

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Off-Label Use of Drugs in Pediatrics: Focus on Pediatric Gastroenterology and Approaches for the Future

Andrew E. Mulberg, MD
Deputy Director, Gastroenterology and
Inborn Errors Products (DGIEP)
United States Food and Drug Administration
October 9, 2015

1

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Disclosure


- Nothing to disclose
- The views expressed in this presentation are my own and not necessarily those of the FDA

2

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Take Home Messages

- Medications used to treat pediatric conditions, including many GI illnesses, are frequently prescribed off-label.
- Providers may choose to prescribe off-label, such as
 - To lack of awareness that the product is off-label
 - to lack of approved alternatives
 - to prescribing in accordance with treatment guidelines.
- Pediatric studies conducted under current federal laws are generating much-needed data on the safety and effectiveness of medications used in pediatric patients.
- Development of pediatric age-appropriate formulations is truly needed.



 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Gaps and Opportunities: Long Time Lapse Between Initial Adult Label and Pediatric Label Updates

Time Lapse (in years)		
Difference between Adult NDA and Pediatric Label		
1998–2003	2004–2009	2010–2013
9.64	9.32	9.09
n=31	n=49	n=38


Sources: Analysis was completed using this data set: Orphan@FDA.gov (adult NDA) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed June 2014. Sample size N = 118 pediatric labels randomly selected.

- On average, it takes 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric data.
- Off-label use occurs during this time period.


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov


Explanation of Off-Label Use¹

- Off-label** prescribing refers to use that is not included in or is disclaimed in the regulatory body approved product information (e.g. for a different indication, age group, dose, frequency or route).
- Prescribing an **unlicensed** medicine is when a medicine or dosage form of a medicine has not been evaluated nor approved by regulatory authorities for any purpose (e.g. extemporaneous preparation of a formulation for pediatric use).
- Up to** 40-90% of pediatric inpatients worldwide receive at least one unapproved medicine during their hospitalization, with higher rates in younger and sicker patients. Use in community settings is less and most often associated with new medicines, younger ages, specialist treatment and low-use medicines.


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov


Impact of Off-Label Use

- Pediatric off-label medication use even higher in neonatal intensive care units.
- In 2006, the World Health Assembly, the governing body for the World Health Organization (WHO), and WHO subcommittees for pediatric medications identified the need for approved medications and dosing data for pediatric patients.
- Some long-established and well accepted off-label uses have been shown to be either ineffective or harmful when prospectively evaluated in randomized controlled trials in the pediatric population, e.g. proton pump inhibitors. Further, evidence supporting their longer-term safety is still lacking despite widespread use.

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov


Why Pediatric Off-Label Use Occurs

- There are multiple reasons why providers may prescribe drugs off-label:
 - Providers may not be aware that they are prescribing off-label, or may intentionally choose off-label treatments that are supported by widely accepted recommendations or treatment guidelines.
 - Providers may also prescribe drugs off-label because other on-label treatments have been ineffective, or because there is an established effect from that class of medications
 - Providers might choose an off-label product based on their own experiences, or treatment recommendations
 - Off-label prescribing may be necessary to provide a product in a pediatric-appropriate strength and formulation

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Regulatory Efforts in the US¹⁻⁵

- Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), work together toward the goal of improving pediatric information in labeling.
- The 1997 Food and Drug Administration Modernization and Accountability Act provided incentives to encourage pediatric pharmacologic research. These incentives formed the basis of BPCA, which was initially signed into law in 2002.
- Under BPCA, pharmaceutical companies can be awarded an additional 6 months of exclusivity (market protection) by studying their product in pediatric patients as pre-specified by the FDA

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Regulatory Efforts in the US


- Mandatory pediatric studies were required under the Pediatric Rule (1998), which, although invalidated in 2002, formed the basis for PREA, which was initially enacted in 2003
- Under PREA, manufacturers of certain marketed products are required to conduct studies to provide sufficient data to support directions for pediatric use for the indications claimed in all relevant pediatric age groups.
- Of recent significance, both BPCA and PREA were made permanent and modified in 2012 under new legislation, the Food and Drug Administration Safety and Innovation Act (FDASIA)


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Regulatory Efforts in the US


- Currently under FDASIA in the US, pharmaceutical companies are required, in most circumstances, to create pediatric drug/biologic development programs before phase 3 (pivotal) adult efficacy and safety trials are underway.
- The goal of considering pediatric research relatively early in the development process is ultimately to improve children's access to medicines that have been appropriately studied for the management of their diseases.

