February 3, 2020

The Honorable Mike Braun
374 Russell Senate Office Building
Washington, D.C. 20510

Re: Request for Comments on the *Conditional Approval Act* (S.3133)

Dear Senator Braun,

On behalf of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) writes to thank you for your dedication to accelerating therapeutic development and access for our community, and to comment on the proposed *Conditional Approval Act* (S.3133 and H.R.5497).

We thank Senator Braun and all co-sponsors and supporters for their concerted efforts to accelerate therapeutic development, regulatory review, and patient access to innovative treatments for individuals with severe and unmet medical needs. We are eager to work with you and all partners to craft legislative interventions that will genuinely accelerate access to promising therapies currently unavailable to the neuromuscular disease community.

While we are supportive of Senator Braun's goal, before proceeding with this legislation, we urge Senator Braun to consider the following challenges that may prevent this bill from successfully accelerating regulatory review and subsequent access to innovative safe and effective therapies. These challenges, if left unaddressed, could hinder accelerated access to innovative safe and effective therapies for the neuromuscular community.

Pathway Specifications: We ask Senator Braun to provide greater clarity on the specifications of the proposed conditional approval pathway. We ask the legislation better clarify or define:

1. The definition of the "likelihood" that a sponsor will be able to provide comprehensive clinical data after the therapy is conditionally approved. How is "likely" defined in this circumstance?
2. How the Food and Drug Administration (FDA) is to ascertain the benefit/risk profile of a therapy without clinical trial data traditionally needed for full marketing approval.
3. The definition of a "costly" confirmatory clinical trial. What is a non-costly confirmatory clinical trial?
4. The number of alternative therapies available, and how satisfactory they are to the intended patient population, in order for a therapy to qualify for conditional approval.

5. The definition of "completed in a timely manner" for FDA-required confirmatory clinical trials.
6. The duration of time allowable for a product to be conditionally approved. Is the product allowed to be conditionally approved for up to five one-year terms, or for no more than a total of three years?
7. What regulatory mechanism will sponsors use to request conditional approval? Will it entail a modified new drug application (NDA) or biologics license application (BLA), or an alternative approval application mechanism?
8. Are user fees currently authorized by the Food and Drug Administration Reauthorization Act (FDARA) applicable to reviewing a product for conditional approval? If not, what resources will FDA have to implement this pathway?

Clinical Trial Recruitment: We urge Senator Braun's office to consider challenges to clinical trial recruitment that may arise if conditional marketing approval is granted to a therapy while clinical trials are ongoing. Many rare disease clinical trials, including those in neuromuscular diseases, can struggle to recruit enough patients to participate, and lengthy delays caused by recruitment challenges can deter biopharmaceutical companies from pursuing rare neuromuscular disease therapeutic development in the first place.

If individuals are able to purchase a therapy that received a conditional marketing approval through the traditional means of accessing an FDA-approved therapy, this could potentially hamper clinical trial recruitment as individuals would prefer to purchase the therapy without stipulations rather than participating in a clinical trial. Furthermore, with neuromuscular disease therapeutic development evolving to better target the genetic underpinnings of diseases, trial sizes are inherently smaller and harder to recruit for as eligible patient populations are chosen based upon genetic subtypes. This also exacerbates methodological challenges in testing the safety and effectiveness of the therapy, further challenging therapeutic development.

We encourage Senator Braun to consider how this legislation may impact clinical trial recruitment, and how to ensure clinical trials would not be negatively impacted by a conditional marketing approval pathway.

Affordable Access: Many neuromuscular disease patients and their families face challenges gaining access to FDA-approved therapies due to coverage denials and utilization management techniques employed by payers. This can result in children and adults having delayed or denied access to what can be life-changing therapies, despite the treatments having full marketing approval from FDA.

We request that Senator Braun consider how these access challenges may be present, or even exacerbated, with conditionally approved therapies. Many insurers already have expressed skepticism on the effectiveness of therapies approved via FDA's accelerated approval pathway. We envision payers may express even more skepticism of the effectiveness of therapies conditionally approved that have not yet shown substantial evidence of effectiveness.

Moreover, Europe's conditional approval pathway for promising therapies exists in a paradigm where many jurisdictions guarantee subsequent coverage and access to the conditionally approved therapy through a centralized healthcare system. This is a key difference between the European and U.S. models, and should be considered if the European conditional approval pathway is to be a model (at least in part) for a U.S. conditional approval pathway.

