Retrospective Review of PREA-Related Safety Waiver Language in Labeling

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Abstract/Introduction

The Pediatric Research Equity Act (PREA) gives FDA authority to require pediatric studies under certain circumstances. PREA also allows FDA to waive conducting pediatric studies when evidence strongly suggests that the product would be unsafe. When safety waivers are granted, FDA must include the safety information in labeling. We reviewed FDA databases to determine the number of safety waivers granted under PREA over time and to determine whether the waiver-related safety information was consistently described in labeling.

Materials and Methods

The DARRTS and DRUGS@FDA databases were reviewed to identify products receiving safety waivers under PREA, and to evaluate corresponding labeling for inclusion of relevant safety information. Descriptive comparisons were conducted across four approximately equal time periods: Cohort 1: 2003-2007, Cohort 2: 2008-2011, Cohort 3: 2012-2015, and Cohort 4: 2016-August 2020.

Results

Safety waivers were lowest in Cohort 1 (2003-2007) and highest in Cohort 3 (2012-2015). Data collection for Cohort 4 (2016-2020) was truncated in August 2020 (Figure 1). Safety waivers were most common and approximately equal in patients <17 years (n=55) and <10 years (n=53), and least common in patients 0 to <1 year (n=11) (Figure 2).

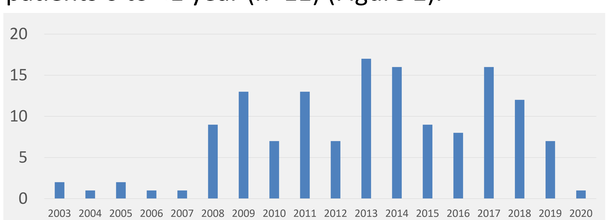

Figure 1. Count of number of Safety-related waivers per year

Results continued

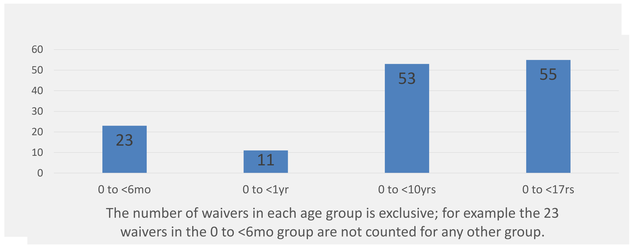

Figure 2. Waivers by ages

Most safety waivers were for drugs rather than biologics (131:11; Figure 3).

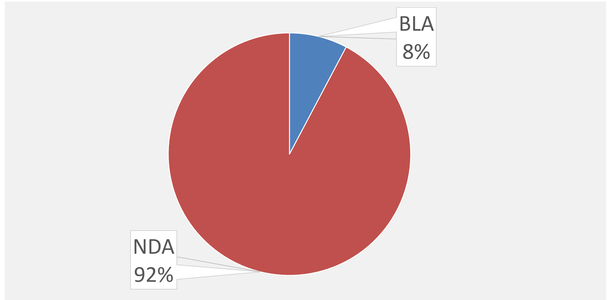

Figure 3. Percent of safety waivers as based on drug or biologic

In Cohorts 2 to 4, the majority of safety waivers were reflected in labeling (Figure 4).

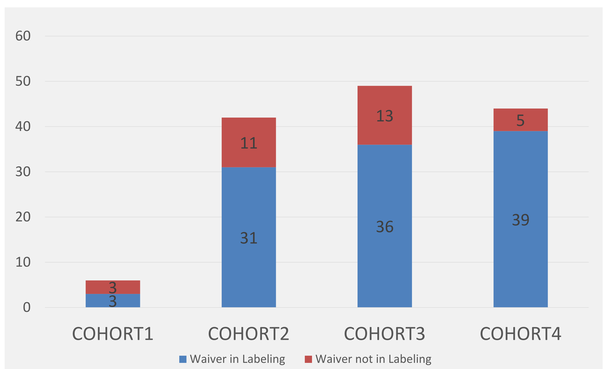

Figure 4. Number of pediatric safety waivers in each cohort that are and are not in labeling

Figure 5 displays waivers by reasons for use (e.g., antihypertensive). Products most commonly receiving safety waivers were for infections (n=38) [antiviral (n=19) and anti-infective (n=19)]. Additional details are found in the legend for Figure 5.
Figure 6 shows waivers by review division. Collectively, DAI and DAV issued the most waivers (13% each). DHM2, DIRM, DMIP, DN1 and DUOG each issued the fewest safety waivers (1% each).

