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A Comprehensive List of Items to be Included on a Pediatric Drug Monograph

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OBJECTIVES Children require special considerations for drug prescribing. Drug information summarized in a formulary containing drug monographs is essential for safe and effective prescribing. Currently, little is known about the information needs of those who prescribe and administer medicines to children. Our primary objective was to identify a list of important and relevant items to be included in a pediatric drug monograph.

METHODS Following the establishment of an expert steering committee and an environmental scan of adult and pediatric formulary monograph items, 46 participants from 25 countries were invited to complete a 2-round Delphi survey. Questions regarding source of prescribing information and importance of items were recorded. An international consensus meeting to vote on and finalize the items list with the steering committee followed.

RESULTS Pediatric formularies are most commonly the first resource consulted for information on medication used in children by 31 Delphi participants. After the Delphi rounds, 116 items were identified to be included in a comprehensive pediatric drug monograph, including general information, adverse drug reactions, dosages, precautions, drug-drug interactions, formulation, and drug properties.

CONCLUSIONS Health care providers identified 116 monograph items as important for prescribing medicines for children by an international consensus-based process. This information will assist in setting standards for the creation of new pediatric drug monographs for international application and for those involved in pediatric formulary development.

ABBREVIATIONS ADR, adverse drug reaction; DDI, drug-drug interaction; HLA, human leukocyte antigen; IV, intravenous

KEYWORDS drug monograph; drug safety; formulary; pediatrics; prescribing; therapeutics

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Introduction

The availability of an information resource specific to pediatric prescribing is essential to guide safe and effective use of medicines for children; these resources are often described as pediatric formularies or compendia.[1] Children represent a unique and challenging population to prescribe and administer medicines due to dynamic developmental physiology impacting drug absorption, distribution, metabolism, and excretion as well as drug-end organ interaction. The current lack of evidence-based information on therapeutic use and drug doses and lack of child-size formulations are great concerns, widely recognized by the field.[2-4]

Formularies consist of a collection of drug monographs that guide national prescribing or are specific for an institution. According to the Health Canada definition, a monograph is "A scientific document on the drug that devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug."[5] Drug monographs contain important information for those who select, prescribe, dispense, prepare, administer, monitor, or advise on medicines for children. Drug monograph are often built around the prescribing needs of adults and frequently contain blanket statements that "safety and effectiveness has not been evaluated in patients under the age of 18." The lack of evidence-based drug monographs containing information regarding pediatric prescribing is a threat to safe and effective use of medications in childhood. Pediatric drug therapy is subject to a high rate of medication dosages and administration errors, and most medication errors in children's hospitals occur in the most vulnerable patients, less than 2 years old and requiring intensive care.[6,7] Many of these drug errors are serious (15%) and even potentially fatal (2%).[8] In hospitalized patients, medication errors are 3-times more likely to cause an adverse drug event in children

Table 1. Process Used to Generate Items for Inclusion in a Comprehensive Pediatric Drug Monograph

Steps	Activity	Goal
1	Establish steering committee	Assemble an international group with pediatric prescribing and research expertise
2	Environmental scan of formularies	Develop an initial list of drug monograph items
3	Delphi – round 1	Ranking of items identified from scan done in step 2, and suggest new items for inclusion
4	Delphi – round 2	Ranking of new items identified in step 3 and prioritization of all items
5	Consensus meeting	Combine and vote on items, and finalize definitions

than in adults.[9] Some of these errors may be due to a lack of harmonized dosage information. A review of the 2005 Canadian Compendium of Pharmaceuticals and Specialties revealed that 50% of drug monographs were missing safety data for children.[10]

Although standards exist regarding information required by regulators to issue a marketing authorization for a new drug,[11] currently there are no standards for what information health care providers require from a pediatric drug monograph to ensure they have the information needed to safely and effectively provide the right drug in the right dose at the right time, to the right patient, with the right formulation through the right route of administration. Although pediatric formularies are commercially available and are managed nationally in countries such as the United Kingdom, the Netherlands, and New Zealand, it is unclear whether these resources contain all of the available information required by the health care provider. Our objective was to build on currently available pediatric formularies and prioritize a comprehensive list of items to be included in drug monograph for use by health care providers when selecting, prescribing, dispensing, preparing, administering, monitoring, or advising on medicines for children.

