii was approved based on 3 out of 12 phase 3 patients experiencing significant improvement in the 6-minute walk test, supported by demonstration of improvement in balance, 1 of 3 phase 1-2 patients experiencing significant improvement in percent predictive FVC over time, and 1 of 2 expanded access patients experiencing clinically significant reduction in the need for supportive ventilation over time. Clinical improvements were also supported by the physiologic reduction in the urine biomarker and the significant efforts by the sponsor to recruit

patient from the very limited population available. This case illustrates that each of the MDRI domains, comprised of both the evaluations and responder definitions, require careful consideration for the concept to be fit-for-purpose for a specific disease and a specific patient population. In the Mepsevii case, the agency exercised considerable flexibility to allow patients to have access to the drug.

As in the preceding case studies, the efforts between FDA and Ultragenyx to better understand the disease and the novel aspects of the pivotal study contributed significantly to the outcome of the program. Previously, enzyme replacement therapy for this disease had languished for decades, the drug development stymied by the challenges presented by traditional study designs.

Case Study Discussion: Moderated by Marshal L. Summar, with panelists Margie Frazier (patient advocate), Chester Whitley (University of Minnesota), Jeffrey D Marrazzo (Spark Therapeutics) and Ken Mills (Regenxbio).

The case presentations illustrated the value of collaboration not only between the sponsor and the agency, but also with the patient and clinician community. They emphasized the need to focus on what the measurable outcomes are, the value gleaned from functional testing, and the multiple, innovate ways to validate information (e.g. video). What are some of the consistencies across the 8000 diseases that can be taken advantage of? The patient voice is so important, how can we achieve more of that? Can we use social sciences to develop better tools to better understand how the disease affects patients and their families, and the opportunity to participate in clinical trials?

One of the consequences of dealing with patient heterogeneity is that many patients will not be accepted into clinical trials because of the inclusion/exclusion criteria. That is why the Mepsevii "all comers" approach was so valuable to the community. Once a trial is announced, expectations within the communities can run high, with a lot of disappointment for those who don't make it into the trial. How can we have more inclusion rather than less? We as a field need to set the right expectations. Understanding the science and realizing that none of the interventions will be perfect and work for everyone is essential. We need to be honest and realistic about how to prioritize the science. It was useful to see how the MDRI approach allows flexibility for a multiple different outcome against that background of heterogeneity.

Disease heterogeneity is a fact that should not surprise us anymore. How can we proceed in spite of it? Can we group diseases, group concepts? We need to go back to Janet Woodcocks proposal to make this about the disease, and not individual interventions.

Identifying Gaps & Needs

A discussion moderated by Scott J. Steele (University of Rochester), with Caroline Loewy (Patient Advocate), John F. Crowley (Amicus Therapeutics), Ilan Ganot (Solid Biosciences), Phillip John Brooks (NIH/ NCATS), Dragos Roman (FDA/ CDER), and Barry Byrne (University of Florida).

Building on the presentation and discussion of the three cases studies, what are the key gaps and needs that need to be addressed to advance translational science to improve diagnosis and treatment of rare diseases? Certainly, it is going to be very challenging to continue conducting

clinical trials in rare diseases the way we have been doing them historically. Key topics that emerged for the gene therapy field are consistency in product manufacturing, immunological responses to viral vectors, clinical readiness and the need for collaboration and data sharing.

Production and manufacturing: we need consistency in product manufacturing that enables early phase studies to be well aligned with the pivotal studies that lead to product approval. Optimization of methodologies is so important for the field, and optimization in rare diseases with larger indications such as Duchenne muscular dystrophy could help the process in diseases with ultra-rare indications. This will help de-risk the development. Immunologic responses to vector are especially important when using AAV vectors. Clinical readiness: We don't have enough qualified investigators and adequate systems for long-term follow up.

The oncology field has changed the approach to develop drugs based on etiology of disease rather than the affected organ. We could follow this example for rare genetic diseases, since a vast majority of them are caused by similar mutations. We would group patients with particular mutations and enroll them in a clinical trial. For some of these diseases where we have fewer patients and support groups, this may never will happen, but if we could develop basket trials around shared molecular etiologies, we could get a lot more progress made a lot more quickly. Similarly, gene therapy is a platform, that we should be thinking on genome editors that specifically correct single-based mutations, rather than focusing on any specific disease. We need to put more thought into, early stage clinical trials that take advantage of the science to move the whole process faster.

