Compounded nonsterile preparations and FDA-approved commercially available liquid products for children: A North American update

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Abstract

The purpose of this work was to evaluate the suitability of recent US Food and Drug Administration (US-FDA) approved and marketed oral liquid, powder, or granule products for children in North America, to identify the next group of Active Pharmaceutical Ingredients (APIs) that have high potential for development as commercially available FDA-approved finished liquid dosage forms, and to propose lists of compounded nonsterile preparations (CNSPs) that should be developed as commercially available FDA-approved finished liquid dosage forms as well as those that pharmacists should continue to compound extemporaneously. Through this identification and categorization process, the pharmaceutical industry, government, and the professions are encouraged to continue to work together to improve the likelihood that patients will receive high quality standardized extemporaneously CNSPs and US-FDA-approved products.

Key words: active pharmaceutical ingredient; compounded drug; compounding; extemporaneous formulation; manufactured material; medication; monograph; pediatric; reference standards

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1. Introduction

Since publication of our last paper, a number of novel commercially scaled pediatric formulations have been approved by FDA that incorporate candidate molecules (active pharmaceutical ingredients - API), which in the past were primarily available only as extemporaneously compounded non-sterile preparations (CNSPs) [1]. In that paper, a list of 16 candidate active pharmaceutical ingredients (APIs) were selected from the universe of CNSPs described in the professional literature which were commonly dispensed in pediatric clinical practice. Bearing in mind the guidance from the U.S. Food and Drug Administration (US-FDA) that discourages the compounding of drug preparations that are "essentially copies of approved products," pharmacists should refrain from compounding any preparation that is now available in an approved finished dosage form appropriate for an individual patient [2]. The following discussion illustrates the variety and formulation characteristics of seven recently marketed mass-produced final oral liquid dosage forms submitted to and approved by US-FDA under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act [3]. Additionally, this report will: (1) evaluate the appropriateness of these newly-marketed products for use in neonatal and pediatric populations: (2) identify the next wave of candidate APIs using the algorithm previously developed and described in the manuscript; and (3) propose two lists of API candidates: (a) those that are listed currently as compounding monographs in the United States Pharmacopeia (USP) Compounding Compendium (CC) and should be considered for development as approved mass produced finished liquid dosage forms [4]; and (b) those not currently listed in USP CC that have limited mass market potential. Currently listed monographs should remain in USP CC to provide guidance globally as well as to mitigate the impact of drug shortages in the approved pharmaceutical supply chain.

2. FDA-approved manufactured dosage forms marketed in the U.S. since 2016

Several authors recently have reviewed the array of pediatric oral formulations on the worldwide market and in development, and it has been suggested that the future of formulation development for children lies

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in mini-tablets and other solid dispersible dosage forms [5-8]. Many, if not most, of these dose forms provide only "close enough" dosing flexibility for individual patients. However, "close enough" often is not good enough, especially for the most vulnerable of patients [9]. In our experience, how to measure exact milligram per kilogram (mg/kg) doses from these solid orals in the in-patient setting would be problematic, considering that the pharmacies in most U.S. pediatric institutions provide a measured, ready-to-give liquid dose form for the nurse to administer for improved patient safety. Table 1 outlines the seven liquid finished dosage forms from the AA list that have become available since 2016.

Table 1. FDA-approved commercially available finished liquid dosage forms from the 2016 AA list

Active pharmaceutical ingredient	Brand name	Strength and dosage form	NDA#	Company and year of approval
lisinopril	Qbrelis™	1 mg/mL oral solution	208401	Azurity - 2016
spironolactone	Carospir™	5 mg/mL oral suspension	209478	CMP Pharma - 2017
metoprolol succinate	Kapspargo™	25, 50, 100, and 200 mg extended release capsules	210428	Sun Pharma - 2018
amlodipine benzoate	Katerzia™	1.3 mg/mL oral suspension (= 1 mg amlodipine)	211340	Azurity - 2019
baclofen	Ozobax™	1 mg/mL oral solution	208193	Metacel - 2019
sildenafil	Revatio™ and generics	10 mg/mL powder for oral suspension	203109	Pfizer, Cipla USA, & Novadoz – 2017-2019
levothyroxine sodium	Tirosint-SOL™	13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg/mL unit dose oral solution	206977	IBSA Pharma - 2019