Methods

We took the stepwise approach summarized in Table 1. A steering committee of international experts in pediatric drug prescribing was established. Criteria for committee membership included expertise in pediatric therapeutics and experience with compendium/formulary development and management. Steering committee members were recruited through email invitations. Following an environmental scan (e.g., Web-based objective search) of existing national formularies, both pediatric and adult, a preliminary list of items to be included in a pediatric drug monograph was identified. The importance of these items was rated using a Delphi approach[12] with participants from 6 continents. Health care providers responsible for prescribing medicines for children were included as participants in this study. "Prescribing" was defined to include selecting, dispensing, preparing, administering, monitoring, or advising on medicines. Participants (n = 46) from 25 countries were invited to participate. A purposive sample was chosen, and the steering committee selected participants with relevant knowledge and experience.

During the first Delphi round, participants were asked to rate the importance of each monograph item on a 5-point Likert scale where 1 = not important at all, 2 = not very important, 3 = undecided on importance, 4 = important, and 5 = very important. Importance was defined as the item's value to be included in a drug product monograph specific for medication use by any health professional in children of all ages in terms of facilitating the participants' ability to safely prescribe, dispense, administer or monitor a medication for their patients. Items were placed into the following categories: general information, adverse drug reactions and overdose, drug-drug interactions, dosages, precautions, formulation, and drug properties. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Hospital for Sick Children, Toronto, ON, Canada. REDCap is a secure, Web-based application designed to support data capture for research studies.[13] During the first round, participants could suggest new items. Demographic information including country of practice, number of years of experience, and subspecialty was collected. Participants were to state their preferred source of prescribing information (open-ended) and were also asked to rank a list of sources according to their preference, where the scale was most preferred (score = 1) to least preferred (score = 11). For the preferred source of prescribing information, the sum of ranks score is reported, where a lower score indicates a preferred source.

Following the first Delphi round, importance scores (mean, median, and standard deviation) were calculated for each pediatric drug monograph item. The items from the environmental scan alongside their importance scores as well as the new items suggested in round 1 underwent a second Delphi round for prioritization. In both rounds, participants could provide comments and ask questions if there were any uncertainties. Pediatric drug monograph inclusion criteria were determined by the steering committee a priori: items scored equal to or greater than a median of 4 of 5. Any item which scored

Table 2. Formularies reviewed resulting from Environmental Scan (n = 23)

