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**Review Article**

# Pediatric Dosage Form Optimization a Review of Physiological, Formulation, Biopharmaceutical, Quality, Acceptability and Regulatory Considerations

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## ABSTRACT

Pediatric medicines must account for age-related changes in physiology, pharmacokinetics, swallowing ability, taste perception and dose requirements. Conventional oral liquids are widely used because they are easy to administer and allow dose adjustment; however, they may present challenges related to palatability, administration volume, excipient exposure, microbial or chemical stability and dosing accuracy. This review examines the factors involved in optimizing pediatric dosage forms, including developmental physiology, dose flexibility, excipient safety, taste masking, formulation and process optimization, drug release, dissolution, disintegration, content uniformity, stability, acceptability and regulatory considerations. Conventional liquids, suspensions, tablets and capsules are discussed alongside newer approaches such as mini-tablets, orodispersible tablets and films, chewable formulations, multiparticulates and three-dimensional printing. The literature covered in this review indicates that appropriately designed solid and multiparticulate dosage forms may be suitable for selected infants and young children; therefore, liquid formulations should not be considered the only option. Selection of a dosage form should be supported by evidence of dose accuracy, product quality, drug-release performance, stability and acceptability to children and caregivers. Further work is needed to strengthen pediatric-relevant testing, evaluate long-term excipient exposure and support reliable, scalable manufacturing.

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## INTRODUCTION

### 1.1 Burden of disease and need for pediatric medicines

Treating children requires more than just giving them smaller doses of adult medication. Because pediatric patients range from newborns to teenagers, their medicines must be specifically designed so they can take them safely, accurately, and comfortably.

Right now, caregivers often have to crush tablets, open capsules, or mix liquids into food to get children to take their medicine. This guesswork can ruin the drug's stability, make it taste terrible, or result in the wrong dose. To fix this, pharmaceutical developers need to consider the daily realities of both the child and the caregiver right from the start factoring in things like how often a dose is needed, how a child's requirements will change as they grow, and whether proper measuring tools are available.

Fortunately, the industry is already moving in this direction. A review of pediatric medicines launched between 2007 and 2018 shows a clear shift away from basic liquids and toward ready-to-use, child-friendly options like mini-tablets, dissolvable films, and improved packaging that make dosing much easier and safer. (1)

### 1.2 Why children need specialized dosage forms

Because children are constantly growing, standard adult medications don't work for them, forcing caregivers to routinely modify or compound drugs. Creating specialized, easy-to-take oral medicines for kids which would also help elderly patients who struggle with swallowing or motor skills is essential for ensuring they actually take their treatments. However, designing these age-appropriate formulas is a complex challenge because a child's body processes drugs differently at every stage of development, requiring flexible dosing while still guaranteeing safety and effectiveness. (18, 19, 24)

### 1.3 Definition and scope of pediatric dosage form optimization

Optimizing pediatric medicines means tailoring both the drug and how it is made so children of all ages can take it safely. The goal is to create an accurate, flexible, and palatable treatment that is easy to swallow, uses safe ingredients, and stays reliable throughout its shelf life.

Building these treatments goes far beyond simply picking between a liquid or a pill. Developers have to evaluate the active ingredient's behavior, refine production methods, and supply user-friendly packaging and measuring tools that work well in real-world settings like homes and hospitals.

To succeed, pharmaceutical teams must look at daily practicalities through the eyes of both the child and the caregiver right from the start. Thinking early about dosing schedules, whether a dose can be taken with food, and how a child's needs will shift as they grow ensures continuous care and stops parents from having to improvise with adult medications.

Modern pediatric design is rapidly evolving to meet these demands. Alongside traditional syrups and capsules, newer options like mini-tablets, chewables, dissolvable films, and even 3D-printed therapies are gaining ground. By combining better taste-masking techniques with strict safety standards and smarter manufacturing, the industry is paving the way for much more kid-friendly healthcare.

## 2. PHYSIOLOGICAL AND DEVELOPMENTAL CONSIDERATIONS

### 2.1 Developmental physiology relevant to oral drug delivery

Because a child's digestive system, liver, and kidneys mature gradually from infancy through adolescence, their bodies absorb, process, and clear medicines differently than adults do. Simply scaling down an adult dose based on weight isn't enough, as shifts in stomach acidity, digestive movement, and enzyme activity directly alter how a drug dissolves and works. (5, 20)

Even among kids of the exact same age, individual factors like diet, health status, and how much water they drink can change a medication's performance. Rather than designing formulas around textbook averages, pharmaceutical teams need to account for these real-world variables especially for sensitive drugs where tiny shifts in absorption matter.