3. Suitability of recently marketed manufactured liquids for children

USP defines an excipient, often called "'inactive ingredients,' … [as comprising] everything except the active pharmaceutical ingredients (APIs). Excipient functions range from helping to guarantee the stability and bioavailability of the API to the drug product's manufacturability to its texture and taste. Excipients are a major component of almost all drugs, as well as foods, cosmetics and dietary supplements" [10]. For children, not all inactive ingredients are inactive. Because a number of excipients are inappropriate for children, the European Pediatric Formulation Initiative (EPFI) and United States Pediatric Formulation

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Initiative (USPFI) have created a searchable common database to assist manufacturers and compounders alike in identifying age-suitable excipients. Common excipients and preservatives found in the labeling of manufactured products marketed in the US include water, citric acid, glycerin, methyl- and propylparaben, sodium benzoate, sodium citrate, and various forms of cellulose, sugars and sweeteners, and sugar alcohols. Based on the EPFI's S.T.E.P database and PubChem as well as a recent comprehensive review, Table 1 lists recently manufactured oral liquid products, their excipients and preservatives, and comments about the suitability for use in pediatric patients [11]. To validate the appropriateness of these newer manufactured oral liquids and to provide additional expert clinical and professional opinion as to the suitability of various APIs that could be formulated and produced on a commercial scale instead of compounded extemporaneously, members of the Pediatrics Practice and Research Network of the American College of Clinical Pharmacy were polled. This informal poll (N=35) was conducted online and was open from January 18 to February 24, 2022 (see Appendix A for the poll). The results of this poll have been integrated into each of the lists together with their rationale. Caution should be exercised in the use of these newly approved oral liquids, especially in neonates.

4. Additional APIs marketed in manufactured oral liquid or granule dosage forms

An additional 20 APIs have been FDA-approved and marketed in the US in an oral liquid or granule/powder for reconstitution (Table 3). Of the products listed in Table 3, several are approved for adult populations only (**bolded),** and their suitability for use as off-label treatment in children needs to be established. Of note, Azurity Pharmaceuticals has INDs submitted for two anti- epileptic medications in oral liquids; lamotrigine and zonisamide. Two other products, topiramate 25 mg/mL (Eprontia™) and baclofen 5 mg/mL oral liquid formulations, were recently FDA-approved. Tacrolimus (Prograf™) is available in two granule strengths that were not listed in the poll. The medications in Table 2 are listed in order of use at US pediatric hospitals from pediatric pharmacists participating in the poll. Interestingly, almost three-fourths of poll

respondents indicated that an unapproved but marketed metronidazole product was utilized at their institutions.

Table 2. Suitability of recently approved and marketed manufactured liquids for children

Product	Excipients listed in the package insert	Rationale for caution
Kapspargo™ (metoprolol succinate) sprinkles 25, 50, 100, 200 mg capsules	ethyl cellulose; hypromellose (hydroxypropyl methylcellulose); polyethylene glycol 400; polyethylene glycol 6000; sugar spheres (corn starch and sucrose); talc; triethyl citrate	Fixed dose may not be suitable for neonates
Qbrelis™ (lisinopril) 1 mg/mL oral liquid	water; xylitol; sodium citrate; citric acid; sodium benzoate; hydrochloric acid; sodium hydroxide	Contains sodium benzoate
Katerzia™ (amlodipine benzoate) 1 mg/mL oral suspension	citric acid monohydrate; silicone dioxide; hypromellose; maltodextrin; polysorbate 80; sodium benzoate; sodium citrate; sodium hydroxide; sucralose; water	Contains sodium benzoate and sucralose
Carospir™ (spironolactone) 5 mg/mL oral suspension	xanthan gum; dimethicone; sorbic acid; potassium sorbate; saccharin sodium; anhydrous citric acid; trisodium citrate dihydrate; ammonium glycyrrhizate (licorice); glycerin; water	Contains ammonium glycyrrhizate and saccharin
Ozobax™ (baclofen) 1 mg/mL oral solution	anhydrous citric acid; glycerin; methylparaben; propylparaben; trisodium citrate dihydrate; sucralose; water	Contains methyl- and propylparaben and sucralose
Revatio™ (sildenafil citrate) 10 mg/mL powder for oral liquid suspension	micronized cellulose; anhydrous dibasic calcium phosphate; croscarmellose sodium; magnesium stearate; hypromellose; titanium dioxide; lactose monohydrate; triacetin	Contains lactose; not labeled for children
Tirosint-SOL™ - unit dose oral solution (levothyroxine sodium) -12 strengths between 13 and 200 mcg/mL	glycerin; water	Many endocrinologists prefer crushing and dissolving tablets; multiple strengths may lead to medication errors

