International Coherence of Pediatric Drug Labeling for Drug Safety: Comparison of Approved Labels in Korea and the United States

Yun-Kyoung Song[1], Nayoung Han[2], Gilbert J. Burckart[3] and Jung Mi Oh[2,*]

The objective of this study was to analyze information on pediatric use in Korean drug product labels and compare it with that in US Food and Drug Administration (FDA) labeling information. Prescription information on pediatric use contained in the commonly used drugs' product labels approved by Korean government was compared with that approved by the FDA. Among the top 50 commonly prescribed drugs, 20 drugs were deemed to have insufficient prescribing information in Korean drug labels. Pediatric prescribing information regarding indication, approved age, formulations, and safety was insufficient in Korean drug labels compared with those in the FDA. Most important, the adverse events frequently reported in Korean children were not sufficiently presented in drug labels. In conclusion, this study highlights the urgent need for the Korean regulatory agency to encourage and accelerate research and development to increase the extent of pediatric prescribing information to be added to drug labels to promote appropriate drug prescribing for children.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Very few regulatory initiatives related to drug labeling for children have been undertaken in countries other than the United States and in Europe.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is pediatric labeling information sufficient in Korea in the absence of a pediatric regulatory framework to promote drug review in children compared with that in developed countries?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Pediatric labeling information for drugs commonly used or frequently reported adverse events in children was insufficient in Korea. This is the first systematic analysis to show a shortage in the pediatric information of drug labels in the absence of a pediatric regulatory framework compared with those in the United States regarding approved age, safety information, and pediatric formulations.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Industry, academia, and government should cooperate with each other to strengthen pediatric drug regulations appropriate for a domestic setting. The establishment of international coherence of pediatric drug labeling based on clinical trials and adverse event information could contribute to pediatric drug safety.

Drug labeling should provide science-based prescribing information to give healthcare professionals the information they need to prescribe drugs safely and effectively for their approved indications.[1] However, due to the lack of evidence or regulatory delays in labeling updates, recommendations for pediatric drug use are often missing. This may expose children to a higher risk for side effects, unwanted drug reactions, and medication errors.

In the past decade, significant attention and effort have been made to overcome gaps in prescription drug labeling by major policy changes and innovations in the field of pediatric pharmacotherapy in developed countries. The adoption of pediatric regulatory initiatives in the United States and then in European Union (EU) has led to more pediatric studies and labeling with both requirements and incentives for pediatric studies of drugs.[2,3] The US Food and Drug Administration (FDA) pediatric labeling

[1]College of Pharmacy, Daegu Catholic University, Gyeongsan-si, Gyeongbuk, Korea; [2]College of Pharmacy, Research Institute of Pharmaceutical Sciences, Seoul National University, Gwanak-gu, Seoul, Korea; [3]Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. *Correspondence: Jung Mi Oh (jmoh@snu.ac.kr)

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rule of 1994, the FDA Modernization Act of 1997, companion legislation of the Best Pharmaceuticals for Children Act in 2002, and Pediatric Research Equity Act (PREA) of 2003 have led to significant advances in the field of pediatric labeling information.[4] The EU pediatric regulation enacted in 2007 also intended to encourage development of suitable medicinal products for children, thereby prioritizing children's real therapeutic needs by promoting high-quality research and improving information available on the use of medicines in children. The results of all pediatric studies were to be submitted to the appropriate authority, and included in the product labels, independent of whether the pediatric indications concerned were approved by the appropriate authority.[5,6] The ultimate aim of these pharmaceutical policy initiatives is to provide additional data on safety, efficacy, and dosing of currently available medicines and to stimulate routine testing that may lead to pediatric labeling at the time of the initial drug approval.[4–6]

Very few regulatory initiatives related to drug labeling for children have been undertaken in countries other than the United States and in Europe. In Korea, 4-year data and marketing exclusivity has been granted for products with pediatric indication and dosage since 2014 through a reexamination system.[7] Although its primary purpose is to secure the safety and efficacy of newly approved drugs, it also protects originator pharmaceutical companies that conduct clinical trials on Korean children from competition in the market by precluding the approval of generic drugs for the prescribed periods.[8] However, there is no comprehensive legislation to mandate development of pediatric medicines or strengthen drug safety for pediatric patients. Therefore, an evaluation of pediatric labeling information in Korea in the absence of a pediatric regulatory framework compared with that in the United States or Europe would be very informative regarding the international application of pediatric drug use and international coherence of pediatric drug labeling. The inclusion of pediatric adverse event (AE) information in such an analysis would be critical since recent information supports the fact that adult AE information is insufficient to predict the incidence of AEs in pediatric patients.[9,10]

The objective of this study was to analyze information on pediatric use in Korean drug product labeling for drugs frequently prescribed and commonly reported AEs and to compare it with that in FDA labeling information.

