Congressmen Paul Tonko (D-NY) and David McKinley (R-WV) introduced the HEART Act (HR 1184) on Feb. 16, 2021. Please contact Emily (Emily.Silverberg@mail.house.gov) or Kirsten (Kirsten.Wing@mail.house.gov) to cosponsor the HEART Act.

The HEART Act contains 5 provisions critical to rare patients:

Advisory Committees
When an advisory committee was largely "saved" and resulted in a positive vote recommending approval by the "accidental" attendance of one physician with experience in the science of small studies, we went looking for a requirement that this should occur systematically. There is no such requirement today.

Solution. Require a rare/ultra-rare expert in the science of small population studies at Advisory Committee meetings when the application under review is for a low prevalence condition.

Review Division Transparency
The "orphan" category is actually fairly broad with respect to impacted population, and there may be issues in patient populations below 15-20,000 that are not present when prevalence approaches 200,000. When a review division asks questions that clearly indicate a lack of experience in ultra-rare applications, we went to see how many applications they had reviewed before. This data is unavailable. Is it also unavailable to Congress and to the FDA itself?

Solution. Require annual report to Congress that sets out, by division, how many rare applications were reviewed, Agency actions, and the prevalence #s for that rare condition (this could be pulled from sponsor submission on orphan designation request.)

Review Division Support.
There is an acknowledged and significant difference between review divisions with expertise in ultra-rare conditions. This is not FDA's "fault" given that there are over 7,000 rare conditions out there. An earlier PDUFA requirement called for inclusion of rare disease experts, however it was not mandated, so it occurs haphazardly and is not integrated into the review process.

Solution. Require review divisions to consistently include Rare Disease Program staff as an integral part of review team when reviewing a first drug/biologic or a first disease modifying agent for a particular indication associated with an orphan condition with very low prevalence (not as a volunteer, advisor, or "guest" that can be removed if their participation is unwelcome). This same rare disease program staff support should be extended to support review division decisions beyond just approval to REMS, post market commitments, etc.

REMS.
With so few treatments and often significant unmet medical need in dire life-threatening, life limiting conditions, patients are more willing than ever to participate in clinical trials and

Jim Caro
CEO
Haystack Project
Jim.caro@haystackproject.org www.haystackproject.org

negotiate associated hurdles and requirements in an effort to access treatments that offer hope. Once clinical studies have demonstrated safety and efficacy, however, patients have a legitimate expectation that they can access treatment for their disease. FDA must consult with patients and patient advocates before setting REMS requirements that involve patient participation and/or making assumptions that a REMS burden is reasonable or unreasonable for every patient potentially benefiting from treatment. Requirements on manufacturers, clinicians, and, particularly on patients can have unintended consequences that effectively impede patient access to treatment options.

Solution. For any very low prevalence orphan applications, require FDA to consult with patients/patient organizations in devising or reviewing any REMS elements that require patient action/participation.

European System.
There are already so few patients for clinical trials in ultra-rare conditions. Because these diseases are almost always associated with significant unmet medical need, trials are also of shorter duration than studies on larger populations where existing treatment options push sponsors to include more substantial durability-of-response data in FDA submissions. There is also already a mandate that FDA consider using Real World Evidence to augment data in pivotal trials. To the extent possible, FDA should consider doing what Europe does, i.e., consider data collected in the expanded access and open label extension study.

Solution. Require a GAO study of how the European system reviews ultra-rare applications and its applicability in the US -- Specifically, how the EU allows submission of updated data during the review, including from open label extension studies for patients who remain/continue on drug or cross-over from a control arm after clinical trial data has been gathered and submitted.

Jim Caro
CEO
Haystack Project
Jim.caro@haystackproject.org www.haystackproject.org