10


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Impact of BPCA


- 2012: Institute of Medicine of the National Academies evaluated the impact of BPCA and PREA, concluded 'Pediatric studies conducted under BPCA and PREA are yielding important information to guide clinical care for children'.
- Under BPCA and PREA, since 1998, there have been more than 460 pediatric labeling changes for medications used to treat a range of pediatric diseases.
- Findings from pediatric studies conducted under BPCA and PREA, including important negative or inconclusive results, are described in product labeling.
- Product labeling informs providers:
 - Approval status for a medication for a particular indication and whether product was studied in pediatric patients,
 - product was studied but not approved for lack of efficacy
 - unacceptable adverse events identified in pediatric patients.


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Impact of BPCA

- If pediatric studies are not conducted because of safety concerns, that determination also must be specified in labeling.
- The increased availability of public data can allow providers to more clearly understand the risks and benefits of using medications in specific situations.
- The 460 labeling changes are valuable advances in pediatric care. However, the products studied under BPCA and PREA are not necessarily the products with the most clinical significance or most commonly used off-label in pediatrics. For example, the top therapeutic classes in pediatrics, such as anti-infectives and anticonvulsants, are not the same as the top therapeutic classes in adults, such as cholesterol reducers and cytostatics.

12


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Impact of BPCA

- Furthermore, although there were 460 pediatric labeling changes, pediatric gastrointestinal products, including treatments for viral hepatitis, gastroenterology made up only approximately 22 (5%) of the total products labeled under BPCA and PREA.
- Despite these advances under BPCA and PREA, there remains a paucity of pediatric gastroenterology specific data related to difficulty to enroll pediatric clinical trials and delays in execution of these trials.

Best Pharmaceuticals for Children Act of 2007 (BPCA), and Pediatric Research Equity Act of 2007 (PREA). 2013; <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.


13


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Regulatory Efforts ex-US

- In France, a law (number 2011–2012, December 29, 2011) and a decree on the “Temporary Recommendations for Use” (decree number 2012– 743, May 9, 2012) attempt to regulate off-label drug use.
- In France, drug companies are responsible for monitoring the reasons for which their product is prescribed, reporting off-label use, and educating health care providers to avoid off-label use. Additionally, an observation period may be created to assess the risks and benefits of an approved drug’s off-label uses


14


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

The Problem in Pediatric GI

- Off-label prescribing in pediatrics tends to be higher among pediatric subspecialists, and the percentage of off-label gastrointestinal medications may be as high as 80% in the pediatric outpatient setting.
- The issues of off-label medication use in pediatric gastroenterology was published as part of the 30th anniversary issue of the Journal of Pediatric Gastroenterology and Nutrition. Authors from Australia, Asia, Europe, and the United States described the need for approved products to treat inflammatory bowel disease, infant GER, and eosinophilic esophagitis (EoE)⁵⁻⁶


15

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov


The Majority of Drugs Used in Pediatric GI Are Off-Label

- Shah: "Most patients hospitalized at tertiary care pediatric institutions receive at least medication outside the terms of the Food and Drug Administration product license."
- Off-label drug use was particularly noticeable with drugs targeting the CNS and drugs related to fluids, nutrients, and GI tract.
- High percentage of patients received off-label treatment with
 - metoclopramide
 - polyethylene glycol electrolyte solution
 - docusate
 - ondansetron.