Consequently, before proceeding with the legislation, we encourage Senator Braun to consider the affordable coverage and access challenges likely to be present with conditionally approved therapies.

Short-Term Impacts: Currently there are only twelve FDA-approved therapies for eight neuromuscular diseases available to treat the neuromuscular disease patient population. While these therapies represent meaningful treatment options for some that can reduce or slow the progression of disease, there are still no cures. This underscores the immediate need for safe and effective therapies to treat neuromuscular disease that are both innovative and accessible, including promising investigational therapies currently in clinical trials.

We encourage Senator Braun to consider policy interventions that could provide more expedient access to promising therapies for patients facing substantial medical challenges today. Even if a conditional approval pathway is created, such a pathway would not necessarily improve patient access to innovative therapies for several years to come due lengthy legislative processes and regulatory implementation.

Consequently, we encourage Senator Braun to consider policies that could increase access to innovative therapies for the neuromuscular community today. Such policies could include alterations to the expanded access process that would make offering investigational therapies to patients outside of clinical trials more enticing to the biopharmaceutical industry. We are eager to work with policy makers to craft policies that could increase access more expediently than a new regulatory pathway.

Accelerated Approval and Regenerative Medicine Advanced Therapy Designation: We ask that Senator Braun consider how a conditional marketing approval pathway may overlap and interplay with the accelerated approval pathway and regenerative medicine advanced therapy (RMAT) designation process. The accelerated approval pathway allows FDA to "base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint".[1] RMAT designation allows certain advanced regenerative medicines to receive increased FDA engagement (as well

[1] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

as other benefits of the breakthrough and fast track designation pathways) based upon "preliminary clinical evidence".[2]

Regulatory redundancy is nonbeneficial to neuromuscular disease patients awaiting a safe and effective treatment, and we encourage you to consider the overlap that may exist between the current accelerated approval pathway and the proposed conditional approval pathway.

Scope of the legislation: As the legislation is currently constructed, it can be interpreted that any treatment for a chronic disease that has been present for longer than three months, requires ongoing medical attention, and limits activities of daily living would qualify for conditional marketing approval. This definition would likely include a vast number of chronic diseases that span the full range of severities and prevalences. This could result in many therapies developed and subsequently considered by FDA each year being eligible for conditional approval, greatly shifting the paradigm of therapeutic regulatory review standards in the U.S. We ask Senator Braun to consider the scope of the efforts to ensure any legislation is appropriately targeted.

Current FDA Mechanisms: MDA requests that you consider the mechanisms that FDA currently employs for accelerating therapeutic development and regulatory review of innovative therapies, and whether a conditional approval pathway would create a meaningful method to further accelerate access beyond FDA's current statutory capabilities. FDA has substantial latitude under current statutory parameters to find a therapy safe and effective, and we request greater evidence and justification be provided showing that a conditional approval pathway would tangibly allow FDA to accelerate access to innovative therapies in ways more expedient than statutorily available today. As advocates for the neuromuscular disease community, we aim to ensure any policy considered in Congress will truly better the lives of the neuromuscular community.

FDA Enforcement Authorities: We ask that Senator Braun consider the enforcement mechanisms available to FDA both in statute as well as in the proposed legislation to allow FDA to revoke conditional approval of a product when appropriate. Currently, FDA has limited authority to remove products from the market as evidenced by challenges FDA has faced in revoking accelerated approval from products that have failed to prove effectiveness in subsequent studies.[3]

Given the further reduction in the quantum of evidence required for conditional marketing approval, we ask you to consider what further statutory abilities FDA may require to be able to efficiently and swiftly remove conditionally approved products from the market if they fail to show effectiveness or violate one of the conditions for eligibility listed in the bill text.

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[2] Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – Guidance for Industry, FDA-2017-D-6159, February 2019

[3] Gyawali B, Hey SP, Kesselheim AS. Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval. JAMA Intern Med. 2019;179(7):906–913. doi:10.1001/jamainternmed.2019.0462

We are incredibly grateful for your support of the neuromuscular disease community, and for your understanding of the immediate need for FDA-approved safe and effective therapies. We are eager to work with you on crafting solutions to these challenges in order to accelerate development, regulatory review, and patient access to innovative treatments.

For questions on the above comments, please contact me at pmelmeyer@mdausa.org, or 202-253-2980.

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs