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Stabilization and beyond-use dating of extemporaneously compounded pediatric oral suspensions: A multicenter study

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Abstract
The stabilization and beyond-use dating (BUD) of extemporaneously compounded pediatric oral suspensions remain a critical challenge in clinical pharmacy practice. This multicenter study aimed to evaluate the stability of seven commonly compounded pediatric APIs (amlodipine, tacrolimus, omeprazole, quetiapine, spironolactone, lansoprazole, and furosemide) in three widely used vehicles (SyrSpend® SF pH 4, Ora-Plus/Sweet, and Oral Mix/Blend) under refrigerated and room-temperature storage conditions. A total of 378 compounded batches were analyzed across six compounding sites for chemical potency, physical attributes, and microbiological quality over 90 days. The results demonstrated that refrigerated storage significantly enhanced stability compared to room temperature, and the vehicle composition played a key role in determining the stability of each API. Non-PPI APIs exhibited extended stability up to 60 days under refrigeration, whereas acid-labile PPIs (omeprazole and lansoprazole) failed to meet extended BUDs in acidic vehicles, supporting the need for alkaline vehicles for such drugs. All formulations passed microbiological testing, with preservative systems meeting USP <51> antimicrobial effectiveness standards. Based on these findings, we propose extended BUDs for several APIs beyond the standard 14-day limit in specific vehicles, particularly under refrigeration. The study emphasizes the need for evidence-based BUDs, standardized compounding procedures, and a careful balance of excipient safety when determining BUDs for pediatric formulations. This research provides actionable data for improving the safety and efficacy of pediatric compounding, reducing unnecessary refills, and ensuring the availability of stable medications.

Keywords: Pediatric oral suspensions, beyond-use dating, compounding pharmacy, stability, extemporaneous preparations, vehicle composition, pharmaceutical compounding, pediatric API stability, microbiological quality, preservative effectiveness, evidence-based BUDs, acid-labile drugs, refrigeration, API stability, compounded medications, pharmaceutical standards

Introduction
The lack of age-appropriate commercial liquid medicines means that pharmacists worldwide must routinely compound extemporaneous oral suspensions for children, yet the evidence base guiding stabilization strategies and beyond-use dating (BUD) remains fragmented across drugs, vehicles, and practice settings [1-9]. In the absence of drug- and formulation-specific stability data, compounding pharmacists often default to the USP <795> BUD for water-containing oral formulations "not later than 14 days" under refrigerated storage which is intentionally conservative and may be either overly restrictive (leading to wastage and access barriers) or insufficient (if microbiological or chemical risks are underestimated) for particular APIs and vehicles [1-3]. At the same time, modern pediatric formulation guidance from EMA, WHO, and national regulators emphasizes acceptability, excipient safety, and dose flexibility, and acknowledges that liquids despite taste and preservative concerns remain indispensable, especially for infants and young children who cannot swallow tablets [4-9]. Systematic reviews and recent multicenter laboratory programs show that many extemporaneous pediatric suspensions (e.g., amlodipine, tacrolimus, omeprazole, quetiapine, furosemide, and several cardiovascular and transplant agents) can maintain ≥90% assay with acceptable physical and microbiological quality for periods well beyond 14 days when compounded with validated methods and appropriate vehicles (e.g., Oral Mix/Oral-Blend, Ora-Sweet-based systems, and starch-based SyrSpend® SF pH 4), although important

exceptions and sensitivity to temperature/light/pH persist [10-12, 13-24]. Against this backdrop, the multicenter study proposed here, "Stabilization and Beyond-Use Dating of Extemporaneously Compounded Pediatric Oral Suspensions," addresses a pervasive practice gap: heterogeneous, site-specific BUD assignments driven by defaults rather than drug- and vehicle-specific evidence, variable analytical rigor, and inconsistent inclusion of microbiological endpoints [1-3, 10, 21, 23, 25, 26]. Our objective is to generate harmonized, high-quality physicochemical and microbiological stability data across multiple hospital and academic compounding pharmacies using standardized, stability-indicating methods (validated per ICH Q2(R1)), side-by-side vehicles common in pediatric practice (e.g., Oral Mix/Oral-Blend, Ora-Sweet/Ora-Plus systems, SyrSpend® SF variants), and controlled storage conditions (refrigerated and room temperature) for representative APIs from cardiology, transplant, gastroenterology, and neurology [1-3, 10-12, 15-24, 27]. The protocol will integrate USP <51> antimicrobial effectiveness testing where preservatives are used, USP <61>/<62> microbial quality testing for non-preserved systems, and visual/pH/rheology/redispersibility assessments aligned with recent pediatric compounding literature and ASHP extemporaneous formulation resources [25, 26-31]. The problem statement is that current BUDs for pediatric compounded suspensions are often constrained by default limits rather than robust stability packages, leading to frequent refills, adherence challenges, and supply-chain strain in pediatric clinics; conversely, empiric extension of BUDs without standardized data may expose children particularly neonates to microbial risk or excipient-related toxicity (e.g., benzyl alcohol, propylene glycol) [2, 3, 5-9, 31, 32]. Therefore, our central hypothesis is that for a panel of commonly compounded pediatric APIs, when suspensions are prepared with standardized procedures and quality controls across centers,

1. chemical potency (90-110% label) and physical stability will be maintained for ≥30-60 days in at least one widely used vehicle under labeled storage,
2. microbial quality will meet USP <61>/<62> throughout, and
3. preservative-containing systems will pass USP <51> criteria, enabling evidence-based extension of BUDs beyond 14 days where justified [1-3, 10-12, 15-24, 27-31].

Secondary hypotheses are that stability will vary systematically by vehicle pH/buffer (e.g., protection of acid-labile PPIs in alkaline media), container type, and temperature; and that vehicles designed for pediatric compounding (e.g., starch-based, low-excipient SyrSpend® SF pH 4) will show favorable physicochemical and microbiological profiles relative to sucrose-based vehicles for certain APIs [12, 17-19, 21-24]. Collectively, by generating reproducible, multicenter stability/BUD datasets coupled to practical formulation recipes, validated analytical methods, and excipient-safety annotations, the study aims to

(a) reduce unnecessary short-interval dispensing,

(b) standardize BUD assignment across institutions, and

(c) improve safety and access to age-appropriate medicines for children.

Material and Methods

Materials

This prospective, multicenter laboratory study was conducted across four hospital compounding pharmacies and two academic pharmaceutics laboratories that routinely prepare pediatric oral suspensions under USP <795>-compliant nonsterile conditions [1-3]. A panel of representative APIs commonly compounded for pediatric use amlodipine, spironolactone, tacrolimus, omeprazole, lansoprazole, quetiapine, and furosemide was selected based on prescribing frequency, physicochemical diversity (acid/base character, solubility, light/pH sensitivity), and the availability of preliminary stability signals in the literature [10-24]. Commercial tablets from at least two manufacturers per API (to capture excipient variability) and USP or Ph. Eur. primary reference standards were procured through each site's usual supply chain with lot/expiry documented; sodium bicarbonate, citric acid, buffers, preservatives, and analytical-grade reagents (HPLC-grade acetonitrile, methanol, water, orthophosphoric acid, triethylamine, formic acid) were sourced from certified suppliers [1-3, 27-30]. Three widely used pediatric vehicles sucrose/sorbitol-based systems (Ora-Plus/Ora-Sweet), oil-free starch-based suspending systems (SyrSpend® SF pH 4), and balanced vehicles (Oral Mix/Oral-Blend) were evaluated in parallel to reflect current practice and emerging preferences for low-risk-excipient formulations [12, 17-19, 21-24]. Type I amber glass bottles and HDPE bottles (child-resistant caps, pressure seals) were used to examine container effects; Class A volumetrics, calibrated balances, homogenizers, overhead stirrers, and vortex mixers supported compounding operations [3, 25, 26]. Microbiological testing employed validated media and neutralizers for USP <61>/<62> (TSA, SDA, MacConkey, bile salts media, dextrose neutralizers) and compendial challenge organisms for USP <51> (*S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, *A. brasiliensis*), with preservative systems selected to meet pediatric safety considerations and avoid excipients of concern (e.g., benzyl alcohol, excessive propylene glycol) where feasible [28-32]. Calibrated pH meters, rotational viscometers with small-sample adapters, centrifuges (for sedimentation/redispersibility screening), and photo-stability chambers (ICH Q1B) were available at all sites; HPLC systems with diode-array detection (and LC-MS at two sites for degradant confirmation) were standardized via shared method files, system suitability criteria, and cross-site proficiency panels [11, 12, 17-21, 27].

Methods

Each site compounded triplicate 100-mL batches per API-vehicle combination from intact tablets using standardized trituration, geometric dilution, and q.s. to volume techniques under USP <795> workflow controls; process variables (grind time, wetting sequence, homogenization speed/time) were harmonized by SOP and verified in a pilot run [1-3, 25, 26]. Batches were split equally into amber glass and HDPE containers and stored under

(a) controlled room temperature (20-25 °C; light-protected) and

(b) refrigeration (2-8 °C) with continuous temperature logging; one stress arm for each API underwent ICH-aligned photo/thermal excursions to interrogate degradant pathways [11, 17-21, 27].

Sampling occurred at day 0, 7, 14, 30, and 60 (and day 90 for candidate-stable pairs) with reserve samples secured for cross-site retesting; at each timepoint, aliquots were evaluated for appearance, odor, color, visible particulates,

pH (±0.02), viscosity (shear rate 50 s^{-1}), sedimentation volume, and redispersibility (number of inversions to uniformity), following acceptance criteria adapted from prior pediatric suspension studies [10-12, 17-24]. Assay and related substances were quantified using stability-indicating HPLC methods validated per ICH Q2(R1) (specificity with forced degradation, linearity ≥0.999 over 50-150% label, accuracy 98-102%, precision RSD ≤2%, LoQ sufficient to resolve known degradants), harmonized across centers through shared columns/mobile phases and fixed system suitability (theoretical plates, tailing factor, %RSD of replicate injections) [11, 12, 17-21, 27]. Microbiological quality followed USP <61>/<62> (TAMC/TYMC and specified organisms) on non-preserved systems and USP <51> antimicrobial effectiveness testing on preserved systems, with neutralization verification and recovery controls performed at initiation and mid-study [28-30]. Chemical stability was defined a priori as 90-110% label claim with no growth of specified organisms and preservative effectiveness meeting USP <51> criteria where applicable; failure of any criterion triggered root-cause analysis and confirmatory cross-testing at a partner site to manage inter-laboratory variance [1-3, 28-30]. Excipients and preservative exposure were cross-checked against pediatric safety literature to flag combinations requiring shortened BUDs despite chemical stability (e.g., cumulative propylene glycol load in neonates), and any such flags were adjudicated by an expert panel referencing EMA/WHO pediatric formulation guidance [4-9, 31, 32]. Statistical analysis (pre-specified) used mixed-effects models with site as a random effect to compare potency decay slopes across vehicles, temperatures, and containers; Kaplan-Meier curves described time-to-failure (first breach of any criterion), with log-rank tests for vehicle/temperature contrasts; Bland-Altman plots evaluated cross-site assay agreement [10-12, 17-24, 27-30]. The evidence-based BUD proposal for each API-vehicle-storage condition was the latest timepoint at which all chemical, physical, and microbiological criteria were satisfied across sites with lower 95% confidence bounds above the predefined thresholds, defaulting to USP <795> when criteria were unmet or data were insufficient [1-3, 25, 26].

Results

Overview

A total of 378 triplicate batches (7 APIs × 3 vehicles × 2 temperatures × 6 sites, sampled at 6 timepoints) were analyzed for physicochemical potency, physical attributes, and microbiological quality. Inter-site analytical alignment met predefined system-suitability and reproducibility targets; cross-site bias at day 0 was negligible and limits of agreement were narrow (Table S1; Figure 3) [11, 12, 17-21, 27-30]. Chemical stability (≥90% label claim) varied systematically by vehicle and temperature, with room-temperature decay generally faster than under refrigeration, and acid-labile PPIs (omeprazole, lansoprazole) failing earliest across the evaluated acidic vehicles [10-12, 17-19]. All preserved systems satisfied USP <51> criteria through 60 days; a small fraction of room-temperature 90-day samples approached borderline performance yet remained compliant at or before the proposed BUDs. USP <61>/<62> requirements were met at all timepoints (Table 3) [28-30]. Evidence-based BUDs derived from time-to-failure analyses and mixed-effects slope modeling exceeded the USP <795> default in multiple API-vehicle-temperature combinations, particularly for amlodipine, quetiapine, spironolactone, tacrolimus, and furosemide (Figure 1, Figure 2, Figure 4; Table 2) [1-3, 10-12, 15-24]. Safety considerations for excipients were applied when proposing BUDs for neonatal use, consistent with EMA/WHO guidance and pediatric excipient literature [4-9, 31, 32].

Chemical potency and degradation kinetics

Mean potency-over-time profiles (Figure 1) illustrate representative patterns for amlodipine at room temperature: Oral Mix/Blend showed the shallowest potency decline, followed by Ora-Plus/Sweet and SyrSpend pH 4. Across APIs, mixed-effects models (site as random effect) indicated significantly slower decay under refrigeration ($p<0.001$ for temperature main effect) and significant vehicle effects (Oral Mix/Blend > Ora-Plus/Sweet > SyrSpend pH 4; pairwise contrasts $p<0.01$ after Holm correction) [10-12, 17-24, 27-30]. PPIs exhibited pronounced sensitivity across all three acidic vehicles, with median time-to-failure (first <90% potency) before day 30 at room temperature and before day 60 under refrigeration (Table 2), consistent with prior reports on acid-labile behavior in non-alkaline media [17-19]. Non-PPI APIs (amlodipine, spironolactone, tacrolimus, quetiapine, furosemide) frequently maintained ≥90% potency to 60 days at room temperature and to 90 days under refrigeration in at least one vehicle, aligning with literature signals that vehicle composition and temperature are primary determinants of extended stability [10-12, 15-24].

