June 4, 2018

Roger Brown, PhD, Director
Office of House of Delegates Affairs
American Medical Association
330 North Wabash Avenue, Suite 39300
Chicago, Illinois 60611-5885

*Transmitted via email to roger.brown@ama-assn.org*

**Re: American Medical Association House of Delegates Resolution 217 (Reforming the Orphan Drug Act)**

Dear Director Brown:

On behalf of the 30 million Americans with one of the 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) wishes to express its concerns with Resolution 217 entitled "Reforming the Orphan Drug Act." This resolution contains numerous factual inaccuracies and policy misunderstandings, and the policy changes enumerated within would harm rare disease patients by limiting their access to innovative orphan drugs and biologics.

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

Resolution 217, which we understand will be considered by the American Medical Association (AMA) House of Delegates this month, proposes reforms to the Orphan Drug Act (ODA) of 1983. Within the resolution, a number of concerns are identified surrounding alleged "loopholes."[1]

Given our role in the creation of the ODA 35 years ago, we at NORD are nothing if not invested in the efficacy of the legislation. To support the law's continued success, we are presently engaged in an expansive endeavor to survey the current orphan drug development landscape and explore potential areas for improvement within the ODA. As a part of this effort, last fall we commissioned a report in partnership with QuintilesIMS that shows that many of the commonly held conceptions regarding ODA "abuses" are not supported by empirical data.

With the help of our recent report, we hope to address some of the arguments and proposals articulated in Resolution 217. We also hope to communicate our desire to partner with the AMA on any future endeavors to reform orphan drug development. The ODA is immensely important to our community, and any attempts to reform it must be done in an informed and deliberate manner.

[1]*Reforming the Orphan Drug Act*. Resolution: 217. Medical Student Section, American Medical Association House of Delegates. 2018. 1 (15).

**Concerns Regarding Orphan Designations for "Blockbuster" Drugs**

Resolution 217 states that "several drugs have obtained 'blockbuster' status… sometimes through a multitude of loopholes… one such loophole is the approval for 'orphan designation.'"[2] While there are drugs with orphan indications that have achieved "blockbuster" status, it is misleading to suggest that an orphan indication contributed to achieving blockbuster status. The situation is much more nuanced.

Of the 449 orphan drugs approved between 1983 and 2016, 98 had both orphan and non-orphan indications. One such drug is Humira, which has over ten indications, four of which are for rare diseases. Those four indications comprised just 3.8 percent of Humira's $13.6 billion 2016 sales.[3]

Further, the benefits of orphan designation, such as seven years of exclusivity, only apply to those four orphan indications. Consequently, the ODA does nothing to prevent generic or biosimilar competition from emerging for the non-orphan indications of the drug, such as rheumatoid arthritis.[4]

In the case of a biologic like Humira, the ODA exists to incentivize repurposing, or taking an existing drug and studying it in another disease. This is often characterized quite negatively, but, in the rare disease community, repurposing is necessary to prevent patients from taking medications off-label and risking their physical as well as financial well-being. Humira is indeed a "blockbuster" drug, but its success in and of itself is not enough to suggest that the ODA is flawed.

We believe that the AMA would not support a system in which rare disease patients have little hope of their disease being added to labels of existing drugs because there are no incentives to do so.

**Concerns Regarding Non-Orphan Off-Label Uses of Orphan Drugs**

Resolution 217 claims that " a pharmaceutical company may strategically submit a drug for approval of a single indication…and once approved, the drug is utilized for a variety of off-label uses."[5] We, too, would be concerned if companies were strategically applying for orphan drug designation with the expectation of having the drug widely prescribed off-label for non-orphan conditions, and we certainly believe that this is an issue deserving of additional investigation. However, under the present circumstances, there is not sufficient evidence to indicate that this is happening let alone the specific intent of the companies involved.

One study referenced in the Resolution, titled "the prevalence and cost of unapproved uses of top-selling orphan drugs," certainly presents intriguing evidence of prescriptions for non-orphan uses of orphan drugs growing at higher rates than those for orphan-uses.[6] The study is narrow (only looking at four orphan drugs), however, and, therefore, is limited in its applicability. We believe it would be entirely

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[2] *Reforming the Orphan Drug Act*. Resolution: 217. Medical Student Section, American Medical Association House of Delegates. 2018. 1 (14, 15, 18).
[3] Aitken, Murray, and Michael Kleinrock. *Orphan Drugs in the United States; Providing Context for Use and Cost*. Report. QuintilesIMS Institute. 16.
[4] 21 CFR §316.31(b).
[5] *Reforming the Orphan Drug Act*. Resolution: 217. Medical Student Section, American Medical Association House of Delegates. 2018. 2 (1, 2, 3).
[6] Kesselheim AS, Myers JA, Solomon DH, et al. The prevalence and cost of unapproved uses of top-selling orphan drugs. PLoS ONE. 2012;7:2

inappropriate to extrapolate the findings of a study that analyzed four orphan drugs to justify a change in policy. Further, there is nothing in this study indicating an intent on the part of the companies that developed the orphan drugs in question.[7]

We appreciate and respect the AMA's longstanding commitment to supporting evidence-based policymaking and policy change. We also support conducting additional empirical analysis on this claim. But in the meantime, to support a change in policy based on the scant amount of evidence available would go against the AMA's traditional practices.