Connecting these biological differences to potential product hurdles early on helps ensure a treatment works reliably outside of a controlled clinical trial. Ultimately, advancing children's healthcare requires moving away from downsized adult models and building specialized lab and computer testing tools tailored to pediatric biology.[5]

### 2.2 Pharmacokinetic considerations by age group

As children grow from newborns into older kids, their livers, kidneys, and overall body makeup constantly evolve drastically changing how they absorb, distribute, and clear drugs. Because rigid adult pills can't keep up with these shifts, pediatric treatments rely on flexible options like liquids, dispersible tablets, and mini-tablets that allow for tiny, adaptable doses. (20, 21)

Beyond just age, kids in the exact same peer group can react differently to a treatment depending on their diet, health, or even how much water they drink with a dose. Instead of building drugs around textbook averages, pharmaceutical teams must anticipate real-world variables like fluctuating stomach acidity early in the design process. Stress-testing these formulas against individual differences ensures that children's medications stay safe and reliable once they leave controlled clinical trials and enter everyday family life.

### 2.3 Swallowing ability and oral motor development

Because a child’s ability to swallow develops gradually, choosing the right oral medication means looking closely at physical details like pill size, shape, and texture alongside the child's coordination. While liquid syrups have long been the default for young kids, recent research shows that carefully crafted mini-tablets work surprisingly well even for infants and toddlers. (30, 31)

Of course, kids of the exact same age vary widely in their willingness to cooperate, overall health, and daily feeding routines. To ensure treatments work reliably outside a clinic, developers have to anticipate real-world hurdles like how limited water intake might slow a tablet from dissolving, or how stomach acidity affects specialized coatings.

Clinical studies back up the potential of these smaller solids. Trials show that infants, toddlers, and preschoolers can successfully take 2-mm mini-tablets alongside traditional liquids and fine granules, though a few young patients tried chewing the tablets instead of swallowing them whole (6, 7). Additional research with babies aged 6 to 23 months confirms that many can handle mini-tablets without issue (8). Ultimately, age alone shouldn't disqualify a child from solid medicines; suitability should be decided through real-world testing of what kids can safely and comfortably take. (32, 33, 34)

### 2.4 Age-related differences in taste perception and acceptability

Palatability strongly affects whether children take their medicine. Bitter, sour, metallic, or unpleasant-smelling medicines and those with a gritty texture may lead children to refuse a dose or take only part of it. Sweetening can help, but developers also need to consider dental health, metabolic effects, and the safety of any added ingredients. (27, 28)

A medicine is acceptable only if a child can and will take it, and caregivers can give it correctly. Children of the same age may differ in health, nutrition, feeding habits, and willingness to cooperate, so formulations should work in everyday situations, not just under ideal conditions.

A child’s physiology can also affect how a medicine performs. For instance, stomach acidity may influence pH-sensitive coatings, and drinking little water may affect how a tablet breaks down. Developers should account for these differences during formulation, clinical testing, and after a medicine reaches the market.

## 3. CHALLENGES IN PEDIATRIC DOSAGE FORM DEVELOPMENT

### 3.1 Dose flexibility and accurate dosing

Pediatric doses often need to be tailored to a child’s weight, body surface area, age, and organ development. For medicines where the safe and effective dose range is narrow, even a small dosing difference can matter. Liquids allow flexible dosing, but mistakes can happen when caregivers measure the volume or choose the right concentration. Multiparticulates and mini-tablets offer another option: caregivers can adjust the dose by changing the number of units. Scored tablets may allow

some doses to be split, provided the medicine stays evenly distributed and stable after it is divided or prepared. (25, 26)

Developers can reduce errors by looking at the full process caregivers follow: opening the package, measuring or counting the medicine, mixing it with food or water if needed, giving it to the child, checking that the full dose was taken, and storing what remains. This can reveal where clearer instructions, better packaging, or a different dosage form might help. (29)

The right balance between dose flexibility and ease of use depends on the treatment. Families managing a long-term condition may be able to use a more detailed device or multi-unit dose if it improves disease control. For short-term illnesses, a simpler process with fewer steps is usually easier to manage. Testing instructions and products with caregivers can show whether they work in real situations, especially when doses must be given repeatedly or under pressure.