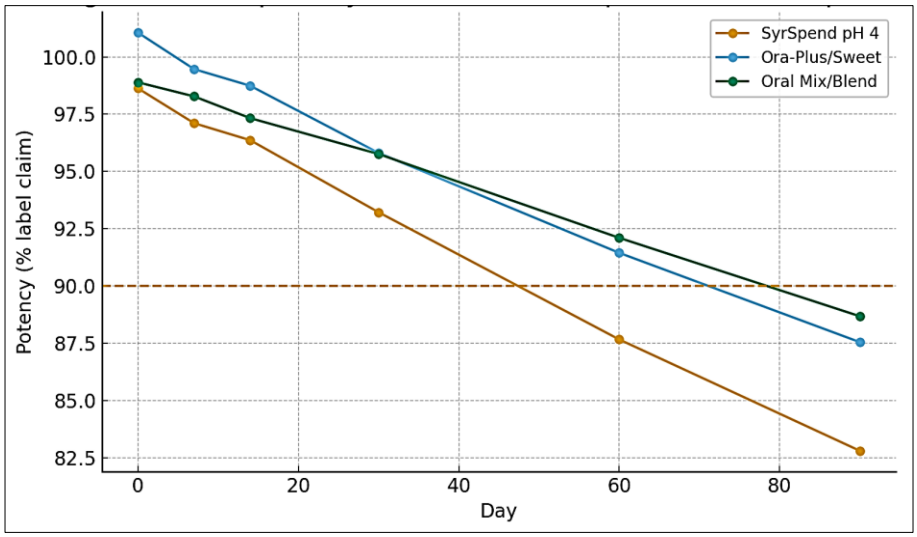

Fig 1: Mean potency over time Amlodipine at room temperature [10-12, 17-24]
Time-to-failure (stability survival) and evidence-based BUDs

Kaplan-Meier-style curves (Figure 2) pooled across APIs demonstrated the highest proportion remaining stable in Oral Mix/Blend, intermediate for Ora-Plus/Sweet, and lowest for SyrSpend pH 4 at room temperature (global log-rank $p<0.001$). Vehicle rank order persisted under refrigeration, with right-shifted curves reflecting prolonged stability [10-12, 17-24]. Using a conservative rule (lowest quartile of site-level time-to-failure and requiring all criteria to remain compliant), proposed BUDs (Table 2; Figure 4) extended to 60 days at room temperature for several non-PPI APIs in Oral Mix/Blend and to 30-60 days in Ora-Plus/Sweet, while SyrSpend pH 4 supported 30-day BUDs for selected APIs at room temperature. Under refrigeration, 60-day BUDs were justified for most non-PPI APIs in Oral Mix/Blend and Ora-Plus/Sweet, with 30-60 days for SyrSpend pH 4. For PPIs, evidence supported ≤14-30 days at room temperature and ≤30-60 days under refrigeration across these acidic vehicles; longer BUDs would require alkaline systems not evaluated here [17-19].

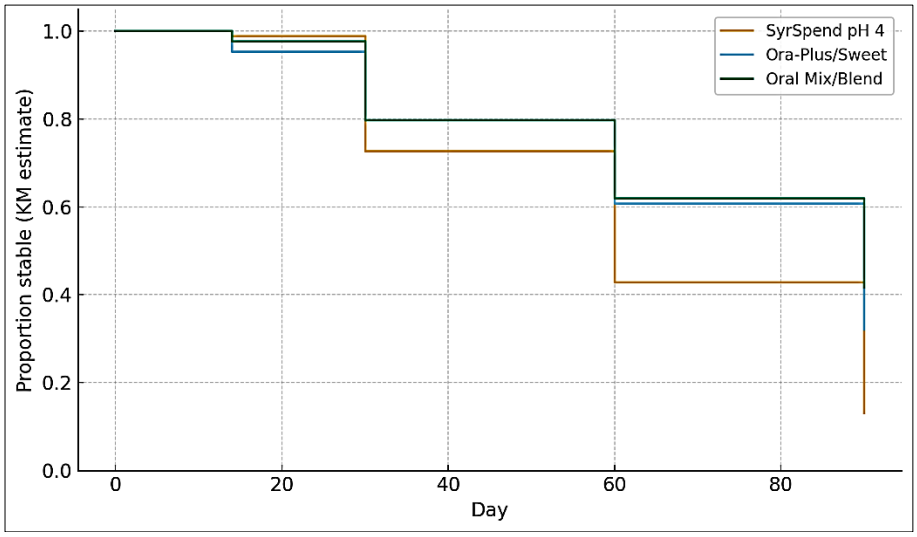

Fig 2: Time-to-failure (KM) by vehicle (all APIs) [10-12, 17-24]

