Deriving Pediatric Doses for Locally Acting Drugs (LADs): A US Food and Drug Administration Evaluation

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INTRODUCTION

- Locally acting drugs (LADs) are drugs not intended to be absorbed into the systemic circulation[1].
- We used a tiered definition for LADs: (i) minimal systemic absorption and (ii) in the presence of some systemic absorption, the indication had to be at the site of drug action.
- Pediatric dose selection for LADs presents a unique challenge because limited systemic exposure hinders the utilization of commonly used approaches (e.g., PK matching to adults).
- We believe that pediatric dose selection for LADs is unconventional and lacks best practices that are generally established for drugs that act systemically.

OBJECTIVES

We systematically evaluated drug development and regulatory practices for LADs to develop best practices on approaches to pediatric dose selection for LADs through accomplishing the following aims:

1. Create a database of approved LADs between 2002 and 2020
2. Compare the approved dose for adult and pediatric populations, and identify the supportive evidence for the approved dose

METHODS

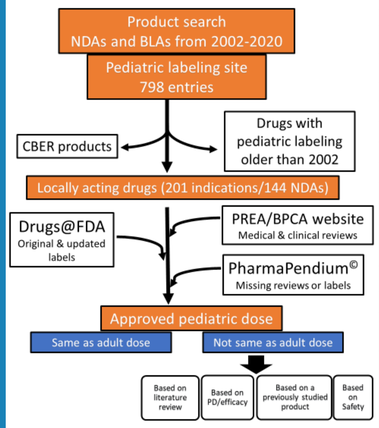


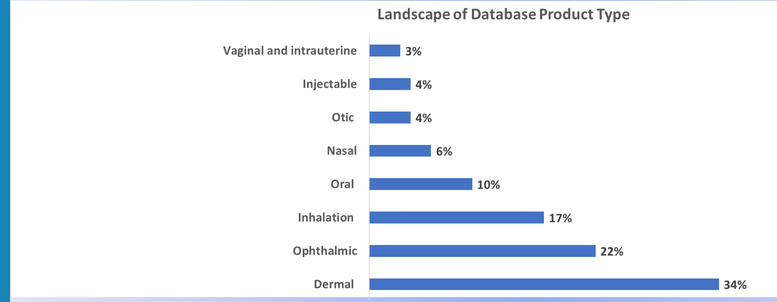
Figure 1. Schematic of the project workflow.

Dose level approach	
Single-dose level	Dose that is given as a single dose level
Titration to target	Dose titration to reach a certain clinical response
Multiple-dose level	Dose that is presented as a range of doses/concentrations/volumes
Other	Dose level that does not fit into any of the above categories
Dose strategy	
Flat dose	Dose strategy without correction for body weight
Weight-based dose (mg/kg)	Dose strategy based on individual's body weight
Weight-band dose	Dose strategy based on body weight cutoffs
Other	Dose strategy that does not fit into any of the above categories
Approved pediatric dose	
Same as adult dose (SAAD)	If the dose language between adults and pediatric dose is the same and the same concentration and dosage strength are used in pediatrics and adults
Not same as adult dose	If the dose language between adults and pediatrics is different
Supporting evidence for approved pediatric dose	
Based on PD/efficacy	Dose supported by independent pediatric PD/efficacy studies with a measurable clinical outcome
Based on literature review	Dose that relies on data and information from the literature
Based on a previously studied product	Dose that is selected based on a previously studied drug product
Based on safety	Dose that is supported based on performing safety clinical studies

Table 1. Definitions used for categorizing approved dose of LADs.

RESULTS

1. Summary of LAD Routes of Administration

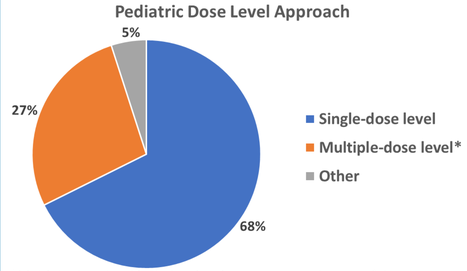


2. Assessment of Labeled Pediatric Dose Level and Strategy

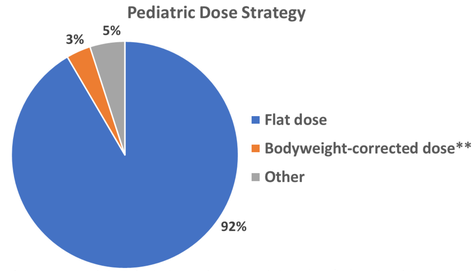
Is the dose level approach between adults and pediatrics different?	
Yes	13%
No	83%

Is the dose strategy between adults and pediatrics different?	
Yes	4%
No	92%

&The values in the tables do not include submissions with only pediatric indications.

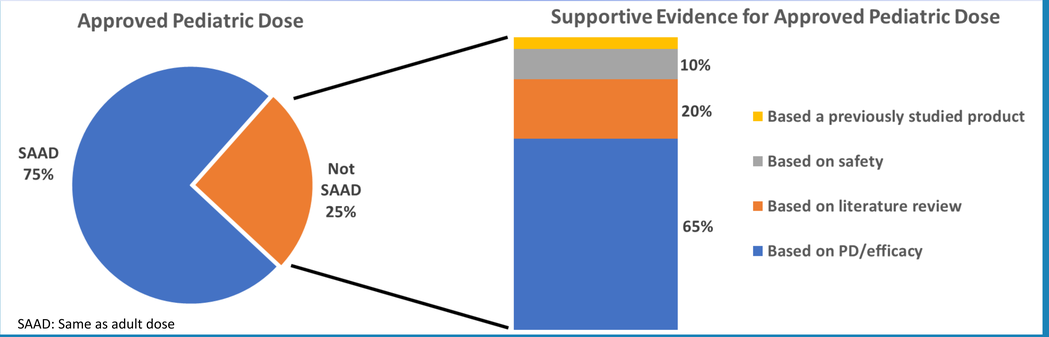


*Multiple-dose level includes titration to target and range of doses



**Bodyweight-corrected dose includes weight-based dose (mg/kg) and weight-band dose

3. Assessment of Approved Pediatric Dose Compared to Adults



SAAD: Same as adult dose

SUMMARY

- The dose level approach was similar between adults and the pediatric population in 83% of the submissions. Majority of the products were labeled for use at a single-dose level.
- The labeled dose strategy was similar between adults and pediatrics in 92% of the submissions. Majority of the products were labeled for use at a flat dose.
- Most LADs were approved at the same dose in pediatrics as in adults (SAAD approach).
- LADs that didn't utilize the SAAD approach were mostly supported by independent PD/efficacy studies in pediatrics.

FUTURE DIRECTIONS

- Learning from these programs will help develop best practices such as guidance documents for LAD dosing in pediatric patients.
- Future work will focus on understanding the pediatric drug development programs for the LADs by looking at the extent of the pediatric clinical programs and initial dose selection approaches at the product type level.

DISCLAIMER

The views expressed in this poster are those of the authors and do not necessarily reflect the official position of the FDA.

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REFERENCES

1. Definition from the Food Drug and Cosmetic Act (FD & C Act).21 USC §355(j)(8).