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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Bridging Drug Efficacy and Safety to the Obese: Considerations and Scientific Approaches

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Obesity Considerations in Pediatric Drug Development- 2016-2021

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Disclaimer

- This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of the FDA

- No conflicts of interest to declare

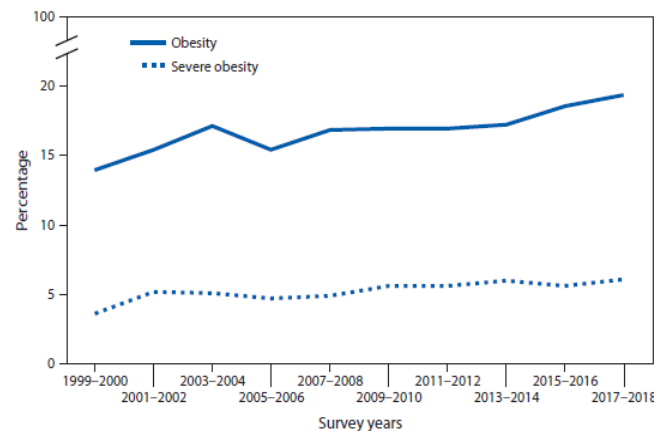
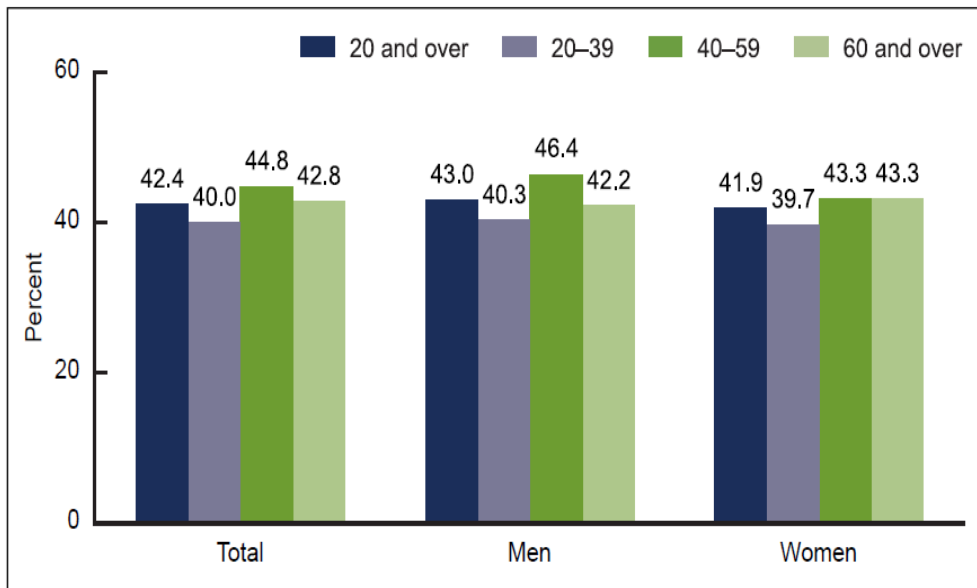
INTRODUCTION



Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2017–2018

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Prevalence of Obesity* and Severe Obesity† Among Persons Aged 2–19 Years — National Health and Nutrition Examination Survey, 1999–2000 through 2017–2018



NOTES: Estimates for adults aged 20 and over were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over. Crude estimates are 42.5% for total, 43.0% for men, and 42.1% for women.

Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db360_tables-508.pdf#1.

SOURCE: NCHS, National Health and Nutrition Examination Survey, 2017–2018.

* Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥95th percentile for age and sex on CDC growth charts (https://www.cdc.gov/growthcharts/cdc_charts.htm).

† Severe obesity was defined as BMI ≥120% of the 95th percentile for age and sex on CDC growth charts (https://www.cdc.gov/growthcharts/cdc_charts.htm).