5. The next wave of oral liquid formulation development – formulation considerations

The following nine APIs were included on the list of 16 and represent the next wave of candidates for conversion from extemporaneously CNSPs to commercially available FDA-approved finished liquid dosage forms products, in order of their potential for development as a commercial market. The most frequently selected CNSPs from those identified in the prior algorithm paper include: ursodiol (79.2%); bosentan (70.8%); captopril (62.5%); pantoprazole (58.3%); valacyclovir (58.3%); clopidogrel (54.2%);

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acetazolamide (50.0%); warfarin (50.0%); and nifedipine (45.8%). The suggested concentrations of oral liquid dosage forms are based on four factors: (1) the usual dosage range; (2) the maximum adult dose and volume (not to exceed 20 mL); (3) the expected water solubility; and (4) the standardized concentration for the extemporaneously compounded preparation, if applicable (Table 4).

Table 3: FDA-approved and marketed in finished oral liquid / granule dosage forms - 2014 to present (§ not listed on the poll)

Active Pharmaceutical Ingredient	Brand Name	NDA #	US-FDA approval year	Labeled pediatric indication (<12 years of age)	% prescribed in selected US pediatric hospitals
glycopyrrolate	Cuvposa™	022571	2018	Yes	85.2
cannabidiol	Epidiolex™	210365	2018	Yes	77.8
vancomycin	Firvanq™	209910	2018	Yes	63.0
mercaptopurine	Purixan™	205919	2014	Yes	48.1
rivaroxaban	Xarelto™	202439	2021	Yes	41.7
methotrexate	Xatmep™	208400	2017	Yes	37.0
hydrocortisone	Alkindi™	213876	2020	Yes	25.9
deflazacort	Emflaza™	208685	2017	Yes	20.8
dronabinol	Syndros™	205525	2016	Yes	18.5
fenfluramine	Fintepla™	212102	2020	Yes	14.8
tacrolimus§	Prograf™	210115	2019	Yes	-
tofacitinib	Xeljanz™	213082	2020	Yes	14.8
tramadol	**Qdolo™**	**214044**	**2020**	**No**	**14.8**
stiripentol	Diacomit™	207223	2018	Yes	14.8
colchicine	**Gloperba™**	**210942**	**2019**	**No**	**14.8**
celecoxib	**Elyxyb™**	**212157**	**2020**	**No**	7.4
sodium zirconium cyclosilicate	**Lokelma™**	**207078**	**2018**	**No**	**3.7**
triheptanoin	Dojolvi™	213687	2020	Yes	0
topiramate§	Eprontia™	214679	2021	Yes	-

- Ursodiol or ursodeoxycholic acid (UDCA) [12-19] inhibits the hepatic synthesis and secretion of cholesterol and its intestinal absorption. It is indicated in primary biliary cirrhosis and for the prevention and treatment of gallstones. It is BCS class II due to low solubility and high permeability. Development

of an oral liquid may be facilitated using methylcellulose and glycerin as excipients and incorporation into polymeric nanoparticle carriers [20,21].