Another gap is the lack of open, accessible platforms for registries or natural history studies that are so critical to developing drugs and understanding the rare disorders better. It is an onerous burden on patients and families to duplicate their participation in numerous registries and numerous natural history studies, that don't necessarily add value because they are each housed in various different silos. If we really intend to re-conceptualize controls in this field, knowing that the best control is very specific for every single drug and for every single program, we need to create a standard level of data that is fairly high and reach an informative comparison as well as do a positive regulatory decision. There has been a mindset in the industry that registries are proprietary and no one else will have access to them, and that cannot longer be. There should be knowledge that we as companies have to share with regulators, with patient groups, with other companies. Registries are not proprietary. Some companies (e.g. Amicus) are implementing a policy that any registry they develop will be open in the public domain.

In terms of clinical endpoints, we need to come up with new quantifiable measures or other surrogate markers for patients facing disorders that are not measurable on the existing cognitive scales. There are many rare diseases that share common phenotypes where these measurements could be applied across large groups and in some collaboration across various neurological or metabolic conditions that could all benefit from the development of some new endpoints.

Diagnosis also present gaps and needs, since many of the new diseases being discovered are not easily recognized. Reimbursement and access to the sequencing since there is a hesitance to sequence patients when a specific treatment is not expected to be available.

With respect to the affordability of medicines in rare diseases, there is consensus that they are too expensive and will not be sustainable. Insurers are pushing back or denying access to approved medicines. We can't just simply have price controls dictating the price of medicines and we need to work to better define those pathways and reduce risk and uncertainty of clinical development, in order to make those programs more affordable by making them less expensive to develop. The industry has a responsibility to make sure that medicines are fairly priced and broadly accessible. Until we truly have cures, we need to have incremental and meaningful improvements. One of the unintended consequences of the Orphan Drug Act is that it created perpetual monopolies where, the sponsor that is first to market is given a seven-year exclusivity which can turn into a seven-year head start in controlling information, data, registries, patients, making it extremely difficult for second and third innovators. Lastly, we need to address the mindset gap that we have regarding our willingness to take smart risks.

Overcoming Barriers/ Practical Approaches

The fifth session included the presentations "Ensuring Regulatory Flexibility: Need for Quality Data" by Kathleen Donohue (FDA/DGIEP); and "Ethical Considerations for Pediatric Studies in Rare Diseases" by Donna Snyder (FDA/ OC). A multi-stake holder panel discussed the following topics: "Patient Focused Drug Development, Direct Benefit for Pediatrics, and 21st Century Cures for Implementation". Panel members included: Dina Zand (FDA/ CDER), Marshall L. Summar (NORD), Kristin Stephenson (Muscular Dystrophy Association), Josh Lehrer (Global Blood Therapeutics), and Matt Wilsey (Grace Science Foundation). The session was moderated by John F. Crowley.

We are operating at a significant disadvantage in designing our clinical trials due to the large knowledge gaps existing in rare diseases. We can build quality by building a better foundation in the design of our trials. Endpoints should be based on feasibility. Accepting a range of potential endpoints will allow the broadest possible number of patients to participate. Patient focused drug development includes developing patient-reported outcome surveys that can be used in program after program, and cognitive testing tools to continue learning more about a drug after it reaches the market. We need to consider more complex, innovative designs, with flexibility, such as seamless designs and platform trials. Lastly, FDA and EMA approaches need to be aligned.

Over time we have evolved from a view that we must protect children *from* research to a view that we must protect children *through* research. We have an obligation to assure that children are only enrolled in research that is both scientifically necessary and ethically sound. The federal regulations, under the 21 CFR part 50, subpart D, the Additional Safeguards for Children in Clinical Investigations, include requirements that must be met for children to be enrolled in clinical trials. Unique ethical considerations impact the design of clinical studies intended for children with rare diseases. Additional points to consider are the following:

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children.