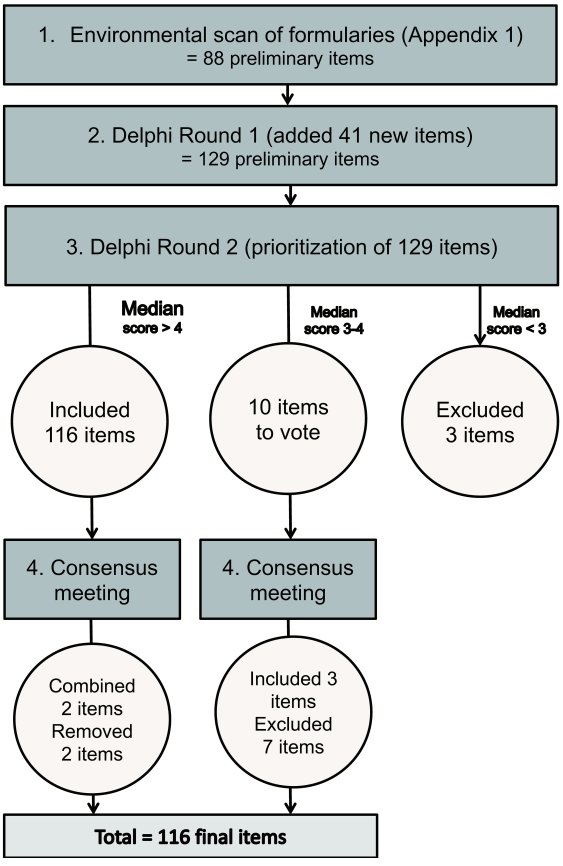
1	American Hospital Formulary Services
2	Lexicomp (Pediatric and Neonatal Lexi-drugs)
3	Health Canada Drug Product Database
4	British National Formulary for Children (UK)
5	eMPR (monthly prescribing registry)
6	Clinical Pharmacology Drug Monographs (Elsevier)
7	Medicinenet.com
8	Pharmaceuticals and Medical Devices (Japan)
8	Pharmacorama connaissance des medicaments (France)
9	Therapeutic Good Association (Australia)
10	Informed Drug Guide (Switzerland)
11	Essential Medicines and Health Products Information Portal
12	Kinderformularium (Netherlands)
13	Sickkids formulary (Canada)
14	New Zealand Formulary for Children
15	Ministere des affaires sociales et de la sante
16	La base de donnees en ligne des prescripteurs liberaux
17	Autoridade national do medicamento e produtis de Sadde (Portugal)
18	EudraPharm
19	Documed compeundium (Swiss)
20	Electronic Medicines Compendiume eMC (UK)
21	Norweigian Medicines Agency (NoMA database - felleskatalogen)
22	Ethiopian National Formulary
23	World Health Organization model formulary for children

greater than or equal to 3 but less than 4 was voted by the steering group at the consensus meeting. Items scoring a median below 3 of 5 were excluded. The most important items were defined as items which scored a median of 5 and a mean score above 4.5. Items were determined to be pediatric-specific if the steering committee agreed by consensus that this item was unlikely to be of value to those prescribing medicines for adults.

Results

We identified 23 formularies from 12 countries and several international formularies including the World Health Organization (WHO) model formulary for children (Table 2). The directors or managers of 4 large formularies (SickKids, Pediatric and Neonatal Lexi-comp, New Zealand Formulary for Children, and

Figure. Flow diagram of items to be included in a comprehensive pediatric drug monograph



Kinderformularium) were invited and agreed to take a role in the steering committee. We extracted 88 preliminary monograph items (Figure). There were 31 participants in the first Delphi round (67% response rate), of whom 29 also completed the second round. Table 3 provides participant demographics and the sum of ranks scores for sources of information consulted for information. Pediatric formularies were the most frequently consulted resource, and the British National Formulary for Children represented the most frequently consulted formulary (Table 4).

Following 2 Delphi rounds, there were 116 items (90%) having a median importance score of 4 or higher of a possible 5 points (Figure). During the consensus meeting, 10 items required considerable discussion, 7 of which were excluded. Two of the remaining items were condensed as both items scored the same median and mean. Drug-drug interactions that requires an increase or decrease in dose were combined into "drug-drug interactions require a dose modification (increase or decrease)." There were 2 items (previously included) which the steering committee felt were important drug formulary items but were not drug-specific and there-

Table 3. Participant Demographics (n = 31)

