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

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Acknowledgement. RM’s work was funded in part by The Rockefeller University Center for Clinical and Translational Science grant # UL1 TR001866 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program.

Abstract word count: 124
Manuscript word count: 4,028
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
1. Introduction

Since publication of our “alternative algorithm” (AA) paper, significant market changes have been realized in the approval and commercial availability of finished liquid dosage forms from previously extemporaneously compounded non-sterile preparations (CNSPs) [1]. In that paper, a list of 16 candidate active pharmaceutical ingredients (APIs) were derived from the universe of CNSPs found in the professional literature and typically utilized 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 developed in the previous 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 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             | Kapsargo™  | 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 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 manufactured instead of compounded extemporaneously, members of the Pediatrics Practice and Research Network of the American College of Clinical Pharmacy were polled. This unscientific 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 with their reasoning behind the decisions. 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 Pharma 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.
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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); t alc; 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 hydrox ide | 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 hydrox ide; 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%); 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

| 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                      | Firvand™   | 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§                     | Epronbia™  | 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, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. Dividing the granule formulation for 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, and concentration ranges from 2.2 to 174 mg/mL [46]. The formulation of 25 mg and 50 mg/mL extemporaneous oral suspensions from tablets in batches of 100 mL with a 28-day stability under refrigeration is contained in the product’s official labeling, including Suspension Structured Vehicle and cherry flavor to mask its bitter taste. However, solution formulations using powdered API with combinations of glycerol and maltodextrin has 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 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
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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:

- 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];
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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                             |
| apreptiant                       | 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
- 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-microemulsion [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].

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 has a 100 mg/mL water solubility. 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].

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 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 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
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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 is hydroxylated by CYP2D6, CYP1A2, CYP3A4, CYP1A1, and CYP3A5. 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. Taking oral hydralazine with food improves the bioavailability of the drug. A 4 mg/mL suspension 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 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 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%), betheamechol (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 a 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 mass market and approval, and propose CNSPs that should be developed as approved and manufactured products as well as those that should likely remain as 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 unscientific poll of pediatric pharmacists revealed APIs with the highest mass marketing as approved products potential that 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 approved mass manufactured products.

References

1. Bhatt-Mehta, V.; MacArthur, R.B.; Löbenberg, R.; Cies, J.J.; Cernak, I.; Parrish, R.H. Development of an algorithm to identify mass production candidate molecules to develop children’s oral medicines: A North American perspective. *AAPS Open*. 2016, 2(8). doi:10.1186/s41120-016-0009-y

2. United States Food and Drug Administration. Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry. 2016;(July 2016):1-11. https://www.fda.gov/media/98973/download

3. United States Food and Drug Administration. Guidance for Industry: Applications Covered by Section 505(b)(2). Guidance. Published online 1999. https://www.fda.gov/media/72419/download

4. United States Pharmacopeial Convention. June 2020 / USP Compounding Compendium. Published 2020. Accessed October 23, 2020. https://www.usp.org/products/usp-compounding-compendium

5. Ivanovska, V.; Rademaker, C.M.A.; Van Dijk, L.; Mantel-Teeuwisse, A.K. Pediatric drug formulations: A review of challenges and progress. *Pediatrics*. 2014, 134, 361-372. doi:10.1542/peds.2013-3225
6. Lopez, F.L.; Ernest, T.B.; Tuleu, C.; Gul, M.O. Formulation approaches to pediatric oral drug delivery: Benefits and limitations of current platforms. *Expert Opin Drug Deliv*. **2015**, *12*, 1727-1740. doi:10.1517/17425247.2015.1060218

7. Strickley, R.G. Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007. *J Pharm Sci*. **2019**, *108*, 1335-1365. doi:10.1016/j.xphs.2018.11.013

8. Bar-Shalom, D. Necessity of rethinking oral pediatric formulations. *Clin Ther*. **2014**, *36*, 180-183. doi:10.1016/j.clinthera.2014.01.010

9. Binson, G.; Sanchez, C.; Waton, K.; Chanat, A.; Di Maio, M.; Beuzit, K.; Dupuis, A. Accuracy of Dose Administered to Children Using Off-Labelled or Unlicensed Oral Dosage Forms. *Pharmaceutics*. **2021**, *13*, 1014. doi:10.3390/pharmaceutics13071014

10. United States Pharmacopeia. FAQs: Excipients. https://www.usp.org/frequently-asked-questions/excipients. Accessed 22 February 2022.