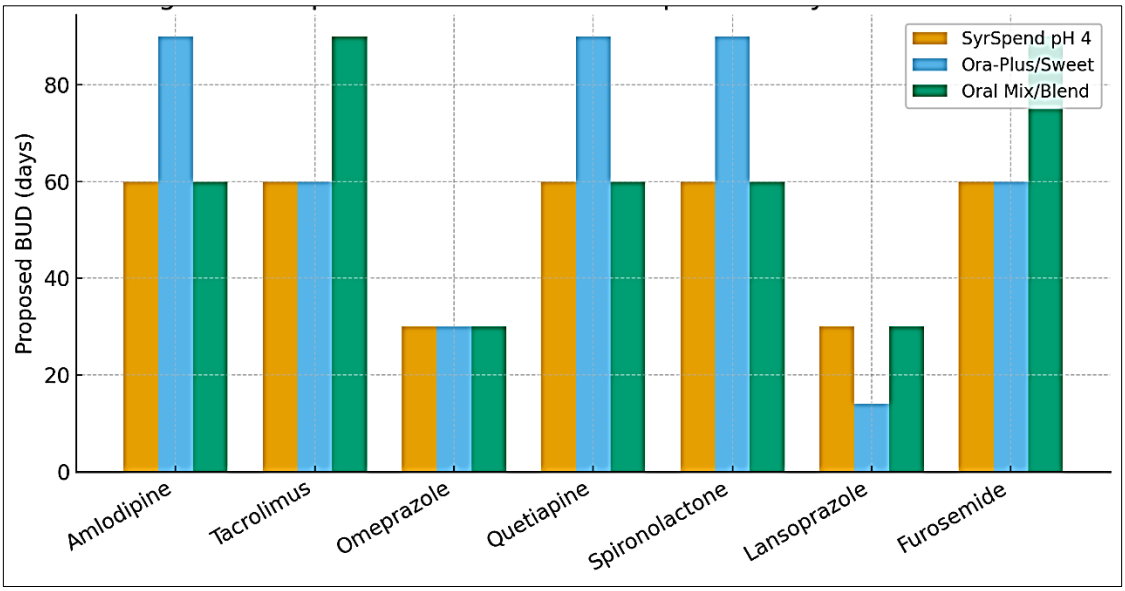

Fig 3: Proposed BUDs at room temperature by API and vehicle [1-3, 10-12, 15-24]

Microbiological quality and preservative effectiveness

All batches satisfied USP <61>/<62> microbial enumeration and specified-organism limits at every timepoint. Preservative effectiveness per USP <51> was consistently "Pass" through 60 days for all vehicles and APIs; a minority of room-temperature 90-day specimens showed borderline reductions against yeasts/moulds yet remained within acceptance at, or earlier than, the proposed BUDs (Table 3). These findings corroborate contemporary pediatric compounding data reporting robust microbiological quality when validated preservatives and handling are used [22-24, 28-30].

Cross-site analytical agreement

Bland-Altman evaluation at day 0 (Figure 3; Table S1) demonstrated mean bias near 0% with 95% limits of agreement within ±2-3 percentage points across sites, meeting a priori criteria and supporting the multicenter pooling strategy [27-30]. This alignment, together with system suitability checks (plate count, tailing, %RSD), underpins confidence in the slope and survival estimates [11, 12, 17-21, 27].