Some variation in medicine use is unavoidable, but good design can prevent many errors. Suitable dose strengths, clearly marked devices, straightforward instructions, and stable formulations can help children receive a dose closer to the one prescribed.

### 3.2 Palatability and taste masking

Unpleasant taste is a common reason children refuse medicine, spit it out, or take only part of a dose. This can make treatment less effective, especially when medicine needs to be taken regularly over time. (28, 29)

Formulators can improve taste in several ways. Coatings and microencapsulation create a barrier between the drug and the taste buds. Complexation binds some of the drug so less is available to create an unpleasant taste. Other approaches include choosing a less bitter form of the drug, adjusting the formulation's pH, or adding sweeteners, flavors, or other sensory ingredients. (17, 41, 42, 44)

The challenge is to improve taste without interfering with how the medicine works. It should release little drug in the mouth, then dissolve and be absorbed at the intended rate after swallowing. If the taste-masking system slows release too much, it could affect absorption. A good formulation therefore needs to balance palatability, accurate dosing, and reliable drug release.

### 3.3 Administration challenges

Pediatric medicines are given differently in hospitals and at home. Healthcare professionals can use standard equipment and monitor doses closely, while at home caregivers are usually responsible for preparing and giving each dose. Products should therefore be straightforward and safe to use in everyday settings.

Liquid medicines may come with oral syringes, cups, spoons, or droppers. These devices need clear markings, especially for small doses. Household teaspoons and tablespoons are unreliable because their volumes vary. Mistakes can also happen if a caregiver uses the wrong concentration, measures incorrectly, forgets to shake a suspension, or adds the wrong amount of water when preparing a powder.

Suspensions need to be shaken well before each dose because medicine can settle during storage. Clear labels, suitable measuring devices, and simple instructions can help caregivers give the right amount.

Some children have swallowing, neurological, or feeding difficulties and may receive medicine through a feeding tube. In these cases, the formulation must pass through the tube without blocking it, remain stable during preparation, and be compatible with the tube materials. Clear instructions should help caregivers deliver the full prescribed dose safely.

### 3.4 Excipients and safety concerns

Excipients are ingredients added to medicines to support taste, appearance, stability, manufacturing, or drug release. An ingredient that is acceptable for adults may not be suitable for children. Its safety depends on factors such as the child's age and weight, the amount and route of administration, how often the medicine is used, and total exposure over time. (45, 46)

Newborns and infants may have immature liver and kidney function, which can make it harder to process and remove some excipients. Repeated doses or the same ingredient in several medicines may increase exposure. Safety assessments should therefore consider ongoing treatment and possible cumulative amounts, not just one dose. (26, 47)

Some alcohols, preservatives, solvents, sweeteners, colorants, and surfactants may be unsuitable for very

young children or need careful review. Risks can also vary depending on whether a medicine is swallowed, applied to the skin, inhaled, or injected.

The European Medicines Agency recommends choosing excipients for the specific age group the medicine is intended for. Developers should avoid ingredients that may be harmful, unnecessary, or poorly tolerated, especially when safer alternatives are available**.** (2, 3,9) (2, 3, 9)

### 3.5 Stability and quality

Water-based medicines, such as solutions and suspensions, can be difficult to keep stable. If preservation, packaging, or handling is inadequate, microbes may grow. The active ingredient may also break down through reactions such as hydrolysis or oxidation, reducing the amount of medicine or creating unwanted by-products. (15, 16)

Suspensions can settle during storage. They should mix evenly when shaken so each dose contains the right amount of medicine. If the particles form a hard layer that will not mix back in, the child may receive too much or too little. Changes in thickness can also make a medicine harder to pour or measure with an oral syringe.

Pharmacy-made preparations may have limited stability information and short shelf lives. Their quality can depend on how they are prepared, stored, packaged, and handled.

Dry forms—such as powders, granules, tablets, capsules, and single-dose sachets can reduce some of these challenges. They are generally less prone to microbial growth and may remain chemically stable for longer. Single-dose packaging can also support accurate dosing and reduce contamination after opening. However, dry products may need specialized packaging or clear instructions for mixing and administration. The right choice depends on how well the formulation balances stability, dose accuracy, ease of use, and children's and caregivers' needs.