Table 4: Next wave mass manufactured API candidates

Medication	Dosing range in children (mg / kg / day)	Solubility in water at RT and neutral pH (mg / mL)	Suggested mass manufacture concentration	Suggested mass production liquid dose form
ursodiol	10 – 40	0.02	60 mg / mL*	Nanoparticle suspension
bosentan	3 – 4	0.43	6.25 mg/mL	Powder for reconstitution
captopril	0.02 – 0.3	160	1 mg / mL*	Powder for reconstitution
pantoprazole	0.5 – 1	0.048	2 mg / mL	Powder for reconstitution
valacyclovir	60 – 120	174	50 mg / mL*	Solution
clopidogrel	0.2	0.051	5 mg / mL	Powder for reconstitution
acetazolamide	8 – 30	0.9	25 mg / mL	Nanoparticle powder for reconstitution
warfarin	0.05 – 0.35	0.017	1 mg / mL	Powder for reconstitution
nifedipine	1 – 2	0.0059	4 mg / mL*	Nanoparticle powder for reconstitution

(* indicates ASHP standardized concentration [70])

- Bosentan [22,23], a hazardous medication, is a sulfonamide-derived, dual endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension [22,24]. It belongs to BCS class II, and is available in solid and quadrisected dispersible tablets. Its oral bioavailability may be increased through nanosuspension [25] and water-rich co-solvent mixtures using propylene glycol [26].
- Captopril, [4,27-34] is an angiotensin I-converting enzyme inhibitor (ACE-I) indicated in the treatment of heart failure and hypertension [34-36]. It is a BCS class I agent, and freely soluble in water (160 mg/mL), but its stability is limited due to disulfide formation, and fast-dispersing tablet formulations in 2.5 and 10 mg strengths for reconstitution have been suggested [37].
- Pantoprazole [4,38] is a proton pump inhibitor prodrug in the benzimidazole family with a provisional BCS class III designation due to high solubility and low permeability. It is currently available in a delayed release granule for the preparation of an oral suspension used to treat erosive esophagitis,

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gastroesophageal reflux disease, and Zollinger-Ellison syndrome. Dividing the granule formulation into smaller doses in children is not recommended in the product's labeling. Formulation options include alginate-pectin polymeric raft-forming systems and divisible buccal films [39-41].

- Valacyclovir [4,42-45] is a valyl ester prodrug that is converted to acyclovir, and is indicated for herpes labialis and zoster in children. A BCS class III agent, its stability in solution is pH dependent, at concentration ranges from 2.2 to 174 mg/mL [46]. Valacyclovir tablet product labeling includes instructions for preparing a CNSP at concentrations of 25 and 50 mg/mL in 100 mL quantities, using a suspension structured vehicle and cherry flavor to mask the bitter taste. This product has beyond use dating of up to 28 days when stored under refrigeration. However, solution formulations using powdered API with combinations of glycerol and maltodextrin have been suggested [47,48].
- Clopidogrel [4,49-51], a prodrug activated in two steps primarily by CYP 2C19, is a BCS class II agent with a bioavailability of about 50%. Its uses in children are for arterial ischemic stroke, heart disease, and management of endovascular stents [52,53]. Stabilization with stearoyl polyoxylglycerides (Gelucire® 50/13) and/or polyoxyethylated castor oil (Cremophor® RH40) have been suggested for self-emulsifying oral drug delivery formulations to improve bioavailability and storage duration [54].
- Acetazolamide [4] is a potent inhibitor of the enzyme, carbonic anhydrase, that catalyzes the reversible hydration of carbon dioxide and dehydration of carbonic acid, resulting in the renal loss of bicarbonate anion, sodium, and water. Its primary uses in children are for the treatment of metabolic alkalosis, seizure disorder, glaucoma (topically), and intracranial hypertension [55-58]. It is available as a lyophilized powder for injection. Acetazolamide is very slightly soluble in water (BCS class IV), and oral formulation bioavailability may be enhanced through application of mucoadhesive nanoparticles and spray drying techniques [59-61].
- Warfarin is an epoxide reductase inhibitor of the synthesis of vitamin K-dependent clotting factors, including the anticoagulant proteins C and S as well as factor II, VII, IX, and X. Its indications include

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the prophylaxis and treatment of venous thromboembolism, pulmonary embolism, and complications associated with atrial fibrillation, myocardial infarction, and ischemic stroke. Warfarin is listed as BCS class I. While the labeled stability of a reconstituted intravenous injection is 4 hours, more dilute oral solutions (1 mg/mL in aqueous media) may have longer stability [62,63]. Use of semisolid extrusion of orodispersible hydroxypropylcellulose films created through the use of 3D printers may hold promise for both the preparation and individualization of doses [63,64].

