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

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.

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

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

[https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/)
[https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present](https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present)
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

https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present
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 (Cmax)
• Time to maximum concentration (Tmax)
• Changes in clearance (CL)
• Changes in volume of distribution (Vd)
Figure 1: Flow diagram of products evaluated for key terms related to obesity

497 drug products identified from FDASIA BPCA/PREA list: 2012-present
(updated on FDA website 8/24/21)

188 products excluded (pre-10/11/2016 PUDURA goal date or submission date missing data)

219 drug products*** included
(post-10/11/2016 PDLIFA goal date, submission date, or date received)

185 Unique drugs (API) **

97 unique drugs with Key terms in medical/clinical pharmacology reviews or in product labels

29 unique drugs with key terms in reviews AND labels

55 unique drugs with key terms in medical/clinical pharmacology reviews only

13 unique drugs with key terms in labels only

***Unique Drug= product with unique active pharmaceutical ingredient (API)

****Drug product= various products/formulations with same API
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

<table>
<thead>
<tr>
<th>Key Term</th>
<th>MR/CR</th>
<th>CPR</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>27</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>12</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Overweight</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>BMI</td>
<td>61</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>28</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Ideal Body Weight</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

MR-Medical review; CPR-Clinical; Pharmacology review

www.fda.gov
**RESULTS**

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Reviews/Labels</th>
<th>Reviews/Labels with Key Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>2017</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>2018</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>2019</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>2020</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>2021</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

- 2016: 8 total, 4 with key terms (42%)
- 2017: 40 total, 17 with key terms (44%)
- 2018: 34 total, 15 with key terms (44%)
- 2019: 48 total, 29 with key terms (60%)
- 2020: 41 total, 22 with key terms (54%)
- 2021: 14 total, 10 with key terms (70%)

(Chart showing the changes in total reviews/labels and reviews/labels with key terms from 2016 to 2021.)

[Chart showing the data]
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

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Products Reviewed</td>
<td>N/A</td>
<td>219</td>
<td>185</td>
</tr>
<tr>
<td>Products with Key Terms (Overall)</td>
<td>89</td>
<td>118</td>
<td>97</td>
</tr>
<tr>
<td>Key Terms in Reviews and Labels</td>
<td>59</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Key Terms in Reviews Only</td>
<td>28</td>
<td>66</td>
<td>55</td>
</tr>
<tr>
<td>Key Terms in Labels Only</td>
<td>2</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Key Terms Relating to PK-PD</td>
<td>4</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

**-Unique APIs
A comparison of Instances of Obesity Related Key Terms in Drug Reviews or Labeling Between 2007-2016 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.
Inclusion of Patient Populations for Which the Drug will be Used

- 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
• Acknowledgements:
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• Thank you for your attention!