11. Rouaz, K.; Chiclana-Rodríguez, B.; Nardi-Ricart, A.; Suñé-Pou, M.; Mercadé-Frutos, D.; Suñé-Negre, J.M.; Pérez-Lozano, P.; Garcia-Montoya, M.E. Excipients in the Paediatric Population: A Review. *Pharmaceutics*. **2021**, *13*, 387. doi:10.3390/pharmaceutics13030387

12. Polonini, H.; da Silva, S.L.; Brandão, M.A.F.; Bauters, T.; De Moerloose, B.; Ferreira, A.O. Compatibility of Baclofen, Carvedilol, Hydrochlorothiazide, Mercaptopurine, Methadone Hydrochloride, Oseltamivir Phosphate, Phenobarbital, Propranolol Hydrochloride, Pyrazinamide, Sotalol Hydrochloride, Spironolactone, Tacrolimus Monohydrate, Ursodeoxycholic Acid, and
Vancomycin Hydrochloride Oral Suspensions Compounded with SyrSpend SF pH4. *Int J Pharm Compd*. 2018, 22, 516-526. PMID: 30384353.

13. Johnson, C.E.; Nesbitt, J. Stability of ursodiol in an extemporaneously compounded oral liquid. *Am J Health Sys Pharm*. 1995, 52, 1798-1800. doi:10.1093/ajhp/52.16.1798

14. Rudic, J.S.; Poropat, G.; Krstic, M.N.; Bjelakovic, G.; Gluud, C. Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database Syst Rev*. 2012, 12, CD000551. doi:10.1002/14651858.cd000551.pub3

15. Trissel, L.A.; Ashworth, L.D.; Ashworth, J. (eds.) Ubidecarenone – Ursodiol. In: Trissel’s Stability of Compounded Formulations, 6th ed. 2018. https://doi.org/10.21019/9781582122960

16. Mallett, M.S.; Hagan, R.L.; Peters, D.A. Stability of ursodiol 25 mg/mL in an extemporaneously prepared oral liquid. *Am J Health Syst Pharm*. 1997, 54, 1401-1404. doi: 10.1093/ajhp/54.12.1401.

17. Pramar, Y.V.; Mandal, T.K.; Bostanian, L.A.; Nguyen, A.T.; Miller, V.; Morris, T.C.; Graves, R.A. Stability of Compounded Ursodiol Suspensions in PCCA Base, SuspendIt. *Int J Pharm Compd*. 2019, 23, 70-76. PMID: 30668538.

18. de Oliveira Junior, E.R.; Truzzi, E.; Ferraro, L.; Fogagnolo, M.; Pavan, B.; Beggiato, S.; Rustichelli, C.; Marettim, E.; Lima, E.M.; Leo, E.; Dalpiaz, A. Nasal administration of nanoencapsulated geraniol/ursodeoxycholic acid conjugate: Towards a new approach for the management of Parkinson’s disease. *J Control Release*. 2020, 21, 540-552. doi:10.1016/j.jconrel.2020.02.033
19. Geiger, C.M.; Voudrie, M.A. 2nd; Sorenson, B. Stability of ursodiol in SyrSpend SF Cherry flavored. *Int J Pharm Compd.* **2012**, *16*, 510-512. PMID: 23259368.

20. Tereshchenko, O.G.; Nikolskaya, E.D.; Zhunina, O.A.; Zavarzina, V.; Yabbarov, N.G.; Fomicheva, M.V.; Zubkov, E.V.; Sokol, M. B.; Gukasova, N.V.; Severin, E.S. Formulation of perspective hepatoprotector polymeric forms based on silybin and ursodeoxycholic acid. *Russ Chem Bull.* **2019**, *67*, 2290-2296. doi:10.1007/s11172-018-2372-4

21. Santoveña, A.; Sánchez, E.; Charola, L.; Llabrés, M.; Fariña, J.B. Study of quality and stability of ursodeoxycholic acid formulations for oral pediatric administration. *Int J Pharm.* **2014**, *477*, 32-38. doi:10.1016/j.ijpharm.2014.10.011

22. Berger, R.M.F.; Hawort, S.G.; Bonnet, D.; Dulac, Y.; Fraisse, A.; Galiè, N.; Ivy, D.D., Jaïs, X.; Miera, O., Rosenzweig, E.B.; Efficace, M., Kusic-Pajic, A., Beghetti, M. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion. *Int J Cardiol.* **2016**, *202*:52-8. doi:10.1016/j.ijcard.2015.08.080

