2019 Rare Diseases and Orphan Products Breakthrough Summit

The aim of this meeting was to facilitate discussion on the most current and urgent topics related to rare diseases and orphan products, to drive innovation, collaboration, advocacy and research

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On 21–22 October 2019, the National Organization for Rare Disorders (NORD) held its annual conference, the 2019 Rare Diseases and Orphan Products Breakthrough Summit, welcoming more than 900 registrants in Washington, DC, US.

The theme of this conference connecting the rare disease community, including patient advocacy groups, government, industry and academia, was: "The time is now". It included perspectives from a diverse group of thought leaders.

The conference was opened with a welcome speech from Peter L Saltonstall, President and CEO of NORD, who reminded the audience that 90% of rare disease patients have no therapy available, and continued with two inspiring keynote addresses from patient advocates. Terry Jo Bichell, Tennessee Rare Action Network Ambassador, NORD, shared her personal story as a parent advocate of a child with Angelman syndrome which has, among other contributions, helped several clinical trials to materialise and resulted in a focus on biomarker research to advance understanding of Angelman disease. Karen Pignet-Aiach, Founder, CEO and Board of Directors Chairperson, Lysogene, spoke about her experience as a parent advocate for mucopolysaccharidosis type IIIA (MPS IIIA), which led her to start a company developing a gene therapy for MPS IIIA patients.

Scott Gottlieb, Partner at New Enterprise Associates and former US FDA Commissioner, gave a much heeded address on drug access and innovation with focus on reimbursement of advanced therapies. He started by stating that Medicare Part D is no longer serving its purpose as drugs have become more innovative, and that the Affordable Care Act has led to bleeding of closed formularies into the commercial market. In his opinion, there is a need to stop monopolies, for example when manufacturers of originator products refuse to make products available to generic companies for basic bioequivalence studies, or in cases where few patients are available for study in clinical trials. Importation of drugs from Europe in the absence of bioequivalence data can increase access to drugs, and innovative trial designs with reliance on natural history studies can minimalise the number of patients on placebo. There are differences in access to curative therapies, as patient access is now based on the type of insurance rather than on the disease's impact. He proposed creating federalised risk pools which would allow premiums to decrease. The major challenge would then be to set the thresholds so patients throughout the country are served equally well; this would also mean that, for example, children would not face delays in access to therapy based on birth date.

Town Hall – A conversation with FDA Centre directors (from second left): Jeffrey Shuren, CDRH; Peter Marks, CBER; Janet Woodcock, CDER. Moderator (far left): Wayne Pines, President, Health Care, APCO Worldwide.

SESSION 1

The time is now: addressing affordability while sustaining innovation

A lively panel discussion considered the relevant focus for affordability: pricing or value. Some considered that insurers were the source of differences among patients, for example when they decide on drug coverage, rather than relying on patient/clinician decision regarding choice of therapy, and clinical guidelines to determine eligibility for clinical trials. Others argued that prioritisation is not panacea and deductibles and co-payments were the real problem. There was general agreement that value (eg, effect on disease, quality of life), rather than pricing or risk, should be the focus. Innovative and novel ways to fund expensive but life-changing treatments, such as pricing for performance and instalment payment were discussed, as well as challenges (for example, when patients change insurer during lifelong payment for a curative drug). Nick Leschly, CEO of Bluebird Bio, noted that industry should regulate itself and make drug pricing sustainable. Finally, it was noted that only nine of the 23 FDA-approved biosimilars are commercially available, which is partly caused by the rebate-based system, and this requires incentives for biosimilars to be adjusted.

SESSION 2

Creating a roadmap for collaboration between patient organisations and industry

The panel discussed ways in which patient organisations can help advance drug development and vice versa. Patient advocacy representatives explained the different ways in which they can help, including raising awareness of clinical trials among patients and physicians,

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thus accelerating recruitment, educating patients, and providing access to key opinion leaders for scientific advisory boards. These organisations have repeatedly stressed that relationships with industry should be established early before there is a need for input (eg, when treatment-naive patients become hard to find). Two examples of such a mutually beneficial relationship were shared: (1) big pharma collaborated on a development of a drug primarily for Ashkenazi Jews and the company subsequently developed a kosher drug, and (2) a company helped to raise awareness of a patient organisation via a meeting with the FDA for the three parties to address a major point. Finally, the panellists considered that neither clinical trial design nor defining clinical endpoints are jobs for a patient organisation. However, the FDA and industry should be led by the question: "Does the patient feel or function better, or survive longer?".

