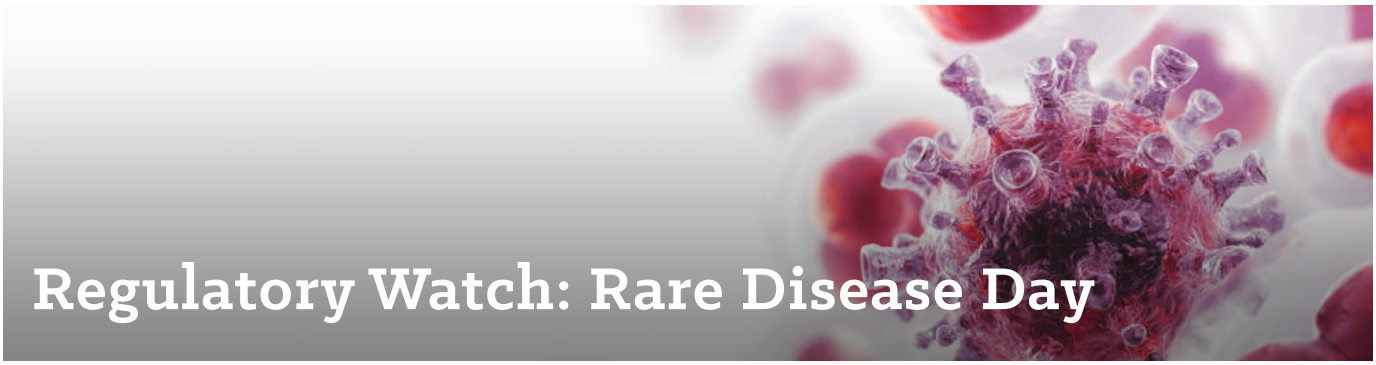

Regulatory Watch: Rare Disease Day

Approvals of orphan drugs have risen significantly over the past two years. The Alliance for Regenerative Medicine said in a report that, at the end of 2019, there were 647 ongoing clinical trials in rare diseases. Of the total, 252 are Phase I trials; 353 are Phase II trials, and 42 are Phase III trials. These trials focus primarily on gene-modified therapies, cell-based IO therapies, cell therapy and tissue engineering.[1]

29 February 2020 was the thirteenth international Rare Disease Day coordinated by EURORDIS[2]. On and around this day, hundreds of patient organisations from countries and regions all over the world hold rare disease awareness-raising activities.

In honour of the day and to continue their long-standing dialogue with the rare disease community, the FDA held their Rare Disease Day 2020 public meeting[3] on 24 February, aimed at "Supporting the Future of Rare Disease Product Development." The day brought together stakeholders to address challenges and opportunities surrounding rare disease product development, and showcased FDA centres' updates and current thinking. The FDA wanted to hear from rare disease stakeholders on strategies to optimise registry and natural history data collection. It also wanted to hear about opportunities and challenges when developing medical products for diseases or conditions that only affect one person, or just a few.

Additionally, in February, the FDA announced their ongoing commitment in this space, in addition to announcing three new actions[4] to support the development of new treatments and support for those living with rare diseases.

- New request for applications (RFA)[5] for the Orphan Products Grants Program[6]. The FDA funds research in rare diseases through congressionally mandated programmes like the Orphan Products Grants Program that supports natural history studies and clinical trials for rare diseases. This new RFA includes "increased clarity of funding goals, continued emphasis on efficiency in all phases of product development and added focus to including patient input into study designs, building successful infrastructure, and leveraging financial resources."
- Additional information on orphan "exclusivity protected uses." This will make information about orphan drug designations and differences between an approved indication and the exclusivity protected indication clearer for patients, providers and drug developers website[7].
- Enhanced rare disease patient website. An enhanced rare disease patient website improved online presence[8] to help patients and their families better navigate the FDA's organisation and its offices supporting the rare disease space.

The morning started with opening remarks from Amy Abernethy, MD, PhD, Principal Deputy Commissioner and Acting Chief Information Officer, FDA and moved swiftly onto the first topic for discussion on "Strategies to Optimise Registry and Natural History Data to Support Rare Disease Product Development". The first session's goals were to provide perspectives on regulatory considerations related to natural history and registry data. The session was moderated by Erika Torjusen, MD, MHS, Director of the Rare Pediatric Disease and Humanitarian Use Device Designation Programs and Pediatric Device Consortia Grants Program, OOPD, FDA, and had panellists including: Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER), FDA, Daniel Caños, PhD, MPH, Acting Director, Office of Clinical Evidence and Analysis, Office of Product Evaluation and Quality, Center for Devices and Radiological Health (CDRH), FDA, Stein, MD, Director, Office of New Drugs and Acting Director for Rare Disease Group, Office of New Drugs (OND), Center for Drugs Evaluation and Research (CDER), FDA.

The second session, Natural History and Registry Data in Rare Diseases, had the goals of outlining the importance of collaboration to support successful registries and natural history studies; identifying common challenges and strategies to address these challenges and to consider the types of data that are being collected, and the intended use of the data. The moderator for this session was Theresa Mullin, PhD, Associate Director for Strategic Initiatives, CDER and panellists included: Kathleen Donohue, MD, Clinical Team Leader, Division of Gastroenterology and Inborn Errors Products (DGIEP), OND, CDER, FDA; Jen Farmer, MS, Chief Executive Officer, Friedreich's Ataxia Research Alliance; Petra Kaufmann, MD, MSc, Vice President R&D, Translational Medicine, AveXis, a Novartis company; Anne Pariser, MD, Director, Office of Rare Disease Research, National Center for Advancing Translational Sciences, National Institutes of Health and Klaus Romero, MD, MS, Executive Director Clinical Pharmacology and Quantitative Medicine, Critical Path Institute.