INTRODUCTION

- Obese children are at a higher risk for developing acute and chronic diseases and consequently require more medications than non-obese children
- There is a paucity of information on how to use drugs safely and effectively in obese children
- Defining the optimum therapeutic dose of a drug depends on an understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of the drug. These parameters are largely affected by body composition and the physiologic changes that occur in obese children.
 - (to be discussed in detail in subsequent presentations)

INTRODUCTION

- Obesity has been incorporated into limited pediatric drug development programs under the FDA Amendments Act (FDAAA) of 2007 and the FDA Safety and Innovation Act (FDASIA) of 2012
- 10-year review of Pediatric programs under BPCA-PREA (2007-2016)
 - Objective - examine incorporation of obesity and dosing recommendations into pediatric studies
 - Limited evidence of obesity related terms in review materials and labeling substantiating the paucity of dosing guidance in obese children



Obesity and Pediatric Drug Development 2016-2021

Objective:

5-year follow-up study to determine changes in obesity considerations in Pediatric Drug Development Program applications submitted to the FDA

METHODS



- New pediatric drug applications submitted under the BPCA and PREA between October 2016 and August 2021 were evaluated
- Determined if **obesity considerations** were included as a variable affecting drug dosing in new product approvals for children
- Data source: Publicly available information
 - Medical and Clinical pharmacology reviews
 - Drug product labels

METHODS



- 5-year survey of pediatric medical and clinical pharmacology reviews BPCA-PREA website (October 2016 to 2021)
- Relevant product labels accessible through FDASIA and Drugs@FDA labels listings after October 2016 were surveyed
- **Obesity related terms** previously used by Vaughn and colleagues:
 - obesity
 - obese
 - overweight
 - BMI
 - body mass index

METHODS



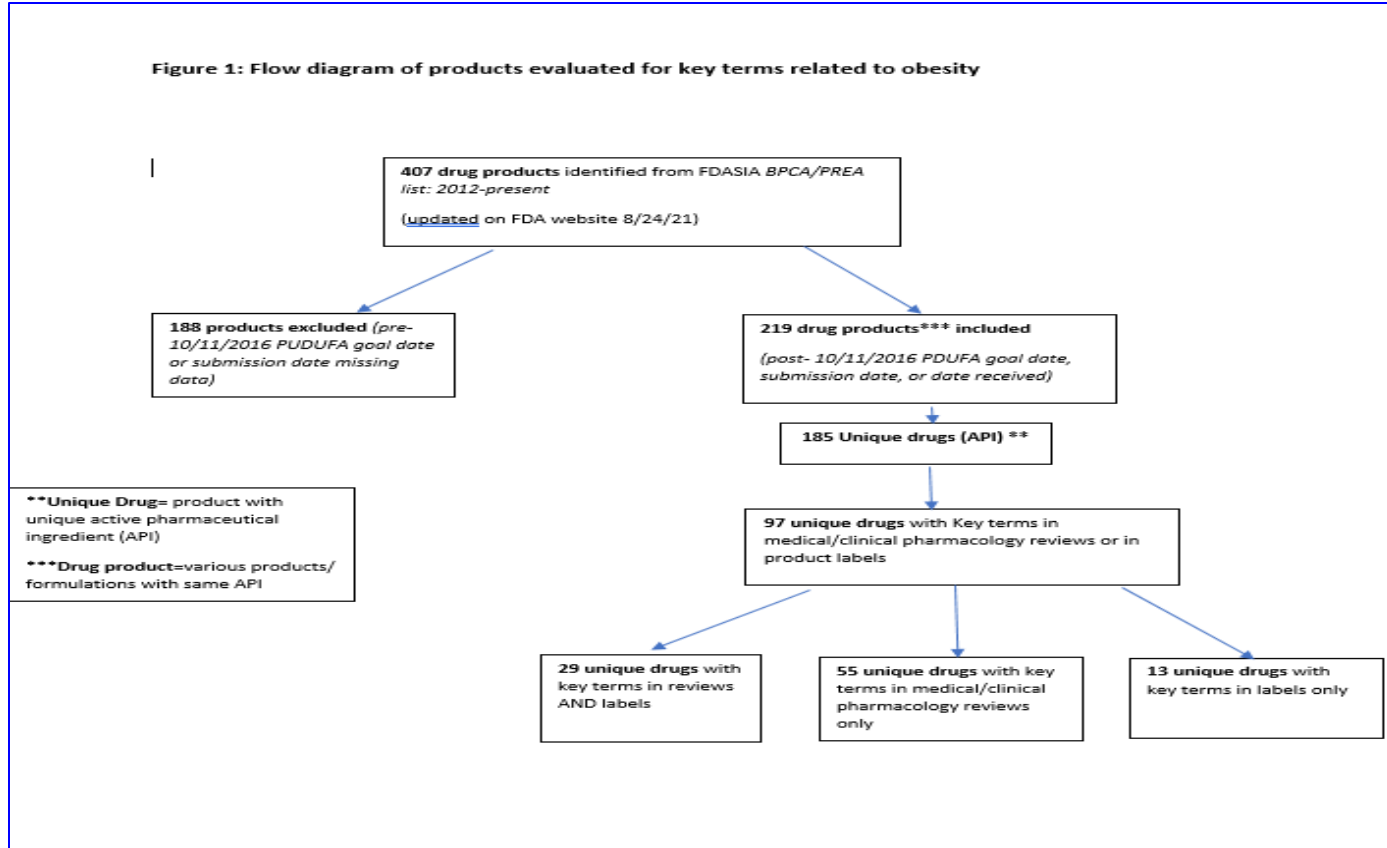
- Information relative to pediatric patients was reviewed for obesity related changes in:
 - Safety
 - Efficacy
 - PK/PD
 - Dosing
- Only drugs with a unique, non-recurring active pharmaceutical ingredient (API) were included in the final analysis