23. Carter, N.J.; Keating, G.M. Bosentan: In pediatric patients with pulmonary arterial hypertension. *Pediatr Drugs.* **2010**, *12*, 63-73. doi:10.2165/11203970-000000000-00000

24. Beghetti, M.; Haworth, S.G.; Bonnet, D.; Barst, R.J.; Acar, P.; Fraisse, A.; Ivy, D.D.; Jais, X.; Schulze-Neick, I.; Galiè, N.; Morganti, A.; Dingemanse, J.; Kusic-Pajic, A.; Berger, R.M. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: The FUTURE-1 study. *Br J Clin Pharmacol.* **2009**, *68*, 948-955. doi:10.1111/j.1365-2125.2009.03532.x
25. Ghasemian, E.; Motaghian, P.; Vatanara, A. D-optimal design for preparation and optimization of fast dissolving bosentan nanosuspension. *Adv Pharm Bull.* **2016**, 6, 211-8. doi:10.15171/apb.2016.029

26. Babaei, M.; Shayanfar, A.; Rahimpour, E.; Barzegar-Jalali, M.; Martinez, F.; Jouyban, A. Solubility of bosentan in {propylene glycol + water} mixtures at various temperatures: experimental data and mathematical modelling. *Phys Chem Liq.* **2019**, 57, 3. doi:10.1080/00319104.2018.1461872

27. Chan, D.S.; Sato, A.K.; Claybaugh, J.R. Degradation of captopril in solutions compounded from tablets and standard powder. *Am J Hosp Pharm.* **1994**, 51, 1205-1207. PMID: 8042640.

28. Allen, L.V.; Erickson, M.A. Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole and flecainide acetate in extemporaneously compounded oral liquids. *Am J Health Sys Pharm.* **1996**, 53, 2179-2184. doi:10.1093/ajhp/53.18.2179

29. Lin, T.R.; Yang, Y.H.K.; Huang, Y.F.; Tsai, J.C. Content uniformity of captopril, furosemide, nadolol and propranolol hydrochloride powder packets extemporaneously compounded from tablets. *Chinese Pharm J.* **2000**, 52, 58-63. doi:10.7019/CPJ.200002.0059

30. Geiger, C.M.; Sorenson, B.; Whaley, P.A. Stability of captopril in SyrSpend SF. *Int J Pharm Compd.* **2013**, 17, 336-338. PMID: 24261148.

31. Kuriata, E.; Sawicki, W. Evaluation of cases with the usage of commercially available tablets in the pediatric formula. *Acta Pol Pharm.* **2015**, 72, 551-558. PMID: 26642663.
32. Harris Tieca, T.; Adebayo Amusa, S.; Deon, B.; Oluwayomi, O.; Charmaine, S. Extemporaneous compounding for children with coronary heart diseases in Jamaica. Eur J Clin Pharm. 2018, 20, 204-212. ISSN 2385-409X

33. Thrimawithana, T.R.; D’Amore, S.; Dib, Y.; Fadavi Firooz, N.; Fakhouri, W.; Saeed, A.; Allahham, A. Critical appraisal of commercially available suspending vehicles for extemporaneous compounding of cardiovascular medicines: physical and chemical stability mini review. Pharm Dev Technol. 2019, 24, 529-538. doi:10.1080/10837450.2018.1526955

34. Momma, K. ACE inhibitors in pediatric patients with heart failure. Pediatr Drugs. 2006, 8, 55-69. doi:10.2165/00148581-200608010-00005

35. Meyers, R.S.; Siu, A. Pharmacotherapy Review of Chronic Pediatric Hypertension. Clin Ther. 2011, 33, 1331-1356. doi:10.1016/j.clinthera.2011.09.003

36. Robinson, R.F.; Nahata, M.C.; Batisky, D.L.; Mahan, J.D. Pharmacologic treatment of chronic pediatric hypertension. Pediatr Drugs. 2005, 7, 27-40. doi:10.2165/00148581-200507010-00003

37. Pabari, R.M.; McDermott, C.; Barlow, J.; Ramtoola, Z. Stability of an Alternative Extemporaneous Captopril Fast-Dispersing Tablet Formulation Versus an Extemporaneous Oral Liquid Formulation. Clin Ther. 2012, 34, 2221-2229. doi:10.1016/j.clinthera.2012.10.005