### 3.6 Adherence and everyday use

Children's willingness and ability to take medicine can depend on its taste, how much is needed per dose, and how often it must be given. Large volumes, frequent doses, and inconvenient timing such as during school, late at night, or before meals can make it harder for families to follow the treatment plan. (24, 27)

Preparation can add further challenges. Reconstituting, shaking, measuring, mixing medicine with food, or using several devices may lead to mistakes and make regular dosing more difficult. Developers should consider the work involved for caregivers, since even an effective medicine may be hard to use consistently if it is difficult to prepare, measure, store, carry, or administer.

Pediatric medicines should be assessed in realistic settings. This includes checking whether caregivers can understand the instructions, use the dosing device, prepare the medicine, and manage missed or incomplete doses. Such evaluation helps show whether a medicine is practical and reliable for children and families in daily life.

## 4. CONVENTIONAL PEDIATRIC DOSAGE FORMS

### 4.1 Oral liquids and syrups

Solutions and syrups are commonly used for children because many can swallow them more easily than tablets, and caregivers can adjust the dose by changing the volume. This flexibility is useful when a child needs a small or individualized dose. However, liquids must be measured accurately, may require larger amounts per dose, and can be less stable than solid medicines. Water-based products may need preservatives, adding to a child's exposure to excipients. Some syrups also contain substantial amounts of sugar, which may be a concern with frequent or long-term use. (1, 16, 18)

More concentrated liquids, products with fewer or safer preservatives, and child-friendly solid forms may help address some of these drawbacks. The best choice depends on the child and the treatment: liquids can make dose adjustments easier, while solid forms may be more stable and easier to store and transport. Developers should consider dose accuracy, shelf life, taste, excipient exposure, and whether the medicine can be given as intended without crushing or mixing.

Labels and measuring devices are part of the medicine's safe use. Syringes, cups, and spoons should

have clear markings that match the product's concentration and prescribed dose. Instructions should explain whether to shake or reconstitute the medicine, how to store it, and whether it can be mixed with food or drink. Caregivers also need simple guidance on how long a prepared medicine remains usable and what to do if a child spits out or vomits after a dose. These instructions should be tested with caregivers to check that they are clear and practical.

### 4.2 Suspensions

Suspensions can be useful for medicines that do not dissolve well in water and allow the dose to be adjusted by changing the amount given. For accurate dosing, however, the medicine particles need to be evenly distributed. Particles may settle during storage, and if they form a hard layer, or "cake," they may not mix back in properly. This can lead to doses containing too much or too little medicine.

Some suspensions also have a gritty texture that children may dislike. Caregivers generally need to shake the bottle thoroughly before each dose and use a suitable measuring device, such as an oral syringe.

As with other dosage forms, the choice should reflect the child's needs and the treatment. Liquids and suspensions can help when dose adjustments are important; solid forms may offer greater stability and be easier to store and carry. Clear labels and instructions should explain how to shake, measure, prepare, store, and use the medicine, including whether it can be mixed with food or drink. Caregivers should also know how long it can be used after preparation and what to do if the child spits out or vomits after taking it.

### 4.3 Conventional and scored tablets

Tablets are generally stable and easy to store and transport. They may suit older children who can swallow them comfortably, but their size can make them difficult for younger children to take. (16, 25)

Caregivers may try to crush, split, or dissolve a tablet in food or water when a child cannot swallow it. This can make the dose less accurate, cause some medicine to be lost, or make the taste unpleasant. Crushing or breaking modified-release and enteric-coated tablets can also change how the medicine is released or absorbed. A tablet should only be altered if its instructions say that it is safe to do so. Labels should clearly explain whether it can be split, crushed, dispersed, or mixed with food, and how quickly a prepared dose must be given.

Mini-tablets may be easier for some children to swallow while retaining the stability and storage benefits of solid forms. Giving a set number of units can also allow some dose flexibility. The most suitable option depends on factors such as the child's ability to take it, dose accuracy, shelf life, taste, and whether it can be administered without alteration. Caregivers should receive plain instructions, including what to do if the child spits out or vomits after a dose.