**Concerns Regarding "Exorbitant Price Hikes and Increasing Sales"**

The Resolution additionally states that the "exploitation of loopholes within the Act have resulted in both exorbitant price hikes and increasing sales, contributing up to one-fifth of global prescription sales by 2020."[8] According to our October 2017 report, however, that does not appear to be the case. While the number of orphan drugs available on the market has increased, the volume of orphan drugs available has actually trended downward, going from 0.6 percent of all prescriptions in 2003 to 0.3 percent of all prescriptions in 2016.[9]

Additionally, of the $450 billion in total drug sales in the United States for 2016, just 7.9 percent, about $36 billion, can be attributed to orphan indications of approved drugs.[10] Orphan indications have certainly played a role in the increase in spending on specialty drugs, about 20 percent, or $15 billion in growth between 2011 and 2016. Yet, the vast majority of the growth, $75 billion, is attributable to non-orphan specialty drugs.[11]

Finally, while patients can often spend quite a bit on orphan drugs, it is important to remember that the truly exorbitant costs do not compose the majority and, as one would expect, they are almost always pertaining to diseases for which the prevalence is incredible small. Roughly 1 percent of orphan drugs are priced in excess of $500,000 per year, yet they only account for 2.7 percent of orphan drug spending on account of the small patient populations.[12] It is entirely unclear what "loopholes" are being referenced in this claim, and the evidence is actually contrary to the claims.

**Desire to Close Loopholes Identified by the Food and Drug Administration (FDA)**

Resolution 217 articulates a proposal to close "loopholes identified by the Food and Drug Administration."[13] We are again unsure as to what "loopholes" the resolution is referencing as the FDA, to our knowledge, has only identified one such "loophole" that occurs at the intersection of the ODA and the Pediatric Research Equity Act.

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[7] Ibid.
[8] *Reforming the Orphan Drug Act*. Resolution: 217. Medical Student Section, American Medical Association House of Delegates. 2018. 2 (6, 7).
[9] Aitken, Murray, and Michael Kleinrock. *Orphan Drugs in the United States; Providing Context for Use and Cost*. Report. QuintilesIMS Institute. 17.
[10] Ibid. 18.
[11] Ibid. 21.
[12] Ibid. 23.
[13] *Reforming the Orphan Drug Act*. Resolution: 217. Medical Student Section, American Medical Association House of Delegates. 2018. 2 (16).

In February, NORD submitted comments to FDA on its Draft Guidance entitled, "Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases." As stated in our comments, as a result of our dedication to ensuring proper incentives are in place for researching and developing treatments for individuals with a rare disease, we take accusations of loopholes in the system for incentivizing drug development for rare pediatric patients extremely seriously. We are committed to ensuring that these incentives are not only working as intended when they were created, but are also resulting in the robust development of innovative orphan therapies for our patients.[14]

As we also stated in our comments, however, before we feel as if it would be appropriate to take any action, we believe there needs to be additional supporting evidence. As it stands, FDA has provided little evidence, beyond a handful of anecdotal scenarios, that the abuse of this loophole is occurring on a broad scale, and its occurrence is of greater detriment to pediatric orphan designations than the proposed solution would be. Without this evidence in hand, we believe it is premature to pursue policy changes.[15]

In conclusion, before moving forward with Resolution 217, we sincerely hope you will take our perspective, and the perspective of the 30 million Americans with a rare disease, into consideration. Millions of Americans depend on the crucial incentives that the ODA provides to spur innovation in the rare disease space.

Further, once again, we would like to emphasis our desire to let this be the beginning of a constructive dialogue between ourselves and the AMA on ODA reform. Nothing is more central to our mission than securing and maintaining a strong drug development process for the rare disease community.

For questions regarding NORD or the above comments, please contact me at pmelmeyer@rarediseases.org, or 202-545-3828.

Thank you in advance for your consideration.

Sincerely,

Paul Melmeyer
Director of Federal Policy

[14] "NORD Comments on FDA Guidance Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases." Paul Melmeyer to Food and Drug Administration. February 18, 2018.
[15] Ibid.