	Number of Participants (%)
Occupation	
Medical doctor	17 (54)
Pharmacist	9 (30)
Other (nurse, scientist)	5 (16)
Specialty excluding pediatric medicine and pharmacy	
Clinical pharmacology	8
Neonatology	3
Intensive/critical care	3
Emergency medicine	2
Family medicine	2
Psychiatry	1
Haemato-oncology	1
Pulmonology	1
Rheumatology	1
Number of yrs of experience	
Less than 5 yrs	3 (10)
5-10 yrs	2 (7)
11-25 yrs	15 (48)
More than 26 yrs	11 (35)
Continent of practice	
North America	6 (19)
South and Central America	3 (10)
Europe	8 (26)
Africa	5 (16)
Asia	3 (10)
Australia and New Zealand	4 (13)
Unanswered	2 (6)
Preferred source of information for prescribing medicines to children*	
Pediatric formulary	45
Systematic reviews	121
National clinical practice guidelines	126
Hospital formulary	129
National pediatric association guidelines	136
Clinical trials	158
Adult formularies	173
Local treatment protocols	195
Expert opinion	209
Information from industry	240
Generic search	251

*Sum of rank score: highest possible score, 3. Lowest possible score, 341.

Table 4. Sources of Information Regarding Prescribing Medicines in Children Reported by Participants*

	Number of Participants (%)†
British National Formulary for Children	13 (42)
British National Formulary	7 (23)
Kinderformularium, the Netherlands	5 (16)
Neonatal and Pediatric Lexi-drugs	5 (16)
World Health Organization Model Formulary for Children	5 (16)
Shann Pediatric Drug Doses	4 (13)
World Health Organization Model Formulary	3 (10)
CHLA Pediatric Dosing Handbook	3 (10)
Neofax	3 (10)
New Zealand Formulary for Children	2 (6)
The Hospital for Sick Children Formulary	2 (6)
Lexi-comp	2 (6)
Guy's and St. Thomas Pediatric Formulary	2 (6)

CHLA, Children's Hospital Los Angeles

* Sources of prescribing information reported by only one participant, Epocrates, Micromedix, SmPC, South African Medicines Formulary, Australian Medicines Handbook, Thomspons and Reuters Clinical Editorial, Medico e Bambino (Prontuario Pediatric), drugs.com, Farmacotherapeutish Kompas

† Participants could select more than one resource

fore did not require inclusion on a drug monograph: how to report adverse drug reactions to contribute to phase IV information and an age-weight conversion chart. A final list of all included items (n = 116) can be found in Tables 5-11. Items which were excluded following the Delphi or the consensus meeting can be found in Table 12. Pediatric specific items as defined by the steering committee are identified (Tables 5-12).

There were 24 items with a median score of 5 of 5, and a mean above 4.5 of 5 that were deemed very important items to be included in a pediatric drug monograph (Tables 5-11). The item "contraindications due to drug-drug interactions" was the only item to be scored 5 of 5 for importance by all participants. In the very

Table 5. General Information to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
1	Generic name	4.96	0.20	5.00	No
2	Licensed indication	4.69	0.47	5.00	No
3	Off-label indication	4.62	0.50	5.00	Yes
4	Therapeutic class	4.50	0.71	5.00	No
5	When was the last update	4.31	0.79	4.50	No
6	Advice for patients/carers	4.19	0.85	4.00	Yes
7	References for more information	4.08	0.93	4.00	No
8	Controlled substance category	4.00	0.75	4.00	No
9	Who is responsible for approving the monograph's content	3.88	0.91	4.00	No
10	How often is the monograph updated	3.85	0.97	4.00	No
11	Brand name	3.77	1.11	4.00	No
12	Countries where this product is authorized	3.58	0.90	4.00	No
13	Easy contact information	3.58	0.86	4.00	No
14*	Out of pocket costs for the patient	3.31	0.79	3.00	No

* Item 14 was below the median 4.0 cutoff, but was included following the steering committee's experts' recommendation