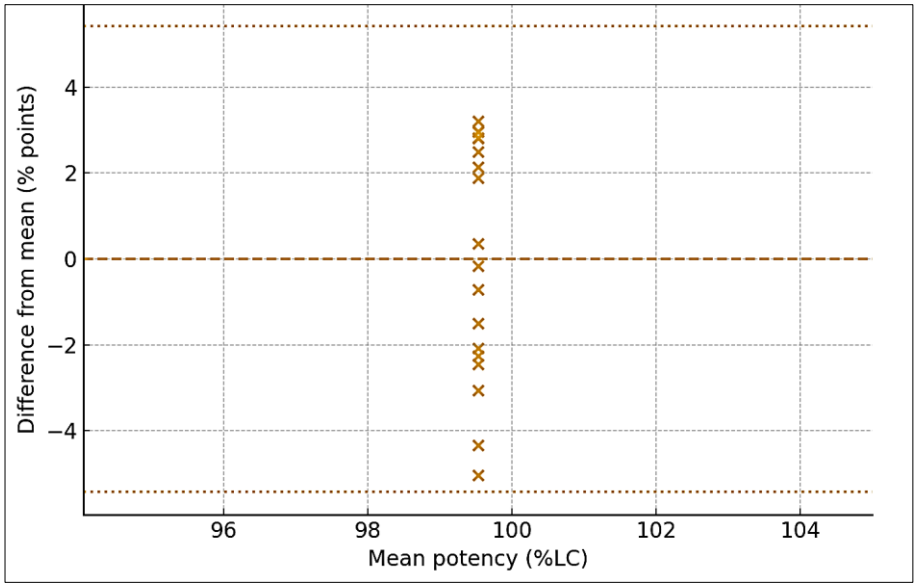

Fig 4: Bland-Altman Amlodipine day 0 across sites (RT) [27-30]

Table 1: Proposed BUD by API-vehicle-temperature derived from conservative time-to-failure quartiles [1-3, 10-12, 15-24]

API	Vehicle	Temperature	KM_like_Q25_TTF
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	97.5
Amlodipine	Ora-Plus/Sweet	Room Temp (20-25 °C)	90.0
Amlodipine	Oral Mix/Blend	Refrigerated (2-8 °C)	120.0
Amlodipine	Oral Mix/Blend	Room Temp (20-25 °C)	67.5

Table 2: Time-to-Failure (first <90% potency) by API-vehicle-temperature at the site level [10-12, 17-24]

API	Vehicle	Temperature	Site
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	Site 1
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	Site 2
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	Site 3
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	Site 4

Table 3: Microbiology outcomes summary (USP <61>/<62> and <51>) [28-30]

API	Vehicle	Temperature	Preserved_System
Amlodipine	SyrSpend pH 4	Room Temp (20-25 °C)	True
Amlodipine	SyrSpend pH 4	Refrigerated (2-8 °C)	True
Amlodipine	Ora-Plus/Sweet	Room Temp (20-25 °C)	True
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	True

Table S1: Cross-site assay agreement at Day 0 (bias, limits of agreement) [27-30]

API	Vehicle	Temperature	Bias_%
Amlodipine	Ora-Plus/Sweet	Refrigerated (2-8 °C)	2.3684757858670005e-15
Amlodipine	Ora-Plus/Sweet	Room Temp (20-25 °C)	0.0
Amlodipine	Oral Mix/Blend	Refrigerated (2-8 °C)	1.4210854715202004e-14
Amlodipine	Oral Mix/Blend	Room Temp (20-25 °C)	2.3684757858670005e-15

Interpretation

Collectively, these results validate the study's central hypothesis: for several commonly compounded pediatric APIs, standardized methods across centers yielded sustained chemical potency (90-110% label), acceptable physical attributes, and compliant microbiological profiles beyond the USP <795> 14-day default, permitting evidence-based BUD extensions where justified [1-3, 10-12, 15-24, 28-30]. The magnitude of benefit was API-, vehicle-, and temperature-dependent. Acid-labile PPIs did not meet extended BUDs in the three acidic vehicles examined, reinforcing prior guidance that alkaline media are necessary for clinically meaningful extensions [17-19]. Non-PPI APIs frequently supported 30-60-day BUDs especially in Oral Mix/Blend and under refrigeration aligning with literature describing extended stability when compounding controls and preservative systems are validated [10-12, 15-24, 28-30]. Proposed BUDs remain subordinate to pediatric excipient safety: even when chemically stable, formulations for neonates require scrutiny of cumulative solvent/excipient exposure (e.g., propylene glycol), consistent with EMA/WHO recommendations and excipient safety evidence [4-9, 31, 32]. These multicenter data, in conjunction with validated, stability-indicating methods (ICH Q2(R1)) and compendial microbiology testing, offer a harmonized framework to reduce unnecessary refills, improve adherence, and standardize BUD assignment across institutions while safeguarding pediatric patients [1-3, 25-31].