RESULTS

Labeling information for frequently prescribed drugs in Korean pediatric patients

As shown in **Table 1** and **Table S1**, among the top 50 commonly prescribed drugs in the pediatric population, 20 drugs were prescribed without adequate pediatric information in labels, accounting for 22.0% of total prescriptions. None of the drugs prescribed frequently in Korean children were approved by the European Medicines Agency (EMA), and 32 drugs among the top 50 were not approved in the United States.

Streptodornase/streptokinase, an antiinflammatory enzyme, was used in 66.0% of pediatric patients, although the drugs are approved only for adults in Korea. Chlorpheniramine, hydroxyzine, and corticosteroids, such as prednisolone and methylprednisolone, were also prescribed frequently in the pediatric population without adequate information in the Korean labels, although they are indicated for children in the FDA-approved labels. Labels for gastrointestinal drugs, such as trimebutine, mosapride, tiropramide, and rebamipide had insufficient information for pediatric use in the Korean drug labels, although these drugs were commonly used in Korean children. There were differences in how drugs were prescribed as off-label treatments due to inadequate prescribing information per age groups. The younger the age, the greater the proportion of children were prescribed drugs not indicated for their age groups. Not only were 17 of the top 50 drugs frequently prescribed used in children aged 2–5 years without adequate labeling information, but 23 drugs have insufficient information for adolescents in Korean labels. With increasing age, drugs for gastrointestinal tract (e.g., cimetidine and mosapride) and analgesics (e.g., loxoprofen and aceclofenac) were prescribed mostly without the adequate information in pediatric patients.

Labeling information for drugs with AEs frequently reported in Korean pediatric patients

Table 2 shows drugs with commonly reported AEs in Korean children and their labeling information, such as the approved age of administration and AEs counted more than 1% of total AE reports, but not listed in the Korean label. There were 42,119 AE reports from the 734 drugs used in pediatric patients in this study. The incidence of AEs was high in drugs for nervous system, including methylphenidate, fentanyl, and tramadol, but some of the reported AEs in children (i.e., burning micturition for fentanyl) were not listed in the label. AEs were also reported frequently for systemic antiinfective agents available for pediatric use, and most of these AEs were listed in the label. With increasing children's age, pediatric patients frequently reported AEs not listed in the Korean label mainly in drugs for the nervous system or antineoplastic agents.

Pediatric information in drug labels of the Korean Ministry of Food and Drug Safety compared with that of the FDA

For the 103 drug products approved by all regulatory authorities in Korea, the United States, and the EU, pediatric labeling information approved by the FDA or EMA was similar in 72.8% of the products. However, compared with the United States, 22.3% of the drug products had no indication for pediatric use, and 11.7% of the products lacked pediatric formulations in Korea (**Table 3**).

In the United States, 456 drug products with 393 active ingredients had new pediatric labeling information until December 2016. This information was derived from 599 label revisions for studies conducted in response to the Best Pharmaceuticals for Children Act, PREA, or the Pediatric Rule. **Table 4** shows pediatric information of drug labels approved by the Korean Ministry of Food and Drug Safety (MFDS) in comparison with those approved by the FDA. Among 456 drug products approved in the United States with pediatric information in drug labels, 155 (34.0%) products were not marketed in Korea, such as amoxicillin extended-release tablets and amphetamine tablets. Seventy-two (15.8%) products were not approved for use in pediatric patients based on Korean drug labels, although the FDA approved their use in children (**Table S2**). These drugs included mainly cardiovascular

Table 1 Labeling information of drugs used without adequate pediatric information among the top 50 drugs prescribed frequently in Korean pediatric patients according to age groups: comparison between Korea and the United States[a]