In the afternoon, the public meeting continued with the topic titled: Rare Disease Product Development: New Opportunities and Challenges. The first of two sessions in this topic was a discussion with FDA Center Directors providing their perspectives on new challenges and solutions for rare disease product development.

Stephen Hahn, the FDA commissioner, stressed the importance of driving rare disease drug development by unleashing the data from very small populations, that is allowing for the modernisation of FDA's approach. FDA has had to revisit an initial decision due to the new data being presented. He spoke to the fact that there was a need to integrate more data sources. It was also stressed that the patient had a voice at the table; FDA was more open to hearing what patients want.

Peter Marks, Director of FDA's Center for Biologics Evaluation and Research, Janet Woodcock, director of FDA's Center for Drug

Evaluation and Research, and Jeff Shuren, director of FDA's Center for Devices and Radiological Health, discussed what their centres are working on with respect to rare diseases.

CDER stressed that the greatest challenge was that not enough was known about rare diseases and not enough patients can be found to enroll for trials. The need to develop more registries and natural history studies was reinforced. It was also noted that FDA has received a number of applications with a single patient in mind and that new policies are coming.

CBER discussed some of the difficulties that companies have in manufacturing cell and gene therapies for such small populations, and how even the not-so-rare diseases become rare when they are split apart into their different genetic mutations. CBER is working on guidance to help companies in cases where a product made with one manufacturing technique can be slightly modified to address a different disease, and whether the drug-maker will be able to just modify that initial application.

On the device side, CDRH discussed the need for new, progressive approvals. It was noted how companies' return on investments can be difficult in the rare disease space because as soon as a new device is brought to market, other companies can re-engineer around intellectual property, making exclusivity periods "generally meaningless". He also noted that there have not been a lot of devices developed under the Humanitarian Device Exemption pathway, noting that there had been "very little innovation" in the paediatric device space.

The next session, Perspectives on Individualised Therapies, had the goal of providing various perspectives on individualised therapies, with an emphasis on regulatory considerations. Panellists included Ella Balasa, a patient with cystic fibrosis and recipient of phage therapy, Virginia Commonwealth University; Patroula Smpokou, MD, Clinical Team Leader, DGIEP, OND, CDER, FDA; Julia Vitarello, Founder and CEO, Mila's Miracle Foundation; Celia Witten, PhD, MD, Deputy Director, CBER, FDA and Timothy Yu, MD, PhD, Attending Physician, Division of Genetics and Genomics, Assistant Professor in Pediatrics, Harvard Medical School.

The session of the Ecosystem of Rare Disease Product Development considered the importance of collaboration to support successful strategies in rare disease product development, discussing factors and considerations in the ecosystem of rare disease product development. The moderator was Susan McCune, MD, Director, Office of Pediatric Therapeutics, FDA. Panellists included Christopher P. Austin, MD, Director, National Center for Advancing Translational Sciences, National Institute of Health; Martha Donoghue, MD, Clinical Lead, Gastrointestinal Cancer Team, Division of Oncology, Office of Oncologic Diseases, FDA; Sheila Mikhail, JD, MBA, CEO, Co-Founder, AskBio; Vasum Peiris, MD, MPH, Chief Medical Officer and Director – Pediatrics and Special Populations CDRH, FDA and Rhiannon Perry, a patient with sickle cell disease and lupus.

At the time of writing this article, the webcast recording can be viewed online[9].

The FDA has approved drugs and biologics for more than 800 rare disease indications. In 2019, the agency approved 22 novel drugs and biologics with orphan drug designation. In CDER, 21 of the 48 novel drug approvals were orphan products. In CBER, one of the five novel biologic approvals was an orphan product.

Since 1990, CDRH has approved 77 medical devices for orphan indications under the Humanitarian Device Exemption program. In

2019, the FDA approved three devices in the programme. CDRH is also currently working with stakeholders from across the medical device ecosystem to vet and further develop a framework, coined 'SHIP' (System of Hospitals for Innovation in Pediatrics), designed to incentivise device development for paediatric and small populations.

Later this year, FDA will begin accepting applications for orphan drug designation through an online portal. The agency said the effort will build on the FDA's Orphan Drug Modernization Plan from June 2017, and will streamline the orphan drug designation request process.

Through the initiatives and communications in this article, FDA and other regulatory authorities are making progress to meet the needs of the rare disease population.

REFERENCES

1. https://alliancerm.org/indication-data/rare-disease-2019-pdf
2. https://www.rarediseaseday.org/
3. https://www.federalregister.gov/documents/2020/01/21/2020-00829/food-and-drug-administration-rare-disease-day-2020-supporting-the-future-of-rare-disease-product
4. https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/rare-disease-day-2020-fda-continues-important-work-treatments-rare-diseases
5. https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-21-001.html
6. https://www.fda.gov/industry/developing-products-rare-diseases-conditions/orphan-products-clinical-trials-grants-program
7. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/
8. https://www.fda.gov/patients/rare-diseases-fda
9. http://fda.yorkcast.com/webcast/Play/465f9f72411b41139af25df30f84b8d51d

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