Bozzano⁸ reported 80% of drugs used for gastrointestinal indications are used off label. Much of this off label use was associated with Miralax


 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Expediting Drug Development

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Background


- Longstanding FDA goal to facilitate and expedite development and review of new drugs to address unmet medical need for serious conditions
- Existing Programs
 - Subpart E regulations (1988)- speeding the availability of new therapies for serious conditions with unmet medical need, while maintaining safety and efficacy standards
 - Accelerated Approval Regulations (1992)
 - Fast Track (1997)
 - Priority Review (1992)


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Regulation and Investigation: The FDA's Role In Advancing GI Innovation

- The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, expands the FDA's authorities and strengthens the agency's ability to safeguard and advance public health by:
- [Promoting innovation](#) to speed patient access to safe and effective products;
- [Increasing stakeholder involvement](#) in FDA processes; and
- [Enhancing the safety of the drug supply chain](#)
- [Giving the authority to collect user fees](#) from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products

19



 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

Regulation and Investigation: The FDA's Role In Advancing GI Innovation

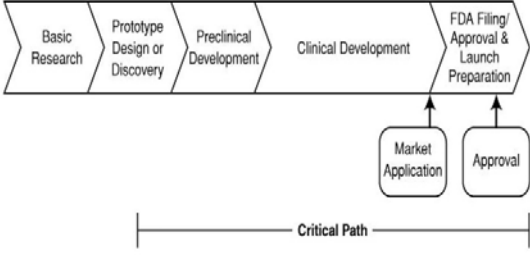
- FDASIA gave FDA a new expedited drug development tool, known as the "[breakthrough therapy](#)" designation.
- This new designation helps FDA assist drug developers to expedite the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases.

Expedited Programs for Serious Conditions — Drugs and Biologics:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

20


 U.S. Food and Drug Administration
 Protecting and Promoting Public Health
www.fda.gov

The Critical Path for Drug Development



<http://inside.fda.gov:9003/downloads/CDER/OfficeoftheCenterDirector/ucm027174.pdf>

21

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

**Best access to safe and effective
treatment is having an approved
product on the market**

22

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Pathway to An Approved Product

- How do we get there?
- What are the obstacles?
- How can a partnership among stakeholders facilitate achievement of this shared goal?
 - Assist in identification of clinically meaningful, measurable and interpretable endpoints
 - Assist in identifying acceptable designs for trials that can enroll AND answer key questions
 - Share a commitment to completion of a successful drug development program


23

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Critical Partnerships

- Academic Experts
- Patients and Families
- Industry
- Regulatory Partners


24

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Take Home Messages

- **FDA and stakeholders can work together to achieve innovation and an appropriate balance between:**
 - **Providing access to promising drugs/biologics for patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy**
 - **Protecting patient safety**


25

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Take Home Messages

- **All stakeholders involved in the drug development process including, but not limited to, academia, industry, patient and disease advocacy groups, and regulatory agencies must work collaboratively**
- **Efforts to promote efficient, scientifically sound clinical development programs to address off label use of drugs through the drug approval regulatory pathway should be the goal**

26

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

References

1. Karesh A, Tomaino J, and Mulberg AE. Off-label use of medicine in pediatrics: focus on gastrointestinal diseases. *Curr Opin Pediatr* 2013, 25:612–617
2. Karesh A and Mulberg AE. US Perspective on Off-label Use in Pediatrics. *JPGN* Volume 56, Number 2, February 2013
3. Mulberg AE. Pharmaceutical Industry in Pediatric Drug Development: Partners and Collaborators With Academia and the FDA. *J Pediatr Gastroenterol Nutr*, Vol. 47, November 2008.
4. **Pediatric Drug Development: Concepts and Applications**, 2nd edition. Mulberg AE, Murphy D, Mathis L editors. 2013
5. Wynn E and Mulberg AE. Off Label Use of Drugs for Gastrointestinal Diseases in Children: Focus on EoE. *J PGN* 2012.
6. Yamashiro Y, Martin J, Gazarian M, et al. Drug development: the use of unlicensed/off-label medicines in pediatrics. *J Pediatr Gastroenterol Nutr* 2012; 55:506–510.

References

7. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med* 2007; 161:282–290.
8. Bazzano A, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr* 2009; 9:81–88