			Age of administration in drug label	
	Drug (ATC)	Percentage of patients[b]	Korea	USA
Total (0–18 years)				
1	Streptodornase/streptokinase (M09AB)	59.7	Adults	N/A[c]
2	Chlorpheniramine (R06AB04)	34.9	Adults	≥ 6 years old
3	Loxoprofen (M01AE)	27.6	Adults	N/A
4	Trimebutine (A03AA05)	25.4	Adults	N/A
5	Cimetidine (A02BA01)	20.9	No information on age	≥ 12 years old
6	Prednisolone (H02AB06)	19.4	Adults	All ages
7	Mosapride (A03FA)	18.9	Adults	N/A
8	Methylprednisolone (H02AB04)	15.8	No information on age	≥ 1 month old
9	Tiropramide (A03AC05)	15.4	Adults	N/A
10	Rebamipide (A02BX14)	13.3	Adults	N/A
11	Hydroxyzine (N05BB01)	12.6	Adults	All ages
12	Piprinhydrinate (R06AA07)	12.1	Adults	N/A
13	Bepotastine (R06AX)	11.7	Adults	N/A
14	Lidocaine/epinephrine (N01BB52)	11.5	Adults	≥ 3 years old
15	Sodium chloride (B05CB01)	11.2	Adults	All ages
16	Tramadol (N02AX02)	10.2	Adults	Adults
17	Levosulpiride (N05AL07)	10.2	Adults	N/A
18	Phloroglucinol (A03AX12)	9.5	No information on age	N/A
19	Azelastine (R01AC03)	8.7	Adults	N/A
20	Dexamethasone (H02AB02)	8.7	Adults	All ages
Early childhood (2–5 years)				
1	Streptodornase/streptokinase (M09AB)	92.2	Adults	N/A
2	Acetylcysteine (R05CB01)	88.2	≥ 6 years old	N/A
3	Chlorpheniramine (R06AB04)	75.1	Adults	≥ 6 years old
4	Trimebutine (A03AA05)	49.6	Adults	N/A
5	Domperidone (A03FA03)	37.6	≥ 12 years old	N/A
6	Prednisolone (H02AB06)	37.3	Adults	All ages
7	Ammonium chloride/chlorpheniramine/dihydrocodeine/ methylephedrine (R05FA)	36.7	≥ 12 years old	N/A
8	Hydroxyzine (N05BB01)	32.6	Adults	All ages
9	Bacillus subtilis/streptococcus faecium (A07FA01)	32.5	≥ 12 years old	N/A
10	Pseudoephedrine/triprolidine (R01BA52)	30.4	≥ 12 years old	≥ 6 years old
11	Piprinhydrinate (R06AA07)	23.9	Adults	N/A
12	Phloroglucinol (A03AX12)	19.2	No information on age	N/A
13	Erdosteine (R05CB15)	17.8	Adults	N/A
14	Sodium chloride (B05CB01)	15.1	Adults	All ages
15	Fenoterol (R03AC04)	14.8	Adults	N/A
16	Methylprednisolone (H02AB04)	12.6	No information on age	≥ 1 month old
17	Lidocaine/epinephrine (N01BB52)	11.1	Adults	≥ 3 years old
Middle childhood (6–11 years)				
1	Streptodornase/streptokinase (M09AB)	67.8	Adults	N/A[c]
2	Chlorpheniramine (R06AB04)	41.6	Adults	≥ 6 years old
3	Trimebutine (A03AA05)	31.1	Adults	N/A
4	Domperidone (A03FA03)	25.2	≥ 12 years old	N/A

(Continued)

Table 1 (Continued)

	Drug (ATC)	Percentage of patients[b]	Age of administration in drug label	
			Korea	USA
5	Loxoprofen (M01AE)	20.4	Adults	N/A
6	Prednisolone (H02AB06)	19.8	Adults	All ages
7	Ammonium chloride/chlorpheniramine/dihydrocodeine/methylephedrine (R05FA)	17.4	≥ 12 years old	N/A
8	Cimetidine (A02BA01)	15.7	No information on age	≥ 12 years old
9	Lidocaine/epinephrine (N01BB52)	14.8	Adults	≥ 3 years old
10	Methylprednisolone (H02AB04)	14.1	No information on age	≥ 1 month old
11	Hydroxyzine (N05BB01)	13.9	Adults	All ages
12	Piprinhydrinate (R06AA07)	12.7	Adults	N/A
13	Phloroglucinol (A03AX12)	12.2	No information on age	N/A
14	Mosapride (A03FA)	11.8	Adults	N/A
15	Tiropramide (A03AC05)	11.4	Adults	N/A
16	Bacillus subtilis/streptococcus faecium (A07FA01)	10.1	≥ 12 years old	N/A
17	Pseudoephedrine/triprolidine (R01BA52)	9.5	≥ 12 years old	≥ 6 years old
18	Almagate (A02AD03)	9.2	≥ 12 years old	N/A
19	Bepotastine (R06AX)	9.2	Adults	N/A
20	Caffeine/chlorpheniramine/dihydrocodeine/methylephedrine (R05)	8.2	≥ 12 years old	N/A
21	Sodium chloride (B05CB01)	6.9	Adults	All ages
Adolescence (12–18 years)				
1	Streptodornase/streptokinase (M09AB)	58.0	Adults	N/A[c]
2	Loxoprofen (M01AE)	38.7	Adults	N/A
3	Cimetidine (A02BA01)	27.1	No information on age	≥ 12 years old
4	Mosapride (A03FA)	25.9	Adults	N/A
5	Chlorpheniramine (R06AB04)	24.1	Adults	≥ 6 years old
6	Rebamipide (A02BX14)	20.2	Adults	N/A
7	Tiropramide (A03AC05)	18.5	Adults	N/A
8	Methylprednisolone (H02AB04)	16.8	No information on age	≥ 1 month old
9	Bepotastine (R06AX)	15.3	Adults	N/A
10	Trimebutine (A03AA05)	14.7	Adults	N/A
11	Levosulpiride (N05AL07)	13.6	Adults	N/A
12	Prednisolone (H02AB06)	13.6	Adults	All ages
13	Azelastine (R01AC03)	12.7	Adults	N/A
14	Tramadol (N02AX02)	11.5	Adults	Adults
15	Aceclofenac (M01AB16)	10.9	Adults	N/A
16	Itopride (A03FA07)	9.1	Adults	N/A
17	Piprinhydrinate (R06AA07)	8.5	Adults	N/A
18	Ranitidine/sucralfate/tripotassium bismuth dicitrate (A02BA)	7.4	Adults	N/A
19	Bromelain/dehydrocholic acid/pancreatin/simethicone/trimebutine (A03A)	6.9	Adults	N/A
20	Sodium chloride (B05CB01)	6.8	Adults	All ages
21	Artemisiae argyi folium isopropanol extract (A02X)	6.6	No information on age	N/A
22	Dexamethasone (H02AB02)	6.4	Adults	All ages
23	Mefenamic acid (M01AG01)	6.4	Adults	≥ 14 years old