Table 6. Adverse Drug Reactions and Overdose Items to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
15	Contraindications due to adverse drug reactions	4.92	0.27	5.00	No
16	Precautions, or groups of patients where ADRs may be more common	4.85	0.37	5.00	No
17	How frequently ADRs are expected to occur in the pediatric population	4.77	0.43	5.00	Yes
18	How to avoid ADRs in the pediatric population	4.73	0.45	5.00	Yes
19	What ADRs have been reported in the pediatric population	4.69	0.55	5.00	Yes
20	Symptoms of a drug overdose in the pediatric population	4.46	0.51	4.00	Yes
21	How to manage ADRs in the pediatric population	4.31	0.84	4.00	Yes
22	Management of a drug overdose in the pediatric population	4.31	0.93	5.00	Yes
23	How to monitor for ADRs in the pediatric population	4.27	0.60	4.00	Yes
24	Type of ADR*	3.88	0.86	4.00	No
25	Characterization of important ADR onset	3.88	0.86	4.00	No
26	Ranges of ADR toxicity	3.88	0.77	4.00	No
27	Pre-testing (e.g., HLA, pharmacogenomics)	3.65	0.56	4.00	No
28	Evidences on measures to improve drug safety	3.58	0.95	4.00	No

ADR, adverse drug reaction; HLA, human leukocyte antigen

* A, drug-/dose-related; B, idiosyncratic; C, chronic; D, delayed; E, withdrawal

Table 7. Drug-Drug Interactions Items to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
29	Contraindications due to DDI	5.00	0.00	5.00	No
30	What DDIs require a dose modification in the pediatric population	4.77	0.43	5.00	Yes
31	Can alternative medications be given to avoid DDIs	4.46	0.51	4.00	No
32	Food-drug interactions	4.46	0.65	5.00	No
33	How to monitor DDIs in the pediatric population	4.15	0.88	4.00	Yes
34	Is drug interaction a class effect or related to the individual drug	4.15	0.61	4.00	No
35	Herb-drug interactions	4.15	0.92	4.00	No
36	Is the interaction related to the excipients	4.08	0.63	4.00	No
37	How to distinguish between common and important DDIs versus those that are clinically irrelevant	4.08	0.74	4.00	No
38	Level of evidence for DDI including degree of change in response (increase/decrease)	4.04	0.77	4.00	No
39	What is the mechanism behind DDIs in the pediatric population	4.00	0.63	4.00	Yes

DDI, drug-drug interactions

Table 8. Dosing Items to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
40	Dosing for licensed indication(s)/age group/route	4.88	0.33	5.00	Yes
41	Routes of administration	4.85	0.37	5.00	No
42	Dosing for off-label indication(s)	4.81	0.40	5.00	Yes
43	Therapeutic drug monitoring	4.65	0.56	5.00	No
44	Level of evidence for dose selection in off-label indications(s)	4.50	0.51	4.50	Yes
45	References of evidence for off-label indication dosage	4.38	0.50	4.00	Yes
46	Duration of IV therapy (e.g., infusion over n hrs)	4.35	0.85	5.00	No
47	Suggested dosage intervals with serum concentrations (where applicable)	4.19	0.57	4.00	No
48	Level of evidence for dose selection in licensed indication(s)/age group/route	4.15	0.61	4.00	Yes
49	How to taper off medications (where applicable)	4.15	0.73	4.00	No
50	Availability of clinical practice guidelines	4.12	0.52	4.00	No
51	Web access to clinical practice guidelines	4.08	0.69	4.00	No
52	Bioavailability issues	4.08	0.48	4.00	No
53	Site of absorption in order to be able to judge if a drug can be administered intrajejunally or just intragastrically	4.08	0.98	4.00	No
54	References of evidence for licensed indication dosage	4.04	0.60	4.00	No
55	Bioequivalence issues	4.00	0.69	4.00	No
56	Relevant combination therapy (e.g., dual/ triple therapy) regimens	3.96	0.82	4.00	No
57	Target doses plus acceptable min/max doses (therapeutic window) to support flexible dosage regimens	3.92	0.93	4.00	No
58	Effects of pH on oral absorption	3.69	0.84	4.00	No
59*	Availability of local clinical practice guidelines	3.54	0.95	3.00	Yes

IV, intravenous

* Item 59 was below the median 4.0 cutoff but was included following the steering committee's experts' recommendations

important items, 11 (44%) were pediatric specific. Variability or range in scoring (measurements by variance) was low among participant response, with the highest coefficient of variance (mean and standard deviation) reported for an included pediatric drug monograph item being the brand name (coefficient of variation = 0.29).