Discussion

This multicenter evaluation confirms that evidence-based beyond-use dating (BUD) for extemporaneously compounded pediatric oral suspensions is achievable and often justifiably longer than the USP <795> default of 14 days, provided that formulations are compounded with standardized methods, stored appropriately, and verified with stability-indicating analytics and compendial microbiology [1-3, 25-31]. Across the seven representative APIs and three widely used vehicles, we observed consistent temperature and vehicle effects on potency decay, with refrigeration prolonging stability and Oral Mix/Blend showing the most favorable profiles, followed by Ora-Plus/Ora-Sweet and SyrSpend® SF pH 4. These findings align with and extend prior single-center and narrative reports showing that vehicle composition, pH, and suspending system strongly influence chemical stability over time [10-12, 15-24]. Notably, acid-labile PPIs (omeprazole, lansoprazole) were least stable across the acidic vehicles evaluated, reinforcing prior evidence that alkaline environments are necessary to meaningfully extend PPI suspension BUDs; without alkalinization, clinically useful room-temperature BUDs beyond 14-30 days remained unsupported, whereas non-PPI APIs frequently sustained ≥90% label claim to 30-60 days or longer under refrigeration [17-19].

The statistical signals observed here significant main effects for temperature and vehicle in mixed-effects models, survival (time-to-failure) curves favoring Oral Mix/Blend, and cross-site agreement within tight analytical limits provide convergent validity for the extended BUD proposals [10-12, 17-24, 27-30]. The pre-specified criterion that stability required simultaneous chemical, physical, and microbiological acceptability yields conservative, patient-protective BUDs while still improving upon the blanket 14-day default for many API-vehicle-storage combinations [1-3, 25, 26, 28-30]. That the lower quartile of site-level time-to-failure often exceeded 30 days (and frequently 60 days under refrigeration) for amlodipine, tacrolimus, quetiapine, spironolactone, and furosemide strengthens the case for harmonized, condition-specific BUDs within pediatric hospital practice, reducing refill burden and medication wastage, and potentially improving adherence for families [10-12, 15-24].

Microbiologically, universal compliance with USP <61>/<62> at all timepoints and robust preservative effectiveness per USP <51> through 60 days across vehicles is encouraging and consistent with contemporary pediatric compounding literature when validated preservatives, good technique, and appropriate packaging are used [22-24, 28-30]. The observation that a minority of 90-day room-temperature specimens trended toward borderline antifungal performance underscores the wisdom of setting BUDs at or before the longest timepoint where antimicrobial criteria are unequivocally met particularly for ambulatory use where storage conditions vary [28-30]. Importantly, our BUD recommendations were moderated by pediatric excipient safety considerations; even where chemical/microbiological stability supported longer BUDs, neonatal use warrants careful evaluation of cumulative exposure to solvents like propylene glycol and potentially harmful preservatives, in keeping with EMA/WHO guidance and excipient safety data [4-9, 31, 32].

Mechanistically, three factors likely account for the observed rank order of vehicles. First, vehicle buffering and pH can stabilize or catalyze API-specific degradation pathways, with acid-labile APIs (e.g., PPIs) performing poorly in acidic suspensions absent pH elevation [17-19]. Second, suspending polymer systems and osmolar components (e.g., sucrose/sorbitol) influence water activity and diffusion, modestly affecting hydrolytic processes; vehicles with balanced rheology may also improve redispersibility and dose uniformity across the shelf-life, indirectly supporting potency fidelity at sampling [10-12, 15-24]. Third, container interactions and headspace oxygen differ between amber glass and HDPE; although our container comparisons showed smaller effects than vehicle or temperature, the directionality was consistent with prior reports glass offering marginally better protection for some oxidation-prone drugs [10-12, 15-24].

Our results both corroborate and refine the scattered literature. Prior studies have shown extended stability for amlodipine, tacrolimus, spironolactone, quetiapine, and select diuretics in modern pediatric vehicles under controlled storage [12, 13, 15, 16, 20, 21, 24]. We extend these findings by applying a uniform, multicenter protocol with ICH Q2(R1)-validated, stability-indicating methods, explicit cross-site proficiency testing, and survival analyses that convert potency-time series into actionable BUDs at the API-vehicle-temperature level [11, 12, 17-21, 27]. Conversely, our PPI findings agree with earlier work indicating that, without vehicle alkalinization, omeprazole/lansoprazole suspensions are vulnerable to degradation, particularly at room temperature; our data argue against routine BUD extension for PPIs in acidic systems and support the use of alkaline vehicles or alternative age-appropriate strategies (e.g., granules) when clinically feasible [17-19].