ATC, anatomical therapeutic chemical; USA, United States of America.
[a]None of the drugs prescribed frequently in Korean children were approved by EMA (European Medicines Agency). [b]Number of patients prescribed the drug/number of total pediatric patients × 100 (%). [c]N/A, not applicable, means that the drug has not been approved in the United States.

Table 2 Labeling information of top five adverse event (AE)–reported drugs in Korean pediatric patients

	Drugs (ATC)	Age of administration in Korean drug label	AEs reported > 1.0% in pediatric patients, but not listed in Korean drug label (%[a])
Total (0–18 years)			
1	Amoxicillin and enzyme inhibitor (J01CR02)	≥ 2 months old	N/A[b]
2	Methylphenidate (N06BA04)	≥ 6 years old	N/A
3	Fentanyl (N02AB03)	≥ 2 years old	Burning micturition (3.4)
4	Tramadol (N02AX02)	Adult	N/A
5	Ampicillin and enzyme inhibitor (J01CR01)	Over newborn	N/A
Infancy/toddler (0–23 months)			
1	Hemophilus influenzae b vaccines (J07AG01)	≥ 2 months old	Inside trembling (28.2)
2	Ampicillin and enzyme inhibitor (J01CR01)	Over newborn	N/A
3	Cefotaxime (J01DD01)	Over premature baby	N/A
4	Amoxicillin and enzyme inhibitor (J01CR02)	≥ 2 months old	N/A
5	BCG vaccine (L03AX03)	Over newborn	Pedicardial tuberculosis (1.4)
Early childhood (2–5 years)			
1	Amoxicillin and enzyme inhibitor (J01CR02)	≥ 2 months old	N/A
2	Ampicillin and enzyme inhibitor (J01CR01)	Over newborn	N/A
3	Cefotaxime (J01DD01)	Over premature baby	N/A
4	Vancomycin (J01XA01)	Over newborn	Aggravated cough (1.4)
5	Ceftriaxone (J01DD04)	Over newborn	N/A
Middle childhood (6–11 years)			
1	Methylphenidate (N06BA04)	≥ 6 years old	N/A
2	Fentanyl (N02AB03)	≥ 2 years old	Burning micturition (3.2)
3	Amoxicillin and enzyme inhibitor (J01CR02)	≥ 2 months old	N/A
4	Tramadol (N02AX02)	Adult	Chest pain (1.1)
5	Oseltamivir (J05AH02)	≥ 2 weeks old	N/A
Adolescence (12–18 years)			
1	Tramadol (N02AX02)	Adult	N/A
2	Fentanyl (N02AB03)	≥ 2 years old	Burning micturition (3.7)
3	Methylphenidate (N06BA04)	≥ 6 years old	N/A
4	Vancomycin (J01XA01)	Over newborn	Headache (1.2)
5	Cytarabine (L01BC01)	Over children	Shivering (1.4)

ATC, anatomical therapeutic chemical.
[a]Number of reports on the AE of the drug/number of total AE reported for the drug × 100 (%). [b]N/A, not applicable, means that there are no AEs reported > 1.0% in pediatric patients, but not listed in Korean drug label.

drugs such as amlodipine and candesartan (anatomical therapeutic chemical category C); antiviral agents, such as adefovir and darunavir (category J); and drugs acting on the nervous system, such as escitalopram and fentanyl (category N). The age for which the drug is approved for use was different between labels approved by Korean MFDS and the FDA for 44 (9.6%) products and included mainly drugs for the gastrointestinal tract, such as esomeprazole and ondansetron (category A); drugs for the respiratory

Table 3 Comparison of pediatric information in approved drug labels between Korean MFDS/EMA and the FDA

Classification of comparative analysis of pediatric labeling information	Number of drug products (%)	
	MFDS vs. FDA	EMA vs. FDA
No difference	63 (61.2)	75 (72.8)
No indication for children in Korean or EU drug label	23 (22.3)	15 (14.6)
Differences in available age	13 (12.6)	13 (12.6)
Lack of formulation	12 (11.7)	0

EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; MFDS, Ministry of Food and Drug Safety.