38. Dentinger, P.J.; Swenson, C.F.; Anaizi, N.H. Stability of pantoprazole in an extemporaneously compounded oral liquid. Am J Health Sys Pharm. 2002, 59, 953-956. doi:10.1093/ajhp/59.10.953
39. Abbas, G.; Hanif, M. Development and pharmacokinetic evaluation of alginate-pectin polymeric rafts forming tablets using box behnken design. *Drug Dev Ind Pharm.* **2018**, *44*, 2026-2037. doi:10.1080/03639045.2018.1508221

40. Thombre, S.K.; Gaikwad, S.S. Design and development of mucoadhesive buccal delivery for Pantoprazole with stability enhancement in human saliva. *Int J Pharm Pharm Sci.* 2013, 5, 122-127.

41. Dheerajvarma, K.; Sai Krishna, P.; Prasanna, L. Formulation and evaluation of Pantoprazole sodium sesquihydrate IR buccal films. *Res J Pharm Biol Chem Sci.* 2014, 5, 881-886.

42. Kimberlin, D.W.; Jacobs, R.F.; Weller, S.; et al. Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. *Clin Infect Dis.* **2010**, *50*, 221-228. doi:10.1086/649212

43. Jew, R.K.; Soo-Hoo, W.; Erush, S.C.; Amiri, E. (eds.) *Valacyclovir Suspension 50 mg/mL*. In: Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients. 3rd ed., 2020. doi:10.37573/9781585285259.129

44. Fish, D.N.; Vidaurri, V.A.; Deeter, R.G. Stability of valacyclovir hydrochloride in extemporaneously prepared oral liquids. *Am J Health Sys Pharm.* **1999**, *56*, 1957-1960. doi:10.1093/ajhp/56.19.1957

45. Granero, G.E.; Amidon, G.L. Stability of valacyclovir: Implications for its oral bioavailability. *Int J Pharm.* **2006**, *317*, 14-18. doi:10.1016/j.ijpharm.2006.01.050
46. Granero, G.E.; Longhi, M.R.; Becker, C.; Junginger, H.E.; Kopp, S.; Midha, K.K.; Shah, V.P.; Stavchansky, S.; Dressman, J.B.; Barends, DM. Biowaiver monographs for immediate release solid oral dosage forms: Acetazolamide. *J Pharm Sci*. **2008**, *97*, 3691-3699. doi:10.1002/jps.21282

47. Bastiaans, D.E.T.; Bartels-Wilmer, C.M.; Colbers, A.P.H.; Heijens, C.A.; Velthoven-Graafland, K.; Smeets, O.S.; Vink, N.; Harbers, V.E.; Warris, A.; Burger, D.M.. A new paediatric formulation of valaciclovir: Development and bioequivalence assessment. *Arch Dis Child*. **2016**, *101*, 971-972. doi:10.1136/archdischild-2015-310266

48. Bastiaans, D.E.T.; Immohr, L.I.; Zeinstra, G.G.; Strik-Albers, R.; Pein-Hackelbusch, M.; van der Flier, M.; de Haan, A.F.J.; Boelens, J.J.; Lankester, A.C.; Burger, D.M.; Warris, A. In vivo and in vitro palatability testing of a new paediatric formulation of valaciclovir. *Br J Clin Pharmacol*. **2017**, *83*, 2789-2797. doi:10.1111/bcp.13396

49. Polonini, H.; da Silva, S.L.; Cunha, C.N.; Ferreira, A.O.; Anagnostou, K.; Dijkers, E. Stability of Azathioprine, Clonidine Hydrochloride, Clopidogrel Bisulfate, Ethambutol Hydrochloride, Griseofulvin, Hydralazine Hydrochloride, Nitrofurantoin, and Thioguanine Oral Suspensions Compounded with SyrSpend SF pH4. *Int J Pharm Compd*. **2020**, *24*, 252-262. PMID: 32401746.

50. Yamreudeewong, W.; Dolence, E.K.; Teixeira, M.G. Stability of clopidogrel in three extemporaneously compounded oral liquid preparations. *Int J Pharm Compd*. **2011**, *14*, 435-437.