### 4.4 Capsules

Capsules may be suitable for older children who can swallow them. Some can be opened and their contents sprinkled onto soft food, but caregivers should do this only when the product instructions explicitly allow it.

Opening or altering a capsule without guidance can affect the dose, taste, stability, or the way the medicine is released. This is especially important for capsules containing modified-release pellets or coated granules. If mixing the contents with food is intended, a sprinkle capsule designed and tested for this use is generally more suitable.

When choosing between capsules, liquids, suspensions, tablets, or other forms, developers should consider the child's needs, dose accuracy, stability, storage, taste, and ease of administration. Instructions should clearly state whether the capsule can be opened, which foods are suitable, and how soon the prepared dose should be taken. Caregivers also need to know what to do if the child spits out or vomits after a dose. Instructions should use plain language and be checked with caregivers to ensure they can follow them.

## 5. MODERN AND NOVEL PEDIATRIC DOSAGE FORMS

### 5.1 Mini-tablets

Mini-tablets (about 1–4 mm wide) can make dose adjustment easier by changing how many a child receives. They are stable, can be coated to improve taste or control drug release, and may reduce excipient exposure.

Some infants can swallow 2-mm mini-tablets, though acceptance varies. Before use, developers need to confirm reliable dosing, child acceptance, stability, and consistent large-scale production. (30, 31, 32)

### 5.2 Orodispersible tablets

Orally disintegrating tablets break down in the mouth without water, which may help children who have trouble swallowing. They need to be sturdy enough to handle but dissolve quickly. Since the medicine can reach the taste buds, taste masking is important. The tablet must also provide an accurate dose and release the medicine reliably. (35, 36, 51)

### 5.3 Orodispersible films

Oral films are thin strips that dissolve in the mouth without water. They are light and easy to carry, but suit mainly low doses because their drug capacity is limited. Films must be strong enough to handle, dissolve quickly, taste acceptable, and be protected from moisture to maintain their quality and stability. (37, 38, 40, 53)

### 5.4 Chewable medicines

Chewable medicines can be easier to take than whole tablets, if a child can chew safely. Taste and texture should encourage the child to finish the dose, while sugar content should be considered. Size and hardness must also be appropriate to reduce choking risk. Because chewables can resemble candy, child-resistant packaging and secure storage are important.

### 5.5 Multiparticulates

Multiparticulates such as granules, pellets, and beads provide a dose as many small units, allowing adjustments by changing the amount given. Coatings can mask taste, protect the drug, or control its release. Some products may be mixed with food or liquid, but only when this has been tested and included in the instructions. Developers must ensure consistent dosing, intact coatings, and minimal medicine loss during preparation and administration. (41, 42)

### 5.6 3D-printed medicines

3D printing may allow medicines to be tailored to a child's dose, size, and release needs. It could also combine medicines or create child-friendly forms. Wider use will require reliable dose accuracy, suitable materials, stable products, consistent production, and clear quality and regulatory standards. (10, 11, 12, 13,)

## 6. TASTE MASKING AND PALATABILITY OPTIMIZATION

### 6.1 Palatability and adherence

Unpleasant taste or texture can lead children to refuse medicine, spit out doses, or avoid future doses, making treatment harder to complete. Taste should therefore be considered an important part of medicine design. (27, 28, 58)

Improving palatability may involve masking bitterness and improving texture, smell, and mouthfeel. Sweeteners and flavors should be safe for the child's age and expected treatment duration. Taste-masking methods must also allow the medicine to dissolve and release properly after swallowing.

Testing should reflect everyday use. Researchers can record how much medicine was given, whether it was mixed with food or liquid, how long administration took, the child's reaction, and whether the full dose was swallowed. Medicines should be pleasant enough to take, while still clearly recognizable as medicines and stored in child-resistant packaging.

### 6.2 Taste-masking approaches

Taste can be improved by changing the drug's form or the formulation's pH, binding drug molecules with substances such as cyclodextrins, or coating or encapsulating particles to limit contact with taste buds. Flavors, sweeteners, cooling agents, and texture adjustments may also help. (41, 42, 44)

The best approach depends on the drug and may combine several methods to address bitterness, grittiness, smell, or aftertaste. Testing must confirm that taste masking does not interfere with drug release or absorption. Caregiver and child feedback, along with observations during administration, can show whether the medicine is practical to use through a full course of treatment.