Table 4 Comparison of pediatric labeling information approved by Korean MFDS with that approved by the FDA according to therapeutic categoriesa

ATC[b]	No difference	No indication for children in Korean drug label	Difference in available age	Lack of formulations in Korea
A	17 (9.8)	7 (9.9)	10 (22.7)	9 (28.1)
B	5 (2.9)	2 (2.8)	1 (2.3)	1 (3.1)
C	10 (5.8)	11 (15.3)	0	0
D	13 (7.5)	7 (9.7)	0	0
G	10 (5.8)	2 (2.8)	0	0
H	5 (2.9)	3 (4.2)	0	0
J	19 (11.0)	13 (18.1)	10 (22.7)	12 (37.5)
L	27 (15.6)	4 (5.6)	1 (2.3)	1 (3.1)
M	3 (1.7)	4 (5.6)	2 (4.5)	1 (3.1)
N	27 (15.6)	9 (12.5)	6 (13.6)	7 (21.9)
P	0	0	1 (2.3)	0
R	18 (10.4)	2 (2.8)	10 (22.7)	1 (3.1)
S	14 (8.1)	6 (8.3)	2 (4.5)	0
V	5 (2.9)	2 (2.8)	1 (2.3)	0
Total	173	72	44	32

ATC, anatomical therapeutic chemical; FDA, US Food and Drug Administration; MFDS, Ministry of Food and Drug Safety.
[a]Values are number of drug products (% within category of the comparative analysis). [b]A, alimentary tract and metabolism; B, blood and blood forming organs; C, cardiovascular system; D, dermatologicals; G, genitourinary system and sex hormones; H, systemic hormonal preparations, excl. sex hormones and insulins; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; P, antiparasitic products, insecticides and repellents; R, respiratory system; S, sensory organs; V, various.

tract, such as cetirizine and desloratadine (category R); or antiinfective agents, such as atazanavir and azithromycin (category J). Moreover, most (95.5%) products had a narrower acceptable age range of drug labels approved by the Korean MFDS than that by the FDA (**Table S3**). Pediatric formulations available in the United States were not marketed in Korea for 32 products (7.0%), mainly drugs for gastrointestinal tract such as aprepitant and cimetidine (category A), drugs for nervous system such as escitalopram and gabapentin (category N), or antiinfective agents such as abacavir and atazanavir (category J) (**Table S4**). Among 173 (37.9%) products that did not show differences in pediatric labeling information such as indication, available age, or formulation, Korean drug labels for 69 (39.9%) products lacked information on clinical studies in pediatric patients compared with US drug labels.

As shown in **Figure 1**, based on the order of the product authorization year in Korea, more products showed no differences from the

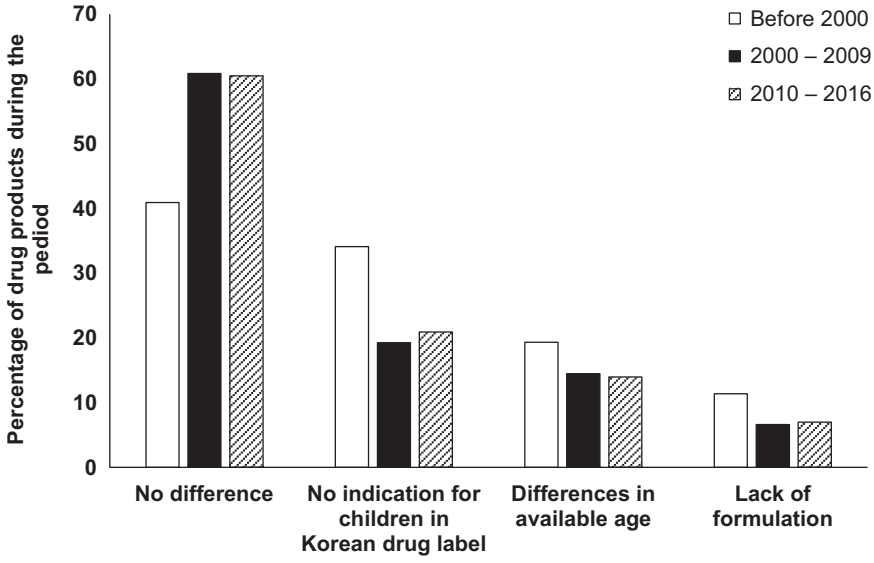

Figure 1 Temporal trend of comparative analysis of pediatric labeling information based on the first approval year in Korea: Korean MFDS vs. the FDA.

US pediatric labeling information in recent years (40.9%, 60.8%, and 60.5% of drug products approved before 2000, in 2000–2009, and in 2010–2016 in Korea, respectively). However, even after 2010, 20.9% of the products did not have indications for children in the Korean drug label and 7.0% lacked pediatric formulations.

DISCUSSION

While pediatric drug development is international in scope, pediatric drug information in regulatory labeling is not uniformly shared and is under the control of national regulatory agencies. The lack of pediatric clinical trials has led to limited or no pediatric documentation with respect to many approved drugs.[11] The current study found that some of the drugs commonly prescribed in children have insufficient information in Korean labels, and safety information was insufficient in labels for drugs with frequently reported AEs in children. To the best of our knowledge, this is the first study to compare the pediatric drug labeling of a country in the absence of pediatric legislation with that of the United States with the legislative and regulatory pediatric frameworks.