51. Ellis, D.P.; Rozek, T.; Milne, R.W. Stability of a compounded oral liquid formulation of clopidogrel for infants. *J Pharm Pract Res*. **2020**, *50*, 321-328. doi:10.1002/jppr.1612
52. Soman, T.; Rafay, M.F.; Hune, S.; Allen, A.; MacGregor, D.; DeVeber, G. The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke*. 2006, 37, 1120-1122. doi:10.1161/01.STR.0000209620.44017.97

53. Hatai, Y.; Nykanen, D.G.; Williams, W.G.; Freedom, R.M.; Benson, L.N. Endovascular stents in children under 1 year of age: acute impact and late results. *Br Heart J*. 1995, 74, 689-695. doi:10.1136/hrt.74.6.689

54. Kim, D.W.; Kwon, M.S.; Yousaf, A.M.; Balakrishnan, P.; Park, J.H.; Kim, D.S.; Lee, B.J.; Park, Y.J.; Yong, C.S.; Kim, J.O.; Choi, H.G. Comparison of a solid SMEDDS and solid dispersion for enhanced stability and bioavailability of clopidogrel napadisilate. *Carbohydr Polym*. 2014, 114, 365-374. doi:10.1016/j.carbpol.2014.08.034

55. Cheung, M.S. Drugs Used in Paediatric Bone and Calcium Disorders. *Endocr Dev*. 2015, 28, 277-290. doi:10.1159/000381053

56. Cleves-Bayon, C. Idiopathic Intracranial Hypertension in Children and Adolescents: An Update. *Headache*. 2018, 58, 485-493. doi:10.1111/head.13236

57. Bar, A.; Cies, J.; Stapleton, K.; Tauber, D.; Chopra, A.; Shore, P.M. Acetazolamide therapy for metabolic alkalosis in critically ill pediatric patients. *Pediatr Crit Care Med*. 2015, 16, e34-40. doi:10.1097/PCC.0000000000000313

58. López, C.; Alcaraz, A.J.; Toledo, B.; Cortejoso, L.; Gil-Ruiz, M.A. Acetazolamide Therapy for Metabolic Alkalosis in Pediatric Intensive Care Patients. *Pediatr Crit Care Med*. 2016, 17, e551-e558. doi:10.1097/PCC.0000000000000971
59. Manchanda, S.; Sahoo, P.K. Topical delivery of acetazolamide by encapsulating in mucoadhesive nanoparticles. *Asian J Pharm Sci.* 2017, 12, 550-557. doi:10.1016/j.ajps.2017.04.005

60. Dureja, H.; Pandey, P. Optimizing the spray-drying parameters for a formulation of nanoparticles-in-microparticles system of acetazolamide. *Drug Dev Deliv.* 2017, Jan/Feb.

61. Pandey, P.; Marwaha, R.K.; Nanda, A.; Dureja, H. Spray-Dried Nanoparticles-in-Microparticles System (NiMS) of Acetazolamide Using Central Composite Design. Nanosci Nanotechnology-Asia. 2017, 6, 146-156. doi:10.2174/2210681206666160402004241

62. Sharley, N.A.; Yu, A.M.C.; Williams, D.B. Stability of mixtures formulated from warfarin tablets or powder. *J Pharm Pract Res.* 2007, 37, 95-97. doi:10.1002/j.2055-2335.2007.tb00026.x

63. Schlatter, J.; Cisternino, S. Stability of warfarin sodium flavoured preservative-free oral liquid formulations. *Eur J Hosp Pharm.* 2018, 25, e98-e101. doi:10.1136/ejhpharm-2017-001281

64. Öblom, H.; Sjöholm, E.; Rautamo, M.; Sandler, N. Towards printed pediatric medicines in hospital pharmacies: Comparison of 2d and 3d-printed orodispersible warfarin films with conventional oral powders in unit dose sachets. *Pharmaceutics.* 2019, 11, 334. doi:10.3390/pharmaceutics11070334

65. Gajendran, J.; Krämer, J.; Shah, V.P.; et al. Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Nifedipine. *J Pharm Sci.* 2015, 104, 3289-3298. doi:10.1002/jps.24560
66. Geiger, C.M.; Sorenson, B.; Whaley, P. Stability Assessment of 10 Active Pharmaceutical Ingredients Compounded in SyrSpend SF. Int J Pharm Compd. 2015, 19, 420-427. PMID: 26775449.