- Nifedipine [65] is a dihydropyridine calcium channel blocker formulated as a liquid-filled capsule. It is indicated for chronic hypertension and vasospastic / chronic unstable angina [34,35]. It is BCS class II with poor water solubility, and undergoes extensive first pass metabolism. Formulation of a powder for reconstitution may be facilitated by reduction in particle size through high pressure homogenization or fabricated nanosponge encapsulation [32,66-69].

5.1 Additional API candidates with high potential for development as commercially available FDA-approved finished liquid dosage forms

Table 5 lists an additional 26 mass production candidate APIs, eight of which are on the hazardous drugs list [71]. BCS class I APIs with the highest mass marketing potential include hydroxyurea (83.3%), allopurinol, and flecainide. For BCS class II, amiodarone, carvedilol, isradipine, and quetiapine have the highest potential marketability. In BCS class III, clonidine (100% of those polled), hydralazine, apixaban, and atenolol topped the list. Finally, BCS class IV APIs included only hydrochlorothiazide. Hazardous APIs with at least 50% selected from the poll included hydroxyurea. Commercial availability of finished liquid dosage forms for hazardous medications for oral administration affords an opportunity to reduce overall inadvertent toxic exposure due to dose manipulation in institutional settings and at-home, irrespective of other evaluation criteria. These APIs:

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- have the highest marketing potential for pediatric populations in terms of off-label use in prioritized therapeutic categories (anti-arrhythmics, antibiotics, anti-hypertensives, anti-neoplastics, central nervous system agents, and proton pump inhibitors) [72];

Table 5. APIs with the highest potential for development as commercially available FDA-approved finished liquid dosage forms by BCS class

Active pharmaceutical ingredient	Biopharmaceutical Classification (BCS)	% selected for mass manufacturing
clonidine	**III**	**100**
hydroxyurea	**I**	**83.3**
hydrochlorothiazide	**IV**	**75**
amiodarone	**II**	**58.3**
carvedilol	**II**	**58.3**
hydralazine	**III**	**58.3**
isradipine	**II**	**58.3**
allopurinol	**I**	**54.2**
flecainide	**I**	**54.2**
quetiapine	**II**	**54.2**
apixaban	**III**	**54.2**
atenolol	**III**	**50**
cyclophosphamide	I	45.8
losartan	II	45.8
ganciclovir	III	41.7
aprepitant	IV	41.7
azathioprine	IV	41.7
spironolactone/HCTZ	II/IV	37.5
labetalol	I	33.3
folic acid	IV	29.2
trazodone	I	8.3
folinic acid	III	16.7
thioguanine	IV	8.3
ticagrelor	IV	0
verapamil	II	0

- appear on the FDA and World Health Organization list of essential medicines [73];
- have a standardized concentration identified on the ASHP Standardize4safety list [70,74];
- are available in an intravenous formulation which would support potential oral formulation feasibility; and

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- have a pediatric Biopharmaceutical Classification System (BCS) classification indicating relative ease of generating suitable oral liquid formulations intended primarily for children [75].

BCS class II and IV APIs have low solubility and high or low gastrointestinal permeability, and several techniques have been forwarded to address them. In many cases, the optimal solubility / permeability balance is based on the extent to which membrane / aqueous partitioning is maximized, that is, the intersection where both are at their highest relative values [76]. Formulation methods to increase either solubility or dissolution rates for BCS class II and IV APIs identified in the literature include:

- 3D printing [63,77-79];
- amorphous solid dispersion [59,80,81];
- complexation [82,83];
- fusion [84,85];
- hot-melt extrusion [84,86];
- lipid-microemlusion [54];
- lyophilization [84,87,88];
- micelles [87];
- nanosizing [60,89]; and
- spray drying [59,60].

Excipients that have been shown to increase gastrointestinal tract permeability include:

- cyclodextrins [67,82];
- surfactants [53,88]; and
- cosolvents [90].

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A brief product profile for the APIs with at least 50% selected for development as commercially available FDA-approved finished liquid dosage forms includes: (1) clinical pharmacology / PK / PD / PG; (2) indications and dosing regimens; and (3) clinical pharmaceutics and potential formulation characteristics.