In this study, pediatric prescribing information was lacking even in labels of frequently prescribed drugs for the pediatric population. Streptodornase/streptokinase is an antiinflammatory enzyme with indications for inflammatory edema of the ankle and expectoration in respiratory disease. In Korea, it was most frequently used in an off-label way in pediatric patients.[12] The drug has been reported to be top ranked as an agent prescribed in duplicate on the same day in children.[13,14] The Korean government recently decided that it would be necessary to review the drug's safety and efficacy and mandated pharmaceutical companies to submit additional clinical trial data as a part of their postmarketing risk assessment.[15] Corticosteroids, such as prednisolone and methylprednisolone, were also prescribed frequently for Korean children. Although corticosteroids can be used in children for the treatment of asthma or inflammatory diseases, it was reported that they had been misused in infants and young children for conditions such as the common cold in Korea (i.e., corticosteroid prescriptions for the common cold in 0–4-year-old infants accounted for 2% in 2012, which was a 64% increase compared with that in 2010).[16,17] Therefore, it is necessary to reevaluate the safety and efficacy of their use in children and ensure that this information is reflected in drug labels as needed. Hydroxyzine, a first-generation antihistamine, was used frequently for children without sufficient information in the Korean drug label. Considering that the main indications for which hydroxyzine is prescribed are urticaria, dermatitis, acute bronchitis, and allergic rhinitis in Korea, it is necessary to provide adequate information on the safety and efficacy of its use in children.[18] In addition, it is necessary to reevaluate the safety and efficacy of gastrointestinal agents such as trimebutine, mosapride, tiropramide, and rebamipide in children and provide detailed pediatric prescribing information.

Off-label use of medications in countries without pediatric regulations, such as India and Brazil, has also been reported to be approximately 70% and 60% of drug prescriptions for children, respectively.[19,20] The rate of off-label drug use in these countries was quite high compared with 3–53% of off-label drug use in children in Europe 5 years after the establishment of pediatric regulation by the European Parliament.[21,22] This study demonstrated that younger children were more likely to be prescribed drugs without adequate pediatric information in labels. At the age extreme, few neonatal labeling changes have been made even under the pediatric legislation by the FDA.[23] The prescription of analgesics and gastrointestinal drugs increased with age in pediatric patients in the United States.[21] The results of this study indicated that off-label drug use related to age information increased with age in Korea as well. The most prominent reason for such drug use in children was a total lack of information in the label about pediatric use of the drug. It could cause pediatricians to use these drugs on a trial-and-error basis. Although governmental initiatives to improve clinical research conducted in children might have a marginal effect on the decrease of off-label drug uses, the legislation has increased the amount of safety and efficacy information on pediatric drug use, which is expected to contribute to the reduction in off-label use in children in the future.[24,25] Therefore, regulatory initiatives are necessary along with efforts at the level of experts, patients, and the healthcare system to improve the quality of drug use in children in Korea.[22,25]

AEs play a major role in the use of medications in pediatric patients. While adult studies are informative regarding the types of AEs that can be expected with a certain drug, the disease process, sensitivity to specific AEs, and growth and developmental process can be very different in pediatric patients.[9,10] Pediatric patients who were prescribed off-label drugs possessed significantly higher risk for developing adverse drug reactions.[19] Moreover, AEs frequently reported in pediatric patients were not listed in Korean drug labels. The labeling information should contain trusted information about suspected AEs based on the level of certainty in association between a drug and an AE. The high incidence of AEs with central nervous system drugs observed in this study corroborates that shown in a recent study of AEs of antipsychotic and antidepressant drugs.[19] It is therefore necessary to conduct studies to assess AEs that are specific to children.

The officially recognized product label is considered a key source document for pediatricians as it summarizes product-specific information along with recommendations for safe and effective use in pediatric patients. The label is intended to assist healthcare professionals in choosing the most appropriate therapy under their circumstances.[26] However, the safety and efficacy information provided in the label may depend on the country in which a drug is marketed due to different requirements from regulatory authorities in each country as well as in their approaches to pediatric risk-benefit analysis.[27,28] In addition, it could be a market-driven decision by the company to improve labeling information for drugs used in children based on data from clinical trials conducted in domestic or foreign pediatric patients.[7] This study indicated that there were limited pediatric indications and narrowly defined age groups based on Korean drug labels compared with pediatric information provided in drug labels approved by the FDA. Moreover, labeling information such as pediatric clinical trials was not commonly available in Korean labeling. Extensive information on pediatric clinical trials, including both positive and negative studies, can generate clinical knowledge for drug use in pediatric patients.[4]

There was also a shortage of pediatric drug formulations available in Korea compared with those in the United States. This lack of formulations might lead to an increased risk of AEs, noncompliance, or incorrect dosage. Development of pediatric formulations should be promoted by pediatric regulations as part of drug development plans.[29]