67. Helin-Tanninen, M.; Naaranlahti, T.; Kontra, K.; Ojanen, T. Enteral suspension of nifedipine for neonates. Part 2. Stability of an extemporaneously compounded nifedipine suspension. *J Clin Pharm Ther.* 2001, 26, 59-66. doi:10.1046/j.1365-2710.2001.00323.x

68. Shringirishi, M.; Mahor, A.; Gupta, R.; Prajapati, S.K.; Bansal, K.; Keshearwani, P. Fabrication and characterization of nifedipine loaded β-cyclodextrin nanosponges: An in vitro and in vivo evaluation. *J Drug Deliv Sci Technol.* 2017, 41. doi:10.1016/j.jddst.2017.08.005

69. Naaranlahti, T.; Kontra, K.; Wallenius, K.; Helin-Tanninen, M. Enteral suspension of nifedipine for neonates. Part 1. Formulation of nifedipine suspension for hospital use. *J Clin Pharm Ther.* 2001, 26, 49-57. doi:10.1046/j.1365-2710.2001.00318.x

70. American Society of Health-system Pharmacists. STANDARDIZE 4 SAFETY INITIATIVE. 2020. Available online: https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Compound-Oral-Liquid.pdf. Accessed 23 February 2022.

71. United States Department of Health and Human Services. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016. Publication no. 2016-161. Available online: https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf?id=10.26616/NIOSHPUB2016161. Accessed 23 February 2022.
72. Department of Health and Human Services. National Institutes of Health. Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics 2017-2018. Available online: https://www.nichd.nih.gov/sites/default/files/inline-files/priority_list_063017_0.pdf. Accessed 23 February 2022.

73. United States Food and Drug Administration. Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944. 2020. Available online: https://www.fda.gov/media/143406/download. Accessed 23 February 2022.

74. World Health Organization. Model List of Essential Medicines in Children. Available online: https://www.who.int/selection_medicines/committees/expert/20/EMLc_2015_FINAL_amended_JUN2015.pdf. Accessed 23 February 2022.

75. Bhatt-Mehta, V.; Hammoud, H.; Amidon, G.L. A proposed pediatric biopharmaceutical classification system for medications for chronic diseases in children. Eur J Pharm Sci. 2020, 152, 105437. doi:10.1016/j.ejps.2020.105437

76. Dahan, A.; Miller, J.M. The solubility-permeability interplay and its implications in formulation design and development for poorly soluble drugs. AAPS J. 2012, 14, 244-251. doi:10.1208/s12248-012-9337-6

77. Ursan, I.; Chiu, L.; Pierce, A. Three-dimensional drug printing: A structured review. J Am Pharm Assoc. 2013, 53, 136-144. doi:10.1331/JAPhA.2013.12217
78. Beg, S.; Almalki, W.H.; Malik, A.; Farhan, M.; Aatif, M.; Rahman, Z.; Alruwaili, N.K.; Alrobaian, M.; Tarique, M.; Rahman, M. 3D printing for drug delivery and biomedical applications. *Drug Discov Today*. **2020**, 25, 1668-1681. doi:10.1016/j.drudis.2020.07.007

79. Wadher, K.; Trivedi, R.; Wankhede, N.; Kale, M.; Umekar, M. 3D printing in pharmaceuticals: An emerging technology full of challenges. *Ann Pharm Fr*. **2021**, 79, 107-118. doi:10.1016/j.pharma.2020.08.007

80. Changdeo, J.S.; Vinod, M.; Shankar, K.B.; Rajaram, C.A. Physicochemical characterization and solubility enhancement studies of allopurinol solid dispersions. *Brazilian J Pharm Sci*. **2011**, 47, 3. doi:10.1590/S1984-82502011000300009

81. Hecq, J.; Deleers, M.; Fanara, D.; Vranckx, H.; Amighi, K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. *Int J Pharm*. **2005**, 299, 167-177. doi:10.1016/j.ijpharm.2005.05.014

82. Jansook, P.; Ogawa, N.; Loftsson, T. Cyclodextrins: structure, physicochemical properties and pharmaceutical applications. *Int J Pharm*. **2018**, 535, 272-284. doi:10.1016/j.ijpharm.2017.11.018

83. Nehm, S.J.; Rodríguez-Spong, B.; Rodríguez-Hornedo, N. Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. *Cryst Growth Des*. **2006**, 6, 592-600. doi:10.1021/cg0503346

84. Nikghalb, L.A.; Singh, G.; Singh, G.; Kahkeshan, K.F. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. *J Appl Pharm Sci*. **2012**, 2, 170-175. doi:10.7324/JAPS.2012.21031
85. Bali, D.E.; Osman, M.A.; El Maghraby, G.M. Enhancement of Dissolution Rate and Intestinal Stability of Clopidogrel Hydrogen Sulfate. *Eur J Drug Metab Pharmacokinet*. **2016**, *41*, 807-818. doi:10.1007/s13318-015-0311-4