5.1.1 High solubility / high permeability (BCS Class I)

- Hydroxyurea [91] is an antimetabolite used to treat sickle cell anemia crisis, management of melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary. It inhibits DNA synthesis through the inhibition of ribonucleoside diphosphate reductase. It is well absorbed orally and water solubility is 100 mg/mL. An oral liquid with a concentration of 100 mg/mL has been studied [92].
- Allopurinol is a xanthine oxidase inhibitor used to reduce urinary and serum uric acid concentrations in patients with gout, recurrent calcium oxalate calculi, and various malignancies. Children, 6 to 10 years of age, with secondary hyperuricemia associated with malignancies may be given 300 mg allopurinol daily while those under 6 years are generally given 150 mg daily. The response is evaluated after approximately 48 hours of therapy and a dosage adjustment is made if necessary. Solubility in water at room temperature is between 0.48 and 0.57 mg/mL. A 500 mg lyophilized injection is available. Hydrophilic carriers such as polyvinylpyrrolidone, polyethylene glycol 6000 in the ratio of 1:1, 1:2 and 1:4 (drug to carrier ratio) have been shown to increase aqueous solubility [80].
- Flecainide [93] is a class Ic antiarrhythmic agent used to manage atrial fibrillation and paroxysmal supraventricular tachycardias (PSVT). Its water solubility is 48.4 mg/mL at 37°C. Dosing in children is usually less than 100 mg per dose. A 20 mg/mL formulation using bulk powder and purified water and simple syrup (50:50) resulted in a transparent solution [94].

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5.1.2 Low solubility / high permeability (BCS Class II)

- Amiodarone, considered a class III antiarrhythmic with α- and β-receptor antagonism, is a benzofuran derivative indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients that are refractory to other therapy. Most patients will require this therapy for 48 to 96 hours, but amiodarone may be safely administered for longer periods if necessary. Pediatric dosing ranges from 10 to 15 mg/kg/day in 1 to 2 divided doses/day for 4 to 14 days or until adequate control of arrhythmia or prominent adverse effects occur. Dosage should then be reduced to 5 mg/kg/day given once daily for several weeks. If arrhythmia does not recur, reduce to lowest effective dosage possible. Usual daily minimal dose: 2.5 mg/kg/day; maintenance doses may be given for 5 or 7 days/week. Amiodarone is available in a 50 mg/mL intravenous injection, exhibits 0.72 mg/mL solubility in water, and is highly lipophilic. A 5 mg/mL formulation at pH=4 with cherry flavoring has been suggested [33].
- Carvedilol [12] is a racemic mixture where the S(-) enantiomer is a beta adrenoceptor blocker and the R(+) enantiomer is both a beta and alpha-1 adrenoceptor blocker. It is currently used to treat heart failure, left ventricular dysfunction, and hypertension. Pediatric dosing ranges from 0.4 to 0.8 mg/kg/day in 2 divided doses. It is virtually insoluble in water, and is highly lipophilic. A 1 – 1.25 mg/mL oral suspension has been suggested [31].
- Isradipine [35,36] belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. It is structurally related to felodipine, nifedipine, and nimodipine, and is the most potent calcium-channel blocking agent of the DHP class. Isradipine binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and arterial smooth muscle cells. It exhibits greater selectivity towards arterial smooth muscle cells owing to alternative splicing of the alpha-1 subunit of the channel and increased prevalence of inactive channels in smooth muscle cells. Isradipine may be used to treat mild to moderate essential hypertension. Pediatric dosing

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ranges from 0.15 to 0.2 mg/kg/day divided every 6 to 8 hours with a maximum dosage of 0.8 mg/kg/day, not to exceed 20 mg/day. It is practically insoluble in water. A 1 mg/mL suspension has been compounded since its initial marketing [95].

- Quetiapine is a dopamine type 2 and serotonin 2A receptor antagonist and binds to the norepinephrine transporter. Additional effects of quetiapine, including somnolence, orthostatic hypotension, and anticholinergic effects, may result from the antagonism of histamine-1, adrenergic α1, and muscarinic-1 receptors, respectively. It is used in the management of bipolar disorder, schizophrenia, major depressive disorder, and delirium [96]. Quetiapine is rapidly and well absorbed after administration of an oral dose, and steady-state is achieved within 48 hours. It is metabolized by CPY 2D6 and 3A4. The water solubility of quetiapine is 0.6 mg/mL with a pKa of 7.06. Pediatric dosing ranges from 0.5 to 6 mg/kg/day. Nanotechnology formulations of 2.5, 5, 10, 20 and 40 mg/mL have been suggested [97,98].