The adoption of pediatric regulatory initiatives in the United States and Europe has significantly changed worldwide legislative frameworks, leading to a significant increase in the number of medicines with information related to children and an improved understanding of medicines used in children.[30,31] The pediatric labeling process in the United States progressed from encouraging the pharmaceutical industry to conduct pediatric studies in the 1980s and 1990s to a combined approach of the FDA Modernization Act's voluntary incentives and mandatory regulation of PREA in 2003.[4] PREA requires drug companies to assess safety and effectiveness of new drugs/biologics in pediatric patients when there is a shared indication in adults and in pediatric patients. PREA authorizes the FDA to require sponsors to conduct pediatric studies for drugs under development using an age-appropriate formulation to increase labeling information relevant to pediatric use.[11] The FDA Amendment Act of 2007 requires that both positive and negative results of pediatric studies should be incorporated in the drug labeling.[3] In Japan, the Pharmaceuticals and Medical Devices Agency established a pediatric working group in 2011 to investigate the drug-related issues for children through international collaboration with the FDA and EMA and to prepare for the introduction of new pediatric legislation.[32] In the era of precision medicine today, there is growing interest in academia and in the FDA in the lack of pharmacogenomic information in pediatric patients.[33,34] As part of the efforts to promote international coherence in pediatric labeling information, the World Health Organization has organized the Peadiatric Medicines Regulators' Network with regulatory authorities from the United States, Europe, and Japan to facilitate collaboration and discussion toward a consensus on regulatory standards for pediatric drugs and to strengthen the approval system for pediatric drugs by increasing regulatory cooperation and information sharing.[35]

Recently, efforts of the Korean government and related academic associations have stimulated clinical trials for pediatric patients in Korea to collect information on drug safety and efficacy for children.[36] Despite regulation that provides an incentive for pediatric-specific medicines by MFDS, a formal legislative and regulatory framework that requires timely pediatric drug development to provide accurate pediatric information on drug labels for safe and efficacious use in the pediatric population is still missing.[7] This study showed that the pediatric labeling information in Korea was relatively inadequate in comparison with that of the FDA's approved drugs, and the difference in this information was larger than the difference between the pediatric labeling information of the FDA and EMA. This might be partially due to differences in regulations for pediatric drug development and labeling information. Moreover, Korean pharmaceutical companies are avoiding the development of pediatric medicines due to the extremely low fertility rate (1.05 per female of reproductive potential in 2017) and the declining pediatric population in Korea.[37] Therefore, government initiatives are needed to promote pediatric drug development and to improve labeling information for pediatric patients to have safe and effective drug therapy. In addition, international harmonization in drug development for pediatric use might be the most useful and productive approach through international regulatory collaboration with the pediatric research network.[35]

This study has some limitations. Considering the characteristics of claims data, actual off-label drug use for age in pediatric patients may differ from patterns of use found in the present study. Moreover, the conservative definition of off-label drug use for age did not include the use by indication in our analysis. This might have resulted in an underestimation of off-label use of drugs in children. In addition, our findings pertain to children enrolled in national reimbursement benefit plans or AEs reported spontaneously to the Korea Institute of Drug Safety & Risk Management (KIDS) or a regional drug safety center. They might not be generalizable to other children without insurance coverage or children who did not report AEs from drug use. Systematic evaluation and research such as signal detection of a specific adverse drug event are needed to change drug labels using AE reporting data.[38] The comparison of pediatric information in domestic drug labels with those of other countries adopting pediatric regulations has been limited to the FDA drug labels at the present time.

In conclusion, this study found that pediatric labeling information for drugs commonly used for children or frequently reported AEs was insufficient in Korea. There was a shortage in the pediatric information of drug labels in Korea compared with those in the United States regarding approved age, safety information, and pediatric formulations. Therefore, this study highlights the urgent need for the Korean regulatory agency to encourage and accelerate research and development to increase pediatric prescribing information to be added to drug labeling in order to promote appropriate drug prescribing for children. Sources of pediatric labeling information such as pediatric clinical trials can be expanded to provide adequate directions for drug use in children. Moreover, international collaboration should be sought to share the current information being placed in pediatric labels, investigate pediatric drug-related issues, and share the information on drug safety and efficacy in the pediatric population that is collected through the regulatory processes of the FDA and EMA.

METHODS

The Institutional Review Board of Seoul National University approved this study (no. 1604/002-002) and waived the requirement of informed consent because all patient data were anonymized and de-identified prior to the retrospective analysis.

Labeling information of frequently prescribed drugs in Korean pediatric patients

The Korea Health Insurance Review and Assessment Service Pediatric Patients Sample (HIRA-PPS) database was used for this study. HIRA is an independent and public insurance agency responsible for reviewing medical fees and evaluating whether prescribed drugs are medically necessary based on indications and dosages in labels. It provides national

insurance coverage for more than 95% of Korean citizens.[39] We obtained HIRA-PPS data submitted from January to December 2013. It contained claims data for 10% of all pediatric beneficiaries. It was constructed and validated using a gender-stratified and age-stratified random sampling.[40] Study subjects were patients younger than 18 years old who were prescribed systemic drugs (oral route or injection) at least once based on drug category 100–600 and 800 as listed in Korean regulations (**Table S5**).[41] The data, such as an unidentifiable code representing each individual, age, and prescribed drug information including active ingredient name and route of administration was used to select the commonly prescribed drugs in children. The number of prescriptions and patients prescribed with the drugs was analyzed using SAS version 9.2 (SAS Institute, Cary, NC).