METHODS

- If PK/PD identified as a factor in the initial review, a further evaluation for selected therapeutic areas occurred to determine differences in the PK parameters between obese and non-obese where available:
 - Area under the curve (AUC)
 - Maximum concentration (C_{max})
 - Time to maximum concentration (T_{max})
 - Changes in clearance (CL)
 - Changes in volume of distribution (V_d)

RESULTS

Figure 1: Flow diagram of products evaluated for key terms related to obesity



RESULTS

USE OF KEY TERMS

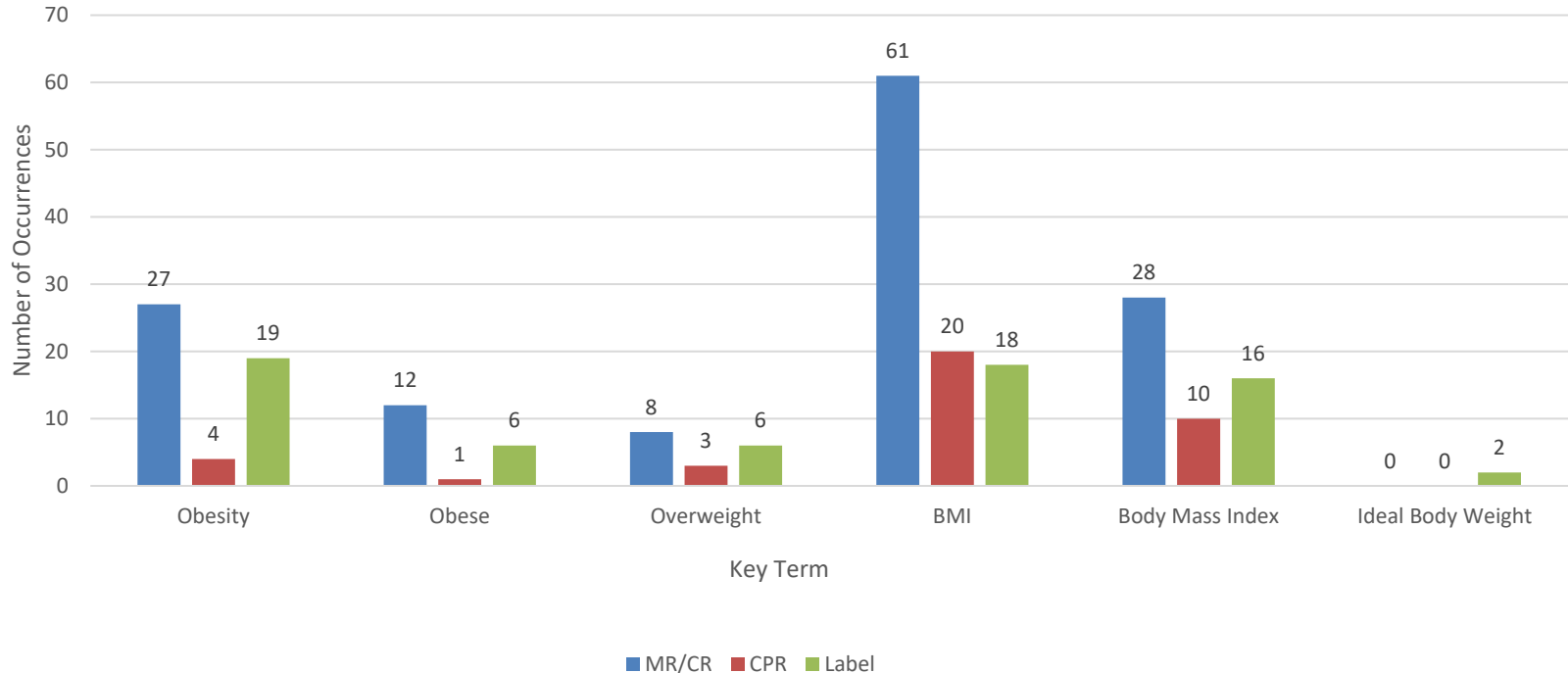


- “BMI” and “Body Mass Index” were the most identified terms across the pediatric unique APIs reviewed in this study followed closely by “Obesity”
- The use of the term “Obesity” was similar to use of “Body Mass Index”
- “Obese”, overweight” and “ideal body weight” were used less frequently.

RESULTS



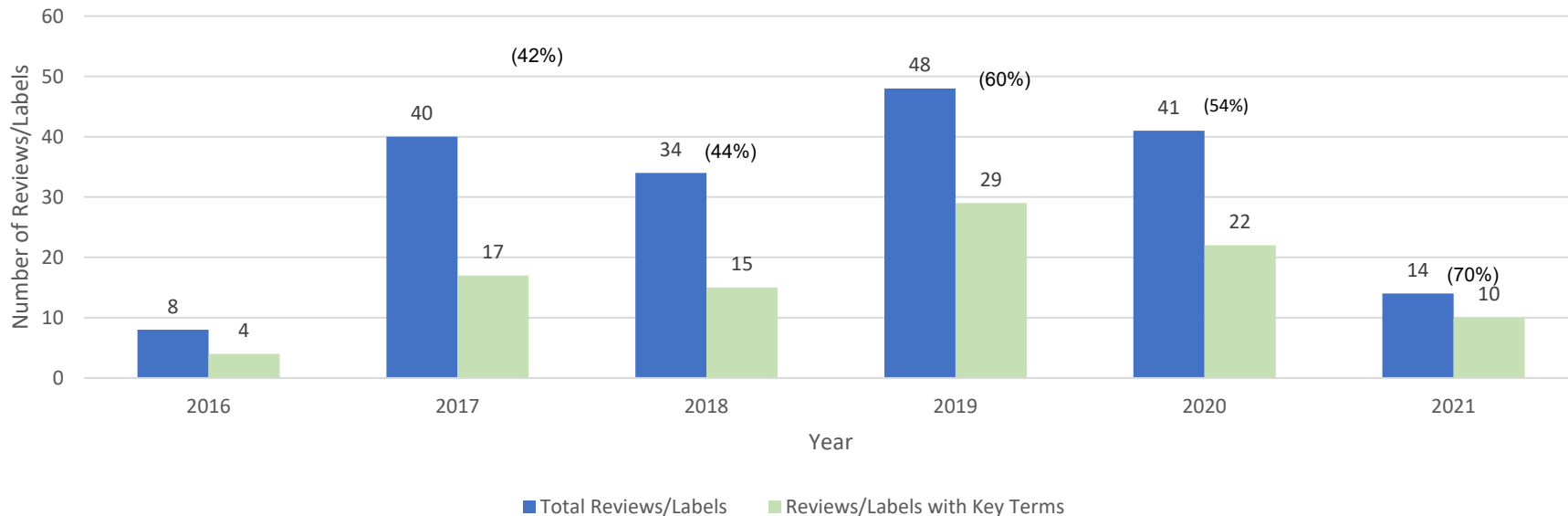
Prevalence of various Key Terms in present study



RESULTS



Reviews and Labels Containing Obesity Key Terms by year (2016-2021)