Discussion

As pediatric formularies are a frequently consulted resource for pediatric health care providers, it is imperative they contain all relevant evidence available with regard to prescribing decisions and are updated frequently. The development of standardized, prioritized lists of items is justified and can be useful to inform scientists, funding agencies, and regulators as to pertinent areas of pediatric drug research and serve as a starting point for the development of a national pediatric formulary in countries such as Canada and the United States, where they currently do not exist. We report that pediatric formularies (or compendia) are a top source consulted for information and evidence on use of medication in children. Health care providers identified 116 items that contain important information when prescribing medicines for children. There was a high degree of consistency between the items, and very few items were excluded in the process. This large number of items reflects the complexity of prescribing medicines to children. Also, as many of these items have not yet been formally evaluated in children, it reflects the pediatric health care provider's meticulous approach and desire to consider all information relevant to prescribing decisions. This list of monograph items is comprehensive and improves on existing formularies as it covers what information is requested by the health care provider, not only what information is currently

Table 9. Precautionary Items That Should be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
60	Impairment of drug elimination organ(s) (kidney, liver, etc.)	4.88	0.33	5.00	No
61	Dosing in premature newborns	4.85	0.46	5.00	Yes
62	Considerations for dosage dependent on route of administration	4.81	0.49	5.00	No
63	Disease specific considerations	4.73	0.53	5.00	No
64	Is TDM recommended for any/all patient groups	4.62	0.64	5.00	No
65	Dosing in obese children	4.58	0.70	5.00	Yes
66	If TDM is required, how often should samples be collected?	4.54	0.65	5.00	No
67	Considerations for newborns/infants exposed to the drug in breast milk	4.50	0.65	5.00	Yes
68	Considerations for newborns exposed to the drug during pregnancy	4.46	0.65	5.00	Yes
69	Dosing in underweight/malnourished children	4.46	0.58	4.50	Yes
70	Dosing in children receiving renal replacement therapies	4.15	0.67	4.00	No
71	Ethnic group variability	4.08	0.84	4.00	No
72	Dosing in pregnant teenagers	3.96	0.66	4.00	Yes
73	Special considerations for oncology patients	3.96	0.87	4.00	No

TDM, therapeutic drug monitoring

available. These items should be used to inform the research agenda for what clinical evidence is useful for prescribing medicines for children.

Off-label prescriptions are not unique to children, yet the frequency of use is much higher, as an estimated 56% of children receive off-label prescriptions,[14,15] increasing up to 80% in hospitalized children.[16,17] The intended use of off-label drugs is not a listed indication on the marketing authorization. Off-label drug use has been associated with an increased risk for adverse drug reactions.[18,19] The use of monographs primarily conveying adult data presents limitations for clinical practice and research. Dosages for off-label indications and level of evidence for dose selection for off-label indications were scored as very important by respondents. As many drugs are used off-label, to inform bedside decision making it is critical that all available evidence be presented in a clear and agreeable fashion and minimize uncertainty for the prescriber. To agree on which monograph items are important for prescribing medicines for children is the first step in this direction.

Many pediatric subgroups require special dosage considerations resulting from their unique development and physiology. These subgroups included premature infants, neonates, underweight or malnourished children, children receiving renal replacement therapies, obese children, and pregnant teenagers for whom authorized dosage data are rarely available. Many of the most important items were specific to pediatrics and, as such, may not be deduced from adult drug monographs; for example, off-label pediatric dosage recommendations and underlying evidence. This exhaustive, comprehensive list of 116 items should ideally be "populated" in a pediatric drug monograph. As most current pediatric pharmacotherapy is off-label, or unlicensed, some of this information, although deemed important by prescribers, may just not yet be available. Off-label means that enough evidence has not been gathered to support licensing, which may simply be due to insufficient clinical trials or inadequate study population size. The process of licensing is conservative, time consuming and, conventionally, industry driven. Conversely, an approved (on-label) authorization may not contain the most recent international scientific data, as the update process is variable and often slow. Marketing authorization should be an evolving target and should be regularly updated with phase IV long-term safety and effectiveness data.