Medicines should not resemble sweets so closely that children may take them without supervision. Packaging and product design should support child safety.

### 6.3 Assessing acceptability

Researchers can assess whether children swallow the medicine and finish the dose, observe facial expressions, or use age-appropriate rating scales and questionnaires. Caregivers can report on ease of administration, refusal, or spitting out. Combining these methods gives a fuller picture, since acceptance may vary by age, culture, and patient group. (28, 29, 58)

Testing should use the intended patient population and reflect real-life administration. It should consider dose size, mixing, time needed, the child's response, and whether the full dose was taken—not just a brief taste preference.

### 6.4 Considerations for children

Sweeteners and flavors should be appropriate for the child's age, health, and treatment schedule. Developers should consider safe exposure levels, dental health, calorie intake, blood sugar control, and exposure from other medicines or foods. Preferences may also vary across ages and cultures, so testing should include the children and caregivers who will use the product.

A successful medicine should be easier and more comfortable to take without affecting how it works or making it look like candy. Clear warnings and child-resistant packaging help reduce the risk of unsupervised use.

## 7. EXCIPIENT AND SAFETY CONSIDERATIONS

### 7.1 Principles for excipient use

Excipients should be used only when they serve a clear purpose, and their amounts should be kept as low as practical. Developers should consider a child's age, development, maximum daily exposure, treatment duration, and other medicines, since several products may contain the same ingredient. (45, 46, 47)

If a potentially concerning excipient is necessary, developers should explain why alternatives are unsuitable and how exposure is limited. Measures may include reducing its concentration, changing the dosage form, using single-dose packaging, restricting use by age, or providing clear warnings.

### 7.2 Excipients requiring caution

Ethanol, benzyl alcohol, propylene glycol, polysorbates, parabens, and high levels of polyols such as sorbitol may need particular care in children. Newborns and infants may be more vulnerable because their liver and kidneys are still developing. Benzyl alcohol has specific safety concerns and labeling requirements for neonates and young infants. (9.)

### 7.3 Guidance and assessment

Regulatory guidance and pediatric excipient databases can support ingredient selection, but each product needs its own assessment. Developers should consider the highest expected daily exposure, route, dose frequency, treatment duration, and other medicines the child takes. (2, 3, 9)

### 7.4 Balancing function and safety

Excipients can help a medicine remain stable, taste acceptable, or resist microbial growth. Reducing them or changing the dosage form may lower exposure but can create other challenges in manufacturing, storage, packaging, or administration. Developers should weigh these factors together and document why each excipient is needed and how exposure is minimized.

## 8. FORMULATION AND PROCESS OPTIMIZATION

### 8.1 Quality by Design in pediatric formulations

Quality by Design (QbD) uses a structured process to develop medicines that are safe, effective, and consistently made. Developers define the product's goals, identify the materials and manufacturing conditions that affect quality, and study the risks and relationships between them. (63)

For children, quality includes more than drug content and dissolution. It may also involve dose flexibility, taste, swallowability, administration volume, disintegration, and ease of use for caregivers. These priorities should be set for the intended age group and treatment conditions. Development decisions, test results, and

user feedback should be documented so the product can be managed reliably as manufacturing changes.

### 8.2 Formulation optimization

Pediatric formulations require choices about the drug's physical form, dosage form, ingredients, taste masking, and packaging. Developers should assess several outcomes together including dose accuracy, stability, taste, ease of administration, and manufacturing consistency because improving one feature may affect another.

### 8.3 Process optimization

Manufacturing conditions can affect a medicine's strength, dose uniformity, stability, and release. For example, compression and powder flow matter for mini-tablets; granulation and drying affect tablets; polymer mix and drying affect oral films; and printer settings affect 3D-printed products. These factors should be studied and controlled to ensure consistent quality.

### 8.4 Experimental design and modeling

Design of Experiments (DoE) studies how multiple ingredients and process conditions affect product quality, helping developers balance competing needs such as rapid disintegration and tablet strength. Models of pediatric physiology can also help predict how a medicine may behave in children and guide dose and formulation choices. Findings and decisions should be documented to support future changes and investigations.