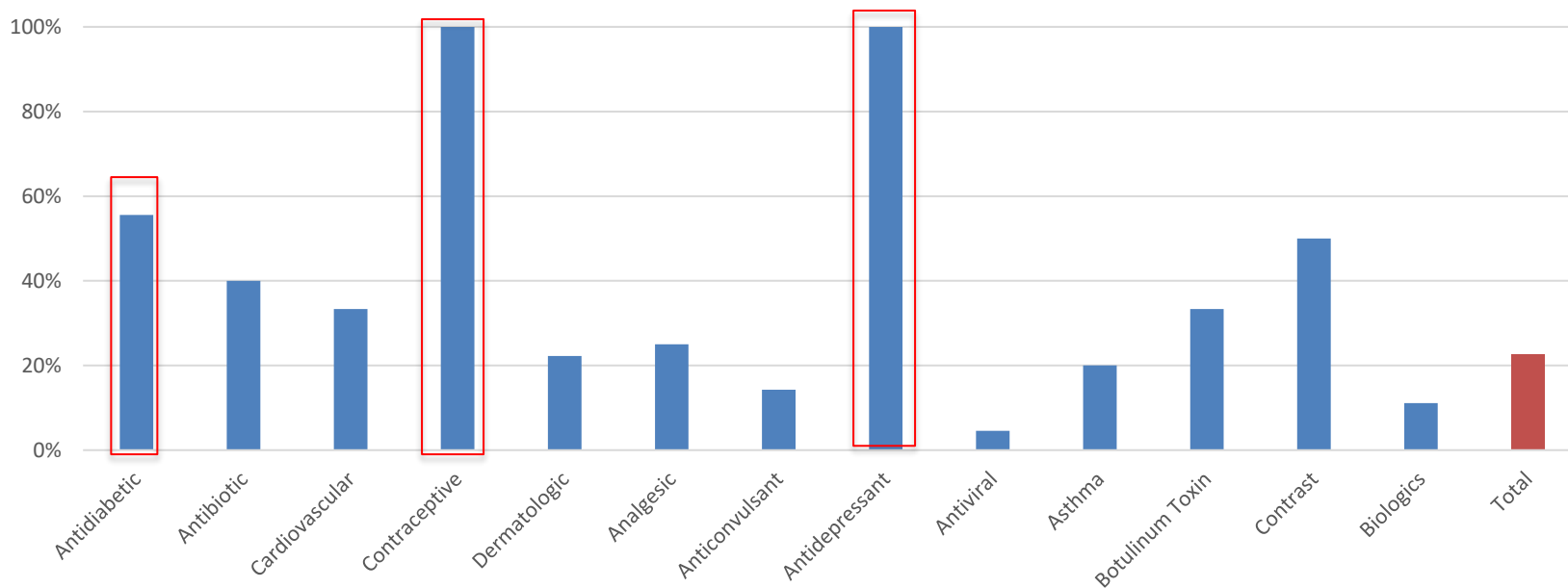


RESULTS

PK/PD AND OBESITY



Percentage of drugs containing obesity related key words for PK/PD



RESULTS

PK/PD AND OBESITY

- Twenty-five unique APIs had terms relating to obesity and PK/PD. Most common therapeutic categories to mention PK/PD as terms along with other key terms for obesity in this study included **antidiabetics, antidepressants and contraceptives**
- A detailed evaluation of selected therapeutic categories for actual PK/PD parameter changes in the normal and obese populations did not reveal any further information on the purported PK/PD changes mentioned in the first round of reviews of the resources used in this study