BREAKOUT SESSION ON GENE THERAPY

Overcoming challenges for both patients and manufacturers

The panel discussed the main challenges for manufacturers, including manufacturing of the vector, which is the limiting factor for such therapies. The Alliance for Regenerative Medicine is pushing for regulatory standardisation in the field of gene therapies. Natural history studies are necessary as a baseline for gene therapy medicinal products, which is why patient groups are investing in collecting this information. Parent advocates discussed why families should be included in early clinical trial planning, as they might need to travel significant distances for treatment or follow-up, which results in a huge financial, emotional and psychological burden.

TOWN HALL

A conversation with FDA Centre directors

The panellists agreed that artificial intelligence and machine learning are important topics at the FDA. Another increasingly important topic for rare diseases is the use of Bayesian statistics to tackle the challenges of small population sizes, patient heterogeneity and lack of natural history studies that make the design of clinical trials difficult. The size of the population is a challenging one for device developers in the rare disease space, as prices are lower than for drugs and there is no exclusivity.

Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER), FDA, noted the CDER's major goals for 2020:

Ned Sharpless, Acting FDA Commissioner in October 2019.

The goal for real world evidence in rare diseases is randomising patients, which would decrease costs and speed up development

reorganisation and computer modernisation, individualised programmes requiring new policies and a centre of excellence dedicated to rare diseases. Similarly, Peter Marks (Director, Center for Biologics Evaluation and Research [CBER], FDA) sees collaboration with CDER on small populations, a personalised approach to treatment, and working with the National Institutes for Health (NIH) and patient organisations to make products available for patients as major goals for 2020. Furthermore, he mentioned that manufacturing, rather than cost of clinical development (due to higher probability of success), was the main obstacle for advanced therapies. New manufacturing sites to produce gene therapy vectors are needed to address the current lack of manufacturing and development experience that currently slows down development. Essentially, efficient processes will make treatment of patient populations that are too small to be commercially feasible. The FDA has broadened its outreach and education for patients with regard to biologics and biosimilars.

Goals for the Center for Devices and Radiological Health (CDRH) in 2020 include integrated, specialised and more patient-centric teams for particular technologies, as well as real world evidence (RWE), use of more robust statistical methods and a more collaborative approach (eg, ophthalmologic visualisation and RWE). The panellists agreed that, as a tool, RWE can work well for safety, but its accuracy needs to be improved for efficacy. The goal for RWE in rare diseases is randomising patients, which would decrease costs and speed up development. The need for ongoing collaboration of patient groups with the FDA was advised by panellists, and it was recognised that the FDA values understanding the burden of disease and therapy, along with quality of life for patients. In addition, leveraging patient-scientists was advised to help the FDA to understand the disease. Finally, the panel shared a wish for regulatory independence to stop the need to consult with Congress every time there is a new therapy.

SESSION 3

Acting Commissioner keynote speech

Norman Edward "Ned" Sharpless, the now former, Acting FDA Commissioner, emphasised that the FDA supports orphan drugs and patients and seeks patient input on many aspects, including on trial endpoints. It also makes best use of big data, releases guidance relevant for or focused on rare diseases, and supports devices for rare diseases. Moreover, the FDA has approved research grants and RWE programmes and there is a rare disease accelerator programme.

SESSION 4

Keynote from Alex Azar, Secretary of Health and Human Services

Alex Azar (Secretary of Health and Human Services) noted that: "Effective treatments are often hard to come by, requiring years

Scott Gottlieb, former FDA Commissioner.

of expensive maintenance therapies. When successful therapies are developed, they're not cheap. We need to ensure that Americans who suffer from rare diseases have ways to finance their care – while also making sure that our financing system can support innovation toward the cures we need." Furthermore, he stressed that the government has an important role to play when it comes to financing drugs for orphan diseases and noted that the current administration was focused on thinking about new ways of paying for high-impact, costly drugs such as the so-called "Netflix model" for, for example, hepatitis C drugs.