5.1.3 High solubility / low permeability (BCS Class III)

- Clonidine [99-103], is an imidazole derivate that acts as an agonist of alpha-2 adrenoceptors used to treat hypertension and severe cancer pain, among other conditions, and to treat withdrawal symptoms from various substances. It is available in a 0.1 mg/mL liquid solution for injection, and is insoluble in water. Its bioavailability is between 55-87%, and primary metabolism includes hydroxylation via CYP2D6, CYP1A2, CYP3A4, CYP1A1, and CYP3A5 enzymes. The usual pediatric dose range is between 5 and 10 mcg/kg/day orally in divided doses every 8 to 12 hours then titrated based on clinical response, with a maximum dose of 25 mcg/kg/day or 0.9 mg/day.
- Hydralazine [35] is a direct-acting vasodilator that is used as an antihypertensive agent. It inhibits the phosphorylation of myosin protein and chelation of trace metals required for smooth muscle contraction, resulting in an increase in heart rate, stroke volume and cardiac output. Available in a 20 mg/mL injection solution, hydralazine is freely soluble in water. Initial dose is 0.75 mg/kg/day in 4 divided doses with gradual increase over 3 to 4 weeks to a maximum of 7.5 mg/kg/day or 200 mg/day.

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Taking oral hydralazine with food improves the bioavailability of the drug. A 4 mg/mL suspension using crushed hydralazine tablets has been suggested [49].

- Apixaban [104] is an oral, direct, and highly selective factor Xa (FXa) inhibitor of both free and bound FXa, as well as prothrombinase, independent of antithrombin III, for the prevention and treatment of thromboembolic diseases. Children 12 to <18 years old weighing less than 40 kg have received an apixaban dose of 0.2 mg/kg twice daily for 7 days followed by 0.1 mg/kg twice daily, whereas children at the same age weighing more than 40 kg receive the adult VTE treatment dose (i.e., 10 mg twice daily for 7 days followed by 5 mg twice daily). Apixaban is approximately 50% bioavailable, and is mainly metabolized by cytochrome CYP 3A4 and to a lesser extent by CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2. It has a water solubility of 0.11 mg/mL. A 0.25 mg/mL suspension with a 7-day stability has been reported [105].
- Atenolol [36] is a synthetic beta-1 selective blocker used in the management of hypertension and chronic angina, and to reduce mortality in known or suspected myocardial infarction in hemodynamically stable patients. It is available in a liquid injection at a concentration of 0.5 mg/mL. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Its water solubility is 13.3 mg/mL. Typical dosage range for children is 0.5-1 mg/kg/day given once daily or divided in 2 doses per day with a maximum dose of 2 mg/kg/day [106].

5.1.4 Low solubility / low permeability (BCS Class IV)

- Hydrochlorothiazide [34,107] is a thiazide diuretic used alone or in combination for the management of edema associated with congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, and hypertension. Hydrochlorothiazide acts on the proximal region of the distal convoluted tubule, inhibiting reabsorption by the sodium-chloride symporter, also known as Solute Carrier Family 12 Member 3 (SLC12A3). It has a water

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solubility of 0.7 mg/mL. Because of its poor oral absorption, several novel dosage forms have been proposed, including orally-disintegrating mini-tablets, liquid complexation with cyclodextrin, and nanostructured lipid carriers [108-110].