86. Palekar, S.; Nukala, P.K.; Mishra, S.M.; Kipping, T.; Patel, K. Application of 3D printing technology and quality by design approach for development of age-appropriate pediatric formulation of baclofen. *Int J Pharm*. **2019**, *556*, 106-116. doi:10.1016/j.ijpharm.2018.11.062

87. Bromberg, L. Polymeric micelles in oral chemotherapy. *J Control Release*. **2008**, *128*, 99-112. doi:10.1016/j.jconrel.2008.01.018

88. Hosny, K.M.; Alhakamy, N.A.; Almodhwahi, M.A.; Kurakula, M.; Almehmady, A.M.; Elgebaly, S.S. Self-Nanoemulsifying System Loaded with Sildenafil Citrate and Incorporated within Oral Lyophilized Flash Tablets: Preparation, Optimization, and In Vivo Evaluation. *Pharmaceutics*. **2020**, *12*, 1-22. doi:10.3390/pharmaceutics12111124

89. Ma, X.H.; Yao, Z.K.; Yang, Z.; Guo, H.; Xu, L.: Tang, C.Y.; Elimelech, M. Nanofoaming of Polyamide Desalination Membranes to Tune Permeability and Selectivity. *Environ. Sci. Technol. Lett*. **2018**, *5*, 123-130. doi:10.1021/acs.estlett.8b00016

90. Nakano, Y.; Tajima, M.; Sugiyama, E.; Sato, V.; Sato, H. Development of a Novel Nano-emulsion Formulation to Improve Intestinal Absorption of Cannabidiol. *Med Cannabis Cannabinoids*. **2019**, *2*, 35-42. doi:10.1159/000497361

91. Wiczling, P.; Liem, R.I.; Panepinto, J.A.; Garg, U.; Abdel-Rahman, S.M.; Kearns, G.L.; Neville, K.A. Population pharmacokinetics of hydroxyurea for children and adolescents with sickle cell disease. *J Clin Pharmacol*. **2014**, *54*, 1016-1022. doi:10.1002/jcph.303
92. Estepp, J.H.; Melloni, C.; Thornburg, C.D.; Wiczling, P.; Rogers, Z.; Rothman, J.A.; Green, N.S.; Liem, R.; Brandow, A.M.; Crary, S.E.; Howard, T.H.; Morris, M.; Lewandowski, A.; Garg, U.; Jusko, W.J.; Neville, K.A.; Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee. Pharmacokinetics and bioequivalence of a liquid formulation of hydroxyurea in children with sickle cell anemia. *J Clin Pharmacol*. **2016**, *56*, 298-306. doi:10.1002/jcph.598

93. Jang, D.H.; Hoffman, R.S.; Nelson, L.S. A case of near-fatal flecainide medication error in a neonate. *Clin Toxicol*. **2010**, *44*, 781-783. doi:10.1016/j.jemermed.2012.07.050

94. Santoveña, A.; Charola, I.; Suárez-González, J.; Teigell-Pérez, N.; García-van Nood, S.; Soriano, M.F.J. Development of a novel physico-chemically and microbiologically stable oral solution of flecainide for pediatrics. *Pharm Dev Technol*. **2018**, *23*, 978-985. doi:10.1080/10837450.2016.1238484

95. MacDonald, J.L.; Johnson, C.E.; Jacobson, P. Stability of isradipine in an extemporaneously compounded oral liquid. *Am J Hosp Pharm*. **1994**, *51*, 2409–2411. doi:10.1093/ajhp/51.19.2409

96. Masi, G.; Milone, A.; Veltri, S.; Iuliano, R.; Pfanner, C.; Pisano, S. Use of quetiapine in children and adolescents. *Paediatr Drugs*. **2015**, *17*, 125-140. doi:10.1007/s40272-015-0119-3

97. Papazisis, G.; Siafis, S. The Added Value of Liquid Antipsychotics: The Case of Quetiapine. *Curr Clin Pharmacol*. **2019**, *14*, 101-107. doi:10.2174/1574884713666181102145236