SESSION 5

Interactive dialogue with FDA senior staff

The panel opened with an explanation that the Office of Rare Diseases is currently standalone. The panellists clarified that patient input is crucial throughout the lifecycle, including before any actual clinical development. The FDA holds listening sessions for patients and caregivers with orphan diseases, and meetings can be requested, with questions answered via a portal. The agency uses these to assess benefit–risk from a patient perspective. The panellists noted that natural history studies provide much information for drug development, including inclusion criteria (patient subgroups), duration of trials, frequency of assessment, endpoints, clinical outcome measures (including patient-reported data) and biomarkers. The FDA encourages use of natural history studies when randomised studies – still a gold standard for efficacy evidence – are not possible or when it is difficult to control all parameters. However, in order for a natural history study to be used as a control for an interventional trial, the baseline patient characteristics need to be similar. If no natural history data are available in life-threatening diseases, a control such as a different dose level or standard of care is needed.

Identifying comorbidities across orphan diseases is important to the FDA, which can support high-quality natural history studies via grants. Standardised tools valid across diseases can help physicians to engage with patients in a way that prevents marginalisation of some patients, but there is still lots of work to do in this respect. Half of all rare diseases affect children and this needs to be considered when designing clinical trials. This can introduce specific challenges for gene therapy trials where no patients are treated with placebo. This, added to the standard difficulties in extrapolating data from adults to children, results in the need for a fine balance between effect and risk. Crucial questions include who reports the effect in children (mother or father), and what if these reports differ? This needs to be well planned in advance, especially when including children of different ages in the same trial, as age-appropriate endpoints may be needed.

The discussion recognised the burden trial participants face, for example frequency of data collection and how this burden may affect, for instance, performance in endpoint assessments. Some measurements (eg, pain, fatigue, sleep disorders) can be used across different rare diseases. The FDA conducts its own studies on optimal methods for collection of patient information and has issued a draft guidance on this. The panellists recognised the major challenges with development of advanced therapies, including the unknowns (eg, durability of effect), manufacturing (especially in the context of scale-up and process changes), devices for organ-specific delivery, immunogenicity, dose exploration (cellular kinetics) and how the gene product compares with the natural protein, clinical trial designs (eg, approval may be based on the first-in-human study and, if so, this study needs to be robust and provide evidence of efficacy even if the sample size is small), and safety (off-target effects, risk of oncogenicity). It is clear there is still a lot to learn in terms of benefit versus risk. Finally, the panellists identified precision and individualised treatment as the major trends in rare diseases.

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BREAKOUT SESSION

Patient registries and natural history studies – impact, data ownership and ethical issues

The panel emphasised that patient registries are a translational tool as they convert individual patient stories in structured data. They also noted that data sharing is hugely important for the NIH, and research grants include clauses to this effect. The panellists queried who should fund natural history studies and patient registries. It was recognised that the cost of platform development can be covered by NORD or the FDA with low fees. However, volunteers are not paid for their contribution.

BREAKOUT SESSION

Ahead to 2020 – investment opportunities in orphan products and rare disease therapies

The panellists acknowledged that the current focus of investors is on transformative effects, but also that valuations will likely need to be adjusted to reflect the reality of the currently challenging environment (including that of rare diseases). The challenge in addressing ultra-rare diseases, which may need a new business model, is in standardising the process and in grouping diseases together via precision medicine and biomarkers. Finally, the challenge of data sharing was discussed and, in particular, the dichotomy between crucial sharing of information while maintaining confidentiality.

Summary

The meeting was all about patients, patient advocacy and patient-centric development, mostly from the US perspective. There were great discussions with the FDA, including the former Acting Commissioner, the former Commissioner, and Directors of the CDRH, CDER and CBER. ■

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