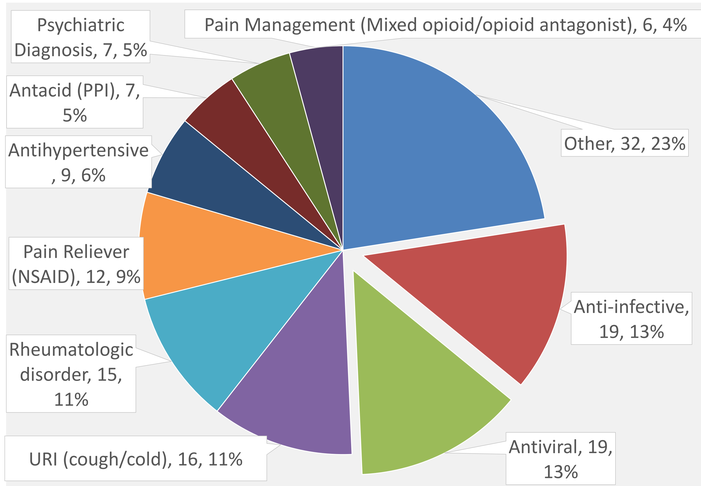

Figure 5. Waiver by reason for use

Legend for Figure 5 (to the left); Other includes: Anti-emetogenic (n=3, 2%), Diabetes, Type 2 (n=3, 2%), Osteoporosis (n=3, 2%), AT III mediated inhibitor of Factor Xa (n=2, 1%), Corticosteroid for topical ophthalmic use (n=2, 1%), Gastroenterologic disorder (IBS) (n=2, 1%), Iron Deficiency Anemia (adults) (n=2, 1%), Imaging agent (n=2, 1%), Neuroinflammatory (multiple sclerosis) (n=2, 1%), Anorectic (sympathomimetic) (n=2, 1%), Acne; non-nodular; necessitating topical antibiotic treatment (n=1, 1%), Allergic Rhinitis; corticosteroid (n=1, 1%), Antidiuretic hormone analog (n=1, 1%), Antihistamine (1st generation) (n=1, 1%), Anti-seizure drug (n=1, 1%), Cancer (hematologic) (n=1, 1%), Phosphate binder (n=1, 1%), Topical Sunscreen (OTC) (n=1, 1%), and Growth hormone-releasing factor (GHRF) analog (n=1, 1%),

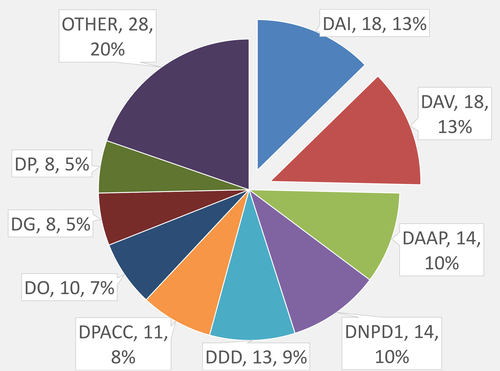

Figure 6: Waiver by drug review division

Legend for Figure 6 (to the right); D = Division. AI = Anti-infective, AV = Antiviral, AAP = Anesthesiology, Addiction Medicine, and Pain Medicine, NPD1 = Nonprescription Drugs I, DD = Dermatology and Dentistry, PACC = Pulmonology, Allergy and Critical Care, O = Ophthalmology, G = Gastroenterology, P = Psychiatry.
Other = Divisions of: Diabetes, Lipid Disorders and Obesity (n=5, 4%), Rheumatology and Transplant Medicine (n=5, 4%), General Endocrinology (n=4, 3%), Cardiology and Nephrology (n=3, 2%), Neurology II (n=3, 2%), Non-malignant Hematology (n=3, 2%), Hematologic Malignancies II (n=2, 1%), Imaging and Radiation Medicine (n=2, 1%), Medical Imaging (n=2, 1%), Neurology I (n=2, 1%), Urology, Obstetrics, and Gynecology (n=2, 1%).

Conclusion

We conclude these data show that FDA has consistently increased the proportion of labeling that includes waiver-related safety information over the four cohorts studied since PREA became law (see blue shading in Figure 4). Fewer waivers in Cohort 4 were likely due to truncation of data collection in August 2020; however, we hope to have additional data in the near future. The data also suggest that the absolute number of safety waivers has increased; however, additional analyses are planned to determine if there is an increase relative to the overall number of PREA studies required over the same time periods.

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