Success for PWS: A Rare Disease Community's Hope for the FDA Creation and Implementation of the Rare Disease Innovation HUB

We represent the Prader-Willi Syndrome Association | USA (PWSA|USA) and the Foundation for Prader-Willi Research (FPWR), two patient advocacy groups that support thousands of individuals with Prader-Willi syndrome (PWS) and their families. We appreciate the opportunity to share our community's perspective on the Rare Disease Innovation HUB and its potential impact on therapeutic development for the rare disorder, PWS.

PWS medical product development requires consideration of its interrelated metabolic, endocrine, psychiatric, and behavioral effects that evolve across the lifespan. With a pipeline of both small molecule and gene therapy approaches on the horizon, having a predictable and consistent approach to product development and review will be key to bringing safe and effective therapies to our patients in need. Specifically, we are eager to partner with you to explore how to effectively leverage the resources that we, as advocacy groups, have developed, and continue to develop, to successfully support product development across our disease space.

"Success" for the PWS community would mean that the FDA's processes are transparent, responsive, and tailored to the unique needs of PWS. We believe increased engagement with the patient community can result in an increased number of safe and effective therapies that address the core symptoms of PWS, a decrease in the time it takes for these therapies to reach the market, and a regulatory environment that reflects the urgency of this disorder. It also means that our voices are heard, our challenges understood, and our needs prioritized in the drug development and approval process. Ultimately, "success" will be measured by the tangible improvements in the quality of life for individuals with PWS and their families.

We look forward to the new opportunities to effectively engage with the FDA through the Rare Disease Innovation HUB. Our priorities for the Hub include:

1. Streamlined Communication and Collaboration

- **Outcome:** When a reviewer raises concerns about a proposed endpoint or clinical trial design for PWS, there is a streamlined, efficient process in place to ensure immediate consultation with another division or expert within the FDA who has a deep understanding of PWS and the scientific data supporting the endpoint.

- **Impact:** This ensures that decisions are made with the most comprehensive understanding of the disease, reducing delays and misinterpretations that could hinder the development and approval of effective treatments.

2. Recognition of PWS-Specific Clinical Outcome Assessments

- **Outcome:** The FDA works proactively with us to develop and/or optimize PWS-specific clinical outcome assessments into the regulatory framework for drugs targeting PWS, recognizing the unique aspects of assess these features of PWS, such as hyperphagia and behavioral challenges, and their impact on quality of life.
- **Impact:** This leads to clinical trials that more accurately reflect the needs and lived experiences of individuals with PWS, ultimately resulting in the approval of therapies that are truly meaningful to the community.

3. Expedited Review Process

- **Outcome:** The Rare Disease Innovation Hub facilitates an expedited review process for therapies targeting PWS by leveraging cross-agency expertise and minimizing bureaucratic delays.
- **Impact:** Patients with PWS gain quicker access to potentially life-changing therapies, improving their quality of life and addressing unmet medical needs more swiftly.

4. Supporting the Development of Innovative Trial Design and Regulatory Flexibility.

- **Outcome:** The Hub advocates for the use of adaptive trial designs and regulatory flexibility in the context of rare diseases like PWS, allowing for adjustments based on interim results and emerging data. Engagement with the patient community is also needed to understand the challenges in the conduct of clinical trials in PWS.
- **Impact:** This increases the likelihood of successful trials, reduces the risk of trial failure due to protocol design, and accelerates the path to new treatments.

5. Enhanced Stakeholder Engagement

- **Outcome:** The Hub consistently engages with PWS advocacy groups, caregivers, and individuals living with the condition to incorporate their insights into the regulatory process, ensuring that their voices are heard at every stage of drug development and evaluation, with a clear understanding of community's acceptance of risk and tolerance for uncertainty of benefit.
- **Impact:** This leads to a regulatory environment that is more responsive to the needs of the PWS community, fostering trust and collaboration between the FDA and those it serves.

6. Post-Market Surveillance and Real-World Evidence

- **Outcome:** The Hub supports robust post-market surveillance and the integration of real-world evidence to monitor the long-term safety and effectiveness of new therapies for PWS.
- **Impact:** This ensures that once a therapy is approved, it continues to meet the needs of the PWS community and that any unforeseen issues are quickly identified and addressed.