Off-label use for age was defined as the patient's age not in agreement with the age of administration in the approved drug label. Approved age of administration in label was compared for frequently used drugs in Korean children using a publicly available online database from MFDS, the FDA, and EMA, respectively, as of May 2019.[12,42,43] The labeling information was also analyzed according to three age groups as follows: early childhood (2–5 years), middle childhood (6–11 years), and adolescence (12–18 years). Infants and toddlers younger than 24 months old were excluded from the analysis due to uncertainty in the sample data.[39]

Labeling information of drugs with frequent AE reports in Korean pediatric patients

The KIDS-Korea Adverse Event Reporting System (KAERS) database (KIDS-KD) was utilized to identify the drugs with frequent AE reports. Of a total of 662,187 AE reports collected by 2014, 90.3% were collected during 2010–2014.[44] Therefore, we obtained the data submitted from January 2010 to December 2014. Each report in KIDS-KD contained information including unidentifiable reporter and patient, report date, date of event, products involved, type of AEs, health conditions, and causality assessments. AEs in the database were coded in terms of Korean translations of World Health Organization Adverse Reactions Terminology (WHO-ART). Only suspected drugs for the AEs reported by patients younger than 18 years old were included in the analysis. The following reports were excluded from analyses: reports in diagnostic agents, concomitant drugs or chemical subgroups, reports that could not confirm the drug label, reports with missing age or event, duplicate reports, and reports with unlikely causality.[45] SAS version 9.2 was used to analyze the number of reported AEs for the drug in KIDS-KD.

Labeling information such as age of administration and adverse reactions was analyzed for 734 drugs with frequently reported AEs using databases from MFDS as of May 2019.[12] In addition, we investigated AEs reported for more than 1% of total AEs reported for the drug, but not listed in drug labels in Korea. If AEs reported in pediatric patients were listed in the adverse reaction section of the approved drug label, the AEs were considered to be listed in the label. Where terms of similar AEs were different in KIDS-KD and drug labeling, two researchers (Y.-K.S. and N.H.) categorized terms considered to be the same AE separately. All analysis was also performed by stratification of the pediatric age into four groups as follows: infancy/toddler (0–23 months), early childhood (2–5 years), middle childhood (6–11 years), and adolescence (12–18 years).[46]

Comparison of pediatric information in the approved label between Korean MFDS and the FDA

The FDA launched the New Pediatric Labeling Information Database in 2012 to house results of drug studies in children through pediatric regulations and related new information on drug labels.[47] For drug products in the FDA pediatric database, the products approved by all three regulatory authorities in Korea, the United States, and EU were analyzed to compare the pediatric labeling information between Korean MFDS and the FDA as of May 2019.[12,43] The pediatric labeling information between the FDA and the EMA was also compared to show a causal relationship between the pediatric regulation and the information.[43,46] Pediatric labeling information of 469 drugs (692 drug products) registered in the database of the FDA as of December 2016 was also compared with the relevant information approved by Korean MFDS as of April 2017 according to the therapeutic category of anatomical therapeutic chemical category code.[12,47] When active ingredient, strength, and route of administration were the same, they were regarded as the same drug and analyzed. Therapeutic categories of biologics used for tissues, gene therapies, vaccines, sunscreen, medical imaging, or diagnostic aid were not included. Generic approvals were also excluded because these drugs were already present on the market. The label was reviewed in detail for the presence of any pediatric information in section of indication, warnings, contraindications, precautions, or pediatric use.[12,48] Results of comparative analysis of pediatric labeling information between the FDA and Korean MFDS or between the FDA and EMA were classified as follows: no difference, the same labeling information; no indication for pediatrics, unapproved drugs for pediatric use in Korean MFDS or EMA but approved for pediatric use in the FDA; difference in approved age, drugs that differed from the age of administration approved by MFDS or EMA in comparison with the FDA; and lack of pediatric formulation, no pediatric formulations in Korea or EMA for drugs with pediatric formulations approved by the FDA. Temporal trends of the comparative analysis were evaluated in newer vs. older products. The first approval date of the drug products with marketing authorization in Korea was obtained from the databases of the MFDS, and they were classified into three groups as follows: before 2000, 2000–2009, and 2010–2016. We examined the number of drug products in each comparative analysis category during these periods.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplementary Material: Tables S1–S5.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.-K.S., J.M.O., and G.J.B. wrote the manuscript; Y.-K.S., N.H., and J.M.O. designed the research and performed the research; Y.-K.S. analyzed the data.

DISCLAIMER

The opinions expressed in this article are those of the authors and should not be interpreted as the position of the Korean Ministry of Food and Drug Safety or the US Food and Drug Administration.

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