RESULTS

USE OF KEY TERMS

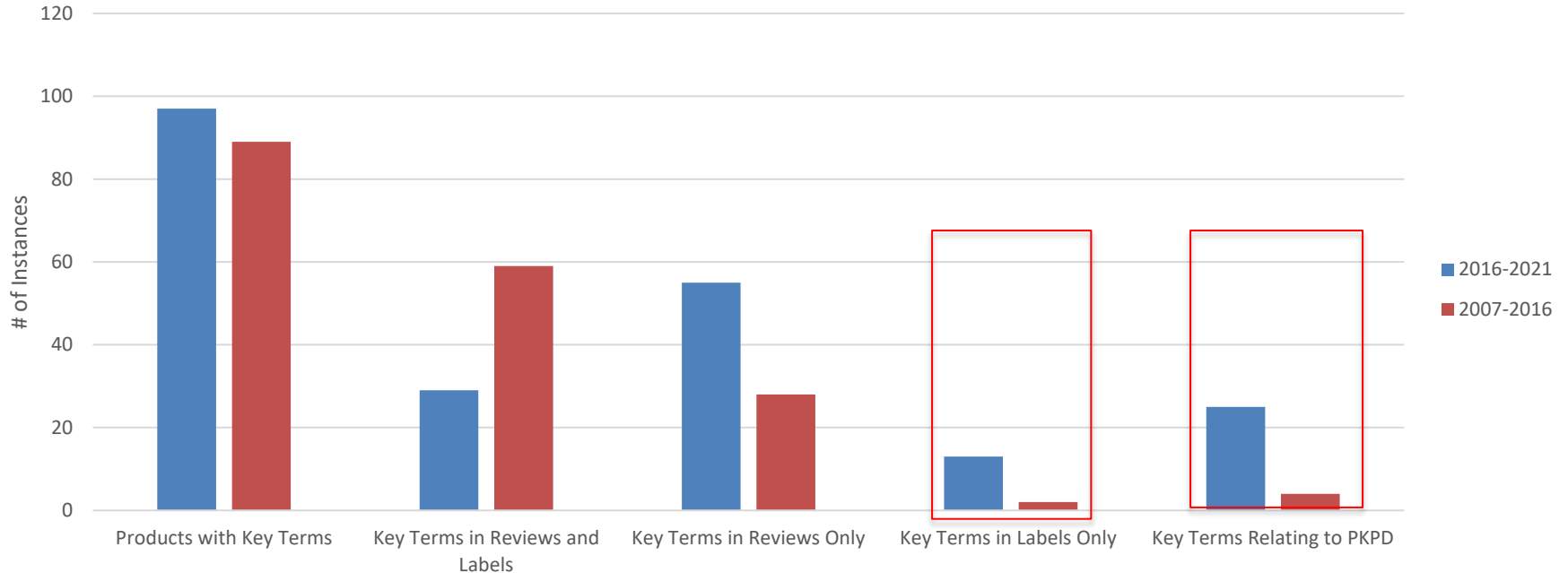
	Vaughns et al (2007-2016)	Present Study (2016- 2021) All Drugs	Present Study, (2016- 2021) Unique Drugs**
Products Reviewed	N/A	219	185
Products with Key Terms (Overall)	89	118	97
Key Terms in Reviews and Labels	59	37	29
Key Terms in Reviews Only	28	66	55
Key Terms in Labels Only	2	15	13
Key Terms Relating to PK-PD	4	30	25

**-Unique APIs

RESULTS



A comparison of Instances of Obesity Related Key Terms in Drug Reviews or Labeling Between 2007-20016 and 2016-2021 study periods



STUDY LIMITATIONS

- Only publicly available data were used preventing detailed evaluation of the implications of the obesity terms found in the reviews
- Due to some methodological differences between the two study periods a direct comparison of the results was not possible
- However, the overall trend suggests some improvement in obesity considerations in the later period



- Obesity considerations in pediatric drug development programs have increased in the last decade but wide knowledge gap still exists for drug dosing in obese children in many therapeutic areas.
 - Most drugs do not contain dosing recommendations for **significant portion of real-world patients for whom the drug is prescribed** (Powell RJ et al .CPT. 2021;1:65-71)
 - Current label recommendations predominately reflect the population studied in pivotal trials that **typically exclude patients who are very young or old, emaciated or morbidly obese, pregnant, or have multiple characteristics likely to influence dosing** (Powell RJ et al .CPT. 2021;1:65-71)
 - Physicians may need to guess the correct dose and regimen for these patients (Powell RJ et al .CPT. 2021;1:65-71)

CONCLUSIONS



- Harmonizing the definitions of obesity amongst various national and international organizations and providing such guidance to industry engaged in drug development may be a first step forward to address this knowledge gap
- Early discussions between regulators, clinicians, and the pharmaceutical industry to discuss pediatric drug development to include a population of pediatric obese patients as a special population within the program to understand the safe and effective use of new drug products in these special patients should be encouraged

CONCLUSIONS

- Tools available to expedite dosing in obesity
 - the availability of real-world data
 - development of predictive models
 - experience with the US Food and Drug Administration (FDA)'s pediatric exclusivity program
 - development of clinical decision software



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- Thank you for your attention!



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