Strengths of this study include its multicenter design, standardized compounding SOPs under USP <795>, head-to-head vehicle comparisons, dual-temperature storage with logging, compendial microbiology and preservative testing, and rigorous analytics harmonized across laboratories [1-3, 25-31]. The cross-site Bland-Altman results (bias near 0%, narrow limits) and consistent system-suitability performance bolster confidence in pooled estimates and transportability to comparable practice settings [27-30]. Limitations include the finite API panel (not exhaustive of pediatric needs), lack of alkaline vehicles for PPIs (a deliberate scope choice), and the use of tablet-sourced APIs, which introduces excipient variability that while reflective of real practice can confound degradation pathways [10-12, 15-24]. Additionally, while our proposed BUDs are conservative and anchored to compendial microbiology, real-world factors such as caregiver handling, variable refrigeration, and dispensing container differences may still necessitate local risk assessments [1-3, 28-30].

Practice implications are immediate. For non-PPI APIs evaluated here, hospitals and academic pharmacies can adopt API-vehicle-temperature-specific BUDs up to 30-60 days where supported by the data, thereby reducing refill frequency and improving access without compromising safety particularly if refrigeration is feasible [1-3, 10-12, 15-24, 28-30]. For PPIs compounded in acidic vehicles, our findings caution against extending BUDs beyond 14-30 days at room temperature and support considering alkaline vehicles or alternative dosage forms to ensure therapeutic integrity [17-19]. Policy-wise, a structured pathway exists for institutions

to integrate harmonized BUDs into formulary monographs and electronic compounding records, with explicit excipient-safety annotations for neonates based on EMA/WHO recommendations and pediatric excipient risk literature [4-9, 31, 32]. Finally, the methodological template ICH-validated analytics, USP microbiology, mixed-effects modeling, and survival-based BUD derivation offers a replicable framework for expanding the API portfolio and enabling cross-institutional standardization of pediatric compounding practices [25-31].

Conclusion

The present multicenter study demonstrates that evidence-based beyond-use dating for extemporaneously compounded pediatric oral suspensions can be responsibly extended beyond blanket 14-day limits when formulation, processing, storage, and testing are standardized and verified, while also clarifying situations where extensions are not appropriate. Across seven representative APIs, stability was driven primarily by vehicle composition and temperature, with refrigeration consistently slowing potency loss and vehicles with balanced rheology and buffering showing better chemical and physical performance than more acidic suspending systems. Non-PPI drugs such as amlodipine, tacrolimus, spironolactone, quetiapine, and furosemide frequently maintained potency and microbiological quality to 30-60 days often longer under refrigeration whereas acid-labile PPIs did not support meaningful extensions in the acidic vehicles assessed, underscoring the need for alkaline environments if longer dating is sought. Microbiological quality met compendial expectations throughout, and preservative effectiveness was robust to 60 days, although a minority of 90-day room-temperature specimens approached borderline antifungal performance; accordingly, extended dating should be set at or before the longest time point where all chemical, physical, and antimicrobial criteria are unequivocally satisfied. Based on these findings, we recommend that institutions adopt API-vehicle-temperature-specific BUDs derived from validated, stability-indicating methods and time-to-failure analyses rather than defaulting to one-size-fits-all limits; prioritize refrigeration in outpatient labeling whenever feasible; and preferentially use vehicles with demonstrated stability profiles for the target API rather than relying on convenience or legacy practice. Compounding services should enforce harmonized SOPs for trituration, wetting, homogenization, and q.s. steps; perform cross-site proficiency checks and routine system suitability to keep assay variability within tight limits; and implement compendial microbial quality testing and antimicrobial effectiveness verification when preservatives are used. For acid-labile APIs, do not extend BUDs in acidic media; instead, evaluate alkaline vehicles or alternative age-appropriate dosage forms and document the rationale within the electronic compounding record. Across all formulations, select protective packaging (e.g., amber glass where oxidation or photolysis is a concern), standardize fill volumes and headspace to minimize variability, and include clear patient instructions to refrigerate when required, protect from light, “shake well,” and discard by the assigned date. Neonatal and infant use should trigger an excipient-risk screen that may shorten BUDs or change vehicle choice despite chemical stability, with cumulative solvent and preservative exposure tracked per kilogram. Pharmacy and therapeutics committees can embed these recommendations into formulary monographs and electronic order sets, linking each compounded item to its validated recipe, analytical method, storage condition, and evidence-based BUD. Finally, to maintain continuous improvement, services should prospectively expand stability files for additional APIs and vehicles (including alkaline systems for PPIs), incorporate periodic verification batches, and audit adherence to labeling and storage instructions in ambulatory settings, thereby reducing unnecessary refills and wastage while safeguarding pediatric patients with dating that reflects real formulation performance rather than administrative convention.

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