7. Educational and Training Initiatives

- **Outcome:** The Hub initiates training programs and centralized educational resources for FDA reviewers, focusing on the specific challenges and nuances of PWS and other rare diseases.
- **Impact:** This results in a more informed regulatory workforce that can make better, faster decisions on PWS-related therapies, reducing the time to market for effective treatments.

8. Long-Term Partnerships

- **Outcome:** The PWS community and the FDA establish long-term, collaborative partnerships through the Hub, ensuring ongoing dialogue and continuous improvement in the regulatory process for PWS treatments.
- **Impact:** This creates a sustained, impact-driven relationship where the evolving needs of the PWS community are continually met, leading to ongoing advancements in treatment and care.

For the Rare Disease Innovation HUB to be truly effective, it is crucial that certain elements are incorporated into the process of developing orphan drugs:

1. **Inclusion of Rare Disease Experts & Multi-Division Review**: Currently, orphan drugs are often reviewed by a single division within the FDA, which can overlook the multi-systemic nature of many rare diseases. For conditions such as PWS, which impact diverse areas like psychiatry and metabolism, it is critical that experts from both relevant divisions, in addition to rare disease experts, be consulted in the evaluation process.

2. **Mechanism for Advocacy Group Engagement**: In addition to sharing critical information like natural history studies and potential outcomes for drug evaluations, it's essential that advocacy groups for rare diseases are not just contributors but active participants in the creation of these resources. There should be a **Formal Mechanism for Advocacy Group Engagement** that allows advocacy organizations to collaborate directly with the FDA in the **development** of tools, resources, and frameworks that will guide drug evaluations and regulatory decisions.

This mechanism should include mechanisms for:

a) **Co-Creation of Natural History Studies and Outcome Measures**: Advocacy groups, in partnership with the FDA, should be involved in the actual creation of natural history studies and defining outcome measures that are meaningful to patients. These groups have a deep understanding of disease progression and can offer patient-centered insights that are often missed in traditional research. Their involvement from the outset would lead to more relevant, effective, and accurate data collection. Because patient groups may be interacting with and developing tools for studies across multiple sponsors, centering such work with the patient groups may improve efficiency across the PWS clinical trial enterprise.
b) **Formalized FDA-Advocacy Group Collaboration**: There should be a structured platform for advocacy groups to engage with the FDA regularly throughout the drug development process. Such a collaboration could provide input into protocols, outcome assessments, clinical trial designs, and regulatory guidelines that reflect the lived experiences of patients. This ensures that the real-world impact of a disease is considered during the evaluation of therapies.

c) **Integration into Decision-Making Frameworks**: Advocacy groups should have a role in the creation of decision-making frameworks that the FDA uses to assess therapies. By helping define the criteria for evaluation, such as patient-reported outcomes or quality of life improvements, advocacy groups can ensure that the most relevant factors are prioritized. This will help ensure that the therapies developed are not just scientifically sound, but also have a meaningful impact on the patient population.

3. **Incorporation of Patient Input and Formal Assessment of Patient Involvement**: An essential component in the development of therapeutics that address patients' priorities is the inclusion of patient input during the protocol development process. Patients and their families, who live with the effects of these diseases daily, bring a unique perspective that can help shape the design of clinical trials and treatment protocols to be more patient-centered and impactful. This can help identify meaningful outcomes that truly reflect improvements in patients' lives. We support a requirement for sponsors to provide a formal assessment of patient involvement during their protocol development phase. This would ensure that patient input is not just an afterthought but an integral part of the process. A transparent mechanism for tracking and evaluating patient engagement would hold companies accountable and create a standard practice for incorporating the patient voice in rare disease drug development. We would also support a formal assessment of how the FDA utilizes the patient experience data from advocacy groups/the patient community in the benefit-risk assessment for medical product approvals.

In conclusion, we stand ready to collaborate with the FDA through the Rare Disease Innovation HUB to advance meaningful and effective therapies for Prader-Willi syndrome. By fostering transparent, responsive, and tailored regulatory processes, we can together enhance the quality of life for individuals living with PWS and their families. We believe that by incorporating patient and advocacy group input, recognizing PWS-specific clinical needs, and prioritizing the rapid development of treatments, we can make substantial progress. The Rare Disease Innovation HUB represents a promising step forward, and we are eager to contribute our insights, resources, and commitment to ensure that this initiative fulfills its potential to transform the landscape of rare disease drug development. We are grateful for the opportunity to collaborate and look forward to building a future where all rare disease patients have access to the treatments they need.

Sincerely,

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