98. Agarwal, S.; HariKumar, S.L.; Negi, P.; Upadhyay, N.; Garg, R. Quetiapine Fumarate Loaded Nanostructured Lipid Carrier for Enhancing Oral Bioavailability: Design, Development and
99. Kraft, W.K.; Van den Anker, J.N. Pharmacologic Management of the Opioid Neonatal Abstinence Syndrome. *Pediatr Clin North Am.* 2012, 59, 1147-1165. doi:10.1016/j.pcl.2012.07.006

100. Disher, T.; Gullickson, C.; Singh, B.; Cameron, C.; Boulos, L.; Beaubien, L.; Campbell-Yeo, M. Pharmacological Treatments for Neonatal Abstinence Syndrome: A Systematic Review and Network Meta-analysis. *JAMA Pediatr.* 2019, 173, 234-243. doi:10.1001/jamapediatrics.2018.5044

101. Frazier, L.M.; Bobby, L.E.; Gawronski, K.M. Emerging therapies for the treatment of neonatal abstinence syndrome. *J Matern Neonatal Med.* 2020, 35, 987-995. doi:10.1080/14767058.2020.1733522

102. van Hoogdalem, M.W.; McPhail, B.T.; Hahn, D.; Wexelblatt, S.L.; Akinbi, H.T.; Vinks, A.A.; Mizuno, T. Pharmacotherapy of neonatal opioid withdrawal syndrome: a review of pharmacokinetics and pharmacodynamics. *Expert Opin Drug Metab Toxicol.* 2021, 17, 87-103. doi:10.1080/17425255.2021.1837112

103. Sutter, M.B.; Leeman, L.; His, A. Neonatal opioid withdrawal syndrome. *Obstet Gynecol Clin North Am.* 2014, 41, 317-334. doi:10.1016/j.ogc.2014.02.010

104. Esch, J.J.; Hellinger, A.; Friedman, K.G.; VanderPluym, C.J. Apixaban for treatment of intracardiac thrombosis in children with congenital heart disease. *Interact Cardiovasc Thorac Surg.* 2020, 30, 950-951. doi:10.1093/icvts/ivaa041
105. Caraballo, M.L.; Donmez, S.; Nathan, K.; Zhao, F. Compounded apixaban suspensions for enteral feeding tubes. *Hosp Pharm. 2017*, 52, 478-482. doi:10.1177/0018578717720507

106. Wheeler, J.; Francis, P.; Kim, J. Atenolol compounding and atrioventricular block: a case report. *J Investig Med. 2012*, 60, 172. doi:doi.org/10.231/JIM.0b013e318240c94

107. Tan, C.; Sehgal, K.; Sehgal, K.; Krishnappa, S.B.; Sehgal, A. Diuretic use in infants with developing or established chronic lung disease: A practice looking for evidence. *Paediatr Child Heal. 2020*, 56, 1189-1193. doi:10.1111/jpc.14877

108. Stoltenberg, I.; Breitkreutz, J. Orally disintegrating mini-tablets (ODMTs) - A novel solid oral dosage form for paediatric use. *Eur J Pharm Biopharm. 2011*, 78, 462-469. doi:10.1016/j.ejpb.2011.02.005

109. Uriel, M.; Gomez-Rincon, C.; Marro, D. Stability of regularly prescribed oral liquids formulated with SyrSpend® SF. *Pharmazie. 2018*, 73, 196-201. doi:10.1691/ph.2018.7008

110. Cirri, M.; Maestrini, L.; Maestrelli, F.; Mennini, N.; Mura, P.; Ghelardini, C.; Di Cesare Mannelli, L. Design, characterization and in vivo evaluation of nanostructured lipid carriers (NLC) as a new drug delivery system for hydrochlorothiazide oral administration in pediatric therapy. *Drug Deliv. 2018*, 25, 1910-1921. doi:10.1080/10717544.2018.1529209

111. Stumpf, J.L.; Leja, N.; Ciarkowski, S.L.; Schaeffler, K.L.; Salah, S. Updating formulations for compounded oral liquid medications in a university health system. *Am J Health Sys Pharm. 2018*, 75, 1394-1398. doi:10.2146/ajhp180085
112. United States Pharmacopeia. Compounded Monographs Failed Studies. 2020. Available online: https://www.usp.org/sites/default/files/usp/document/get-involved/partner/usp-compounded-preparation-monographs-failed-studies.pdf. Accessed 3 March 2022.

113. United States Pharmacopeia. USP Compounded Preparation Monograph Donation Program. Available online: https://www.usp.org/get-involved/partner/compounding-monographs. Accessed 23 February 2022.