The limitations of this study include the small sample size and a lack of nurse and nurse practitioner respondents. We recommend including additional health care professional groups, including community care providers, when prioritizing this list prior to implementation. The minimum items for use at the bedside in day-to-day routine prescribing should be determined at a national level, accounting for institutional practices and policy. The authors note the limitation of item "14 Out of pocket costs for the patient" and recommend that cost should

Table 10. Formulation Items to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
74	Type of dosage form available (e.g., dispersible tablet, chewable tablet)	4.62	0.50	5.00	No
75	IV compatibility	4.50	0.58	5.00	No
76	Appropriateness of peripheral line administration	4.50	0.58	5.00	No
77	Instructions for adding drug to food or drink	4.50	0.51	4.50	No
78	Storage recommendations	4.46	0.76	5.00	No
79	Possible manipulations to dosage form (e.g., ability to halve tablets)	4.42	0.70	5.00	No
80	Excipients/ inactive ingredients	4.31	0.84	4.50	Yes
81	Stability	4.31	0.62	4.00	No
82	Recipe for extemporaneous formulations with references	4.19	0.80	4.00	No
83	Allergy potential of formulation and excipients	4.15	0.67	4.00	No
84	Solubility	4.00	0.63	4.00	No
85	Handling precautions	4.00	0.98	4.00	No
86	Palatability information where available - 'tastes like'	4.00	0.63	4.00	No
87	Shelf-life	3.88	0.86	4.00	No
88	Effects of pH alterations on IV compatibility	3.85	0.73	4.00	No
89	Disposal instructions	3.85	1.05	4.00	No
90	Effects of temperature alterations	3.69	0.93	4.00	No
91	Effects of light alterations	3.69	0.93	4.00	No
92	Sodium content	3.58	0.81	4.00	No

IV, intravenous

be considered regardless of payer as an important consideration for rational use of medicines from a National and health policy perspective. The authors recommend use of a transferable cost categorization code system such as "$," "$$," and "$$$."

Next Steps

The steering committee felt that when designing drug monographs on a national level, the overall format may be global but the content must address the complexities of prescribing in the local population. Drug availability and drug formulation show large international differences. This list is meant as a starting point of global items to be included in a pediatric drug monograph, which requires subsequent national validation. Specifically, local authorities (regulators, health care agencies) will be given the task of balancing this comprehensive list with what age-appropriate evidence is available. Where no evidence is available but the particular item is seen as crucial in prescribing decisions, a problem-driven research agenda can be developed. This research agenda should drive funding initiatives to address these knowledge gaps and increase the evidence base for pediatric drug prescribing. Validation of this comprehensive list in support of the development of a national pediatric formulary (compendium), for example, as recommended by the Canadian Council of Academies call to action to develop a Canadian pediatric formulary,[20] is a priority. Further work is required to adapt a pediatric drug safety and effectiveness evidence hierarchy which would clearly differentiate between off-label and off-evidence prescribing. An example includes work done to generate evidence appraisal frameworks for pediatric antibiotic dosage and pharmacokinetic evidence.[21] Clear guidance on the minimum amount of evidence required for a drug to be put onto a pediatric formulary (compendium) is needed which would help guide the research agenda. Patient and parent needs from a pediatric drug monograph or other more accessible sources of information regarding drug safety such as a parent information leaflet (containing tailored information written in lay format) were not addressed in this report and should be a topic for future research. Information leaflets for parents and patients should build on a current Dutch National Paediatric Pharmacotherapy Expertise Network and Medicines for Children project in the United Kingdom (see http://www.medicinesforchildren.org.uk).