- If extrapolation of efficacy from adults to children is appropriate, data from adults should be used to support studies in children so that children are not exposed to unnecessary or overly burdensome clinical trials.
- Studies in rare diseases may be initiated in children for diseases that occur primarily or only in children and for which there are limited or no other treatment options only if there is sufficient evidence to support that there is a prospect of direct clinical benefit to the individual child that justifies the risks.
- Adaptive pediatric study designs should be considered to minimize the number of studies needed to be conducted in children. The overall message was that we want to reduce the burden to pediatric patients when enrolling them in trials and collect as much information as we can from adults before we move into these studies.

1) What are the barriers to our goals; 2) To brainstorm ideas to overcome those barriers; 3) What are the practical steps we can begin to take; 4) What are the barriers to implement them?

The Grace Foundation is addressing the challenge of ultra-rare diseases with high degree of genetic heterogeneity (NGLY1) by pursuing five or six different therapies from gene therapy, to small-molecule inhibitors, to potentiators, to exosome delivery mechanisms, to deliver the enzyme inside the cell. Their strategy to overcoming the barrier is to bridge NGLY1 to other more common indications, for example, melanoma, multiple myeloma and Parkinson's.

Another approach to overcome barriers is a real effort to take advantage of some of the same approaches in a consistent way, in terms of flexibility and innovation. We need to find ways to leverage what is known about the mechanism of action of the drug and what is known about the biology of the disease to bring drugs to patients more efficiently. Of course, having objectively measured biomarkers that predict clinical outcome will help.

Natural history data with genotype, clinical and patient reported outcomes is another approach to help advance the field. How does the patient voice come in to this equation in a way that we can see some correlation to both the clinical realities of how that individual is living the disease process and what their genetic diagnosis is? The MDA data hub, a neuro muscular observational research data hub gathering these three types of information on the same patient, genetic information, clinical longitudinal information, and patient-reported outcomes is one example. The platform will be shared and can capture multiple diseases. Significantly, the data hub will be open for inquiries to answer research questions to try to kind of move forward both the development space, but also allow clinicians to really think about how they're caring for patients and being able to kind of compare patients from location to location.

As noted above, data from registries needs to be in formats and vehicles that provide consistency and allow use over long periods of time. We need to coalesce around good, stable platforms that are widely publicly shared, that are economically practical and sustainable. Sometimes we come down very much on to let's protect the patient from the study rather than let's protect the patient from the disease. The rare disease community is too small to afford this approach.

Putting it all together

The final session focused on summarizing the main discussions that took place during the day as well as proposing the forum's next steps. Sandra Lehrman (Patient Advocate) acted as the forum's rapporteur. Veronica Miller (The Forum), Marshall L Summar (Academic Co-Chair), John F Crowley (Industry Co-Chair), and Frank J Sasinowski (EveryLife Foundation for Rare Diseases) guided de discussion and conclusions from the forum 1.

Forum participants were encouraged to think and dream big. We, as a community of patients, families, sponsors and regulators are developing significant toolsets. Whether it is through the use of accelerated approval and appropriate biomarkers, we should think more about intermediate clinical endpoints. This could be a very effective way to get medicines to patients sooner, when it has reached an appropriate evidentiary standpoint. We need to be creative, adaptive, flexible, and realize the consequences of not doing this. Decades ago, we declared a war on cancer. Even though there are many different types of cancers – it's a war on cancer itself. We now need a war on rare diseases. We need that mindset to realize the importance of time to these patients. We may not know precisely and with statistical rigor, but we generally know the natural history of these diseases. We need tighten up on our approaches, with much more rigor. This could be an important outcome of what we are going to talk about in the months and years ahead so that those natural histories may serve in many, many cases.

Based on the deliberation and discussions, key areas for continuing Rare Diseases Forum work include the following workstreams:

1. Innovation in trial design, including seamless/adaptive designs and platform approaches
    a. how can we best leverage lessons learned from the oncology field
2. Best practices and uses of natural history, registries and other sources of evidence
3. Use of the totality of evidence and Multi Domain Responder Index/ Every patient count: developing multi-component endpoints
4. Biomarkers and disease intermediates
5. Innovation in biostatics

Appendix A
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