5.2 Extemporaneous CNSP APIs included in USP CC monographs

Extemporaneous CNSP APIs included in USP CC monographs that could be developed as FDA-approved manufactured products as well as those without a mass market are outlined below [111]. The list is broken down into those APIs whose compounding recipes are found currently (1) in the USP CC and (2) those available in other sources. A total of 45 APIs are included in these two lists (23 found in USP CC). Those APIs listed in the USP CC that are suitable for development as commercially available FDA-approved finished liquid dosage forms include: desmopressin (62.5%), phytonadione (54.2%), pyridoxine (54.2%), rifampin (54.2%) and ethambutol (45.8%). Of note, desmopressin, phytonadione, and pyridoxine are available in liquid injections. Those that should remain as extemporaneously CNSPs include: pyrazinamide (33.3%), dapsone (29.2%), diltiazem (29.2%), ketoconazole (20.8%), metolazone (20.8%), pyrimethamine (20.8%), rifabutin (20.8%), bethanechol (16.7%), propylthiouracil (16.7%), dipyridamole (12.5%), chloroquine (8.3%), quinidine (8.3%), temozolomide (8.3%), terbutaline (8.3%), tetracycline (8.3%), tiagabine (4.2%), dolasetron (0%), and phenoxybenzamine (0%). Other APIs that could be developed for approval as commercially available products include: buprenorphine, naltrexone, everolimus, and clonazepam.

5.3 Potentially approvable products from extemporaneously compounded APIs not included in USP CC

Zinc (70.8%) was the only API CNSP formulation available from other sources selected by at least 50% as suitable for development and approval as commercially available finished liquid dosage forms. After appropriate testing for stability, those that could be incorporated into USP CC include: amitriptyline (37.5%), hydroxychloroquine (37.5%), thiamine (37.5%), rifaximin (33.3%), valsartan (29.2%), venlafaxine (25.0%), buspirone (20.8%), phenazopyridine (20.8%), dantrolene (16.7%), mexiletine

(16.7%), nadolol (12.5%), pravastatin (12.5%), topotecan (12.5%), tretinoin (12.5%), chlorpromazine (8.3%), ethacrynic acid (8.3%), flucytosine (8.3%), amiloride (4.2%), primaquine (4.2%), procarbazine (4.2%), and disopyramide (0%). As a result of validating the monographs of over 59 listed APIs, USP identified seven CNSPs that failed stability testing using the present formulation recipe, including methimazole, phenazopyridine, probenecid, and trazodone CNSP liquids [112]. While none are considered to have high mass market potential, efforts to reformulate these APIs as stable CNSPs should be undertaken.

6. Summary

The purpose of this work was to evaluate the suitability of recently FDA-approved and marketed oral liquid, powder, or granule products, to identify the next group of APIs with potential for mass marketing and FDA approval, and to propose CNSPs that should be developed as approved and manufactured products as well as those that should continue to be extemporaneously prepared. There is general support for the following next wave of APIs: ursodiol, bosentan, captopril, pantoprazole, valacyclovir, clopidogrel, acetazolamide, warfarin, and nifedipine. Results from an informal poll of pediatric pharmacists revealed APIs with the highest potential for mass marketing as FDA approved products to include clonidine, hydroxyurea, hydrochlorothiazide, amiodarone, carvedilol, hydralazine, allopurinol, flecainide, quetiapine, apixaban, and atenolol. USP CC-listed APIs that are suitable for development and approval as commercially available FDA-approved finished liquid dosage forms produced products include desmopressin, phytonadione, pyridoxine, rifampin, and ethambutol. Zinc was the only non-USP CC-listed CNSP that should be developed as an approved mass manufactured product. Those CNSPs listed in USP CC without high mass marketing and approval potential include pyrazinamide, dapsone, diltiazem, ketoconazole, metolazone, pyrimethamine, rifabutin, bethanechol, propylthiouracil, dipyridamole, chloroquine, quinidine, temozolomide, terbutaline, tetracycline, tiagabine, dolasetron, and phenoxybenzamine. APIs that USP should consider for addition to the CC, perhaps through active solicitation for the formulation monograph donation program (CPMDonate@usp.org) [113]: amitriptyline, hydroxychloroquine, thiamine, rifaximin, valsartan, venlafaxine, buspirone, dantrolene, mexiletine, nadolol, pravastatin, topotecan, tretinoin,

chlorpromazine, ethacrynic acid, flucytosine, amiloride, primaquine, procarbazine, and disopyramide. Through this identification and categorization process, the authors encourage industry, government, and the professions to continue to work together to improve the likelihood that patients will receive high quality standardized extemporaneously prepared CNSPs and FDA approved mass manufactured products.

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