Table 11. Drug Properties to be Included in a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Included Pediatric Drug Monograph item	Mean	Standard Deviation	Median	Pediatric-Specific
93	Mechanism of elimination	4.65	0.49	5.00	No
94	Pharmacokinetics in children	4.62	0.64	5.00	Yes
95	Mechanism of action	4.50	0.76	5.00	No
96	Long term effects on development	4.46	0.65	5.00	Yes
97	Oral bioavailability	4.46	0.51	4.00	No
98	Half-life	4.46	0.58	4.50	No
99	Clearance mechanism (kidney vs. biliary)	4.35	0.63	4.00	No
100	Impact of food on absorption time (time of administration relative to meals)	4.31	0.62	4.00	No
101	Ability of drug to cross blood brain barrier	4.27	0.83	4.00	No
102	Whether adult pharmacokinetic data can be extrapolated to children	4.23	0.76	4.00	Yes
103	Pharmacological activity of metabolites	4.12	0.65	4.00	No
104	Effect of bilirubin levels in neonates	4.12	0.77	4.00	Yes
105	Maximum concentrations	3.92	0.74	4.00	No
106	Time of maximum concentration	3.92	0.74	4.00	No
107	Percent of protein binding	3.92	0.80	4.00	No
108	Enzymes involved in breakdown of the drug (metabolism)	3.92	0.74	4.00	No
109	Clearance rate	3.92	0.69	4.00	No
110	Evidence of clinically important high inter-individual pharmacokinetic variability	3.92	0.69	4.00	No
111	Volume of distribution	3.88	0.77	4.00	No
112	Pharmacokinetics in adults	3.73	0.96	4.00	No
113	Preferred binding protein (e.g., albumin, AAG)	3.73	0.87	4.00	No
114	Genetic mutations that may affect enzymes involved in metabolism and clearance	3.73	0.60	4.00	No
115	Genetic mutations that may affect receptors and/or transporters	3.69	0.62	4.00	No
116*	Ontogeny of enzymes involved in metabolism and clearance	3.19	0.80	3.00	Yes

AAG, alpha-1 acid glycoprotein

* Item 116 was below the median 4.0 cutoff but was included following the steering committee's experts' recommendations

In conclusion, health care providers identified 116 monograph items as important for prescribing medicines for children by an international consensus-based process. This information will assist in setting standards for those involved in pediatric formulary development and the pediatric clinical research agenda.

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Table 12. Items Excluded From a Pediatric Drug Monograph With Importance Scores (Mean, Standard Deviation, Median)

Item	Excluded Pediatric Drug Monograph Item	Mean	Standard Deviation	Median	Pediatric-Specific
117	What DDIs require a dose increase in the pediatric population	4.77	0.43	5.00	Yes
118	Age-weight conversion for dosage	4.12	0.82	4.00	Yes
119	How to report uncommon ADRs to contribute to phase IV information	3.73	0.83	4.00	No
120	Dosing in drug/alcohol addiction	3.58	0.95	3.50	No
121	WHO essential medicines list status	3.19	0.94	3.00	No
122	Toxicology (including developmental/juvenile animal studies)	3.15	1.05	3.00	No
123	Effects on fertility/reproductive toxicology in animals	3.08	0.89	3.00	No
124	Manufacturer	3.04	0.92	3.00	No
125	Drug names which sound like this product	2.81	1.17	2.00	No
126	Chemical/Empirical formula	2.69	0.88	3.00	No
127	Isomer ratio	2.65	0.98	3.00	No
128	Molecular weight	2.42	0.90	2.00	No
129	Preclinical data (cell culture and animal data)	2.31	0.79	2.00	No

ADR, adverse drug reaction; DDI, drug-drug interaction; IV, intravenous; WHO, World Health Organization

and honoraria. The authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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