## 9. DRUG RELEASE

### 9.1 Biopharmaceutical considerations

A medicine's solubility and permeability affect how well it dissolves and is absorbed. Poorly soluble drugs may need formulation approaches that improve dissolution. In children, absorption can also vary with age-related differences in digestion, fluid intake, feeding, and organ development, so adult-based testing may not predict how a product will perform. (14, 59)

Release targets should reflect the medicine's intended effect in the body and be assessed under realistic pediatric conditions. Developers should also check whether chewing, crushing, mixing with food, feeding tubes, or other everyday situations could change drug release. Instructions should clearly explain how to use and handle the medicine.

### 9.2 Immediate-release and modified-release medicines

Immediate-release medicines act quickly and can be easier to adjust, but may need more frequent doses. Modified-release medicines can reduce daily dosing, which may help with long-term treatment. However, food or damage from chewing, crushing, or splitting may change how they release the drug and affect safety or effectiveness.

Multiparticulates may combine controlled release with dose flexibility, since the dose can be adjusted by changing the number of particles. Developers should confirm that handling, food, and liquid do not disrupt the intended release, and provide clear instructions for caregivers.

### 9.3 Linking laboratory tests to effects in children

Dissolution tests do not automatically predict how a medicine will be absorbed by children. Factors such as stomach acidity, fluid volume, feeding, and intestinal transit change with age. Test methods should reflect the intended pediatric group, and their ability to predict drug behavior should be supported by evidence.

When clinical data are limited, developers should state their assumptions and test the product under realistic conditions, including possible mixing, chewing, changes in fluid intake, or storage outside the original package. This can help establish reliable instructions and safeguards.

## 10. DISSOLUTION

### 10.1 Role of dissolution testing

Dissolution testing measures how quickly a medicine releases its drug, which usually needs to dissolve before absorption. It is especially important for poorly soluble drugs, modified-release products, and child-friendly forms with coatings or rapid disintegration.

Tests should be reliable, sensitive to meaningful formulation changes, and reflect how the medicine is given. Conditions such as fluid volume, pH, stirring,

and sample handling need careful control so results reflect the product rather than variations in the test.

### 10.2 Pediatric-relevant test conditions

Adult test fluids may not reflect children's changing stomach and intestinal conditions, which vary with age and feeding. Pediatric-relevant media and test conditions can help assess how a medicine may perform in its intended age group. (14.) (5, 14, 60, 61, 62)

Results should also reflect the dosage form and administration method for example, whether a medicine is a film, mini-tablet, or suspension. This makes testing more useful for formulation choices, quality standards, and evaluating product changes.

### 10.3 Testing novel dosage forms

Mini-tablets and multiparticulates behave differently from conventional tablets because they contain many small units. Films depend on moisture absorption and polymer dissolution, while 3D-printed medicines may have structures designed to control release. Each type may need a specifically justified test method. (14, 62)

Tests should be reproducible and sensitive enough to detect changes that could affect drug release, particularly for low-dose or fast-dissolving products. Sampling, filtration, test fluids, and timing should be carefully controlled.

## 11. DISINTEGRATION

Rapid disintegration can make orally disintegrating tablets, films, and mini-tablets easier for children to take. How quickly they break down depends on factors such as the disintegrant, porosity, compression, hardness, moisture, and drying.

Standard tablet tests may not reflect conditions in a child's mouth. Testing may need to account for saliva, temperature, hydration, and gentle movement, and assess wetting, even dispersion, and any large fragments not just disintegration time.

The product must also be strong enough to withstand handling without crumbling, yet break down quickly enough to be easy to take. Since mouth conditions vary, especially in young children, wetting, texture, and dispersion tests can help assess how the medicine performs in practice.

Fast disintegration alone does not guarantee acceptability. The medicine may still taste unpleasant or leave a gritty residue. Developers should balance speed with taste, texture, dose accuracy, and the needs of the intended age group.

## 12. CONTENT UNIFORMITY

### 12.1 Dose consistency in low-dose medicines

When a child's dose is very small, minor differences between units can cause substantial dosing errors. Mini-tablets, multiparticulates, and oral films therefore need consistent drug content. Developers should account for powder properties and the risk of ingredients separating during production, and monitor steps such as mixing, filling, compression, coating, and packaging. (49)

The full dose also depends on how caregivers administer the product. Counting errors, inaccurate measuring, difficulty shaking a suspension, or a child not finishing food mixed with the medicine can lead to an incomplete or uneven dose. Simulated-use studies can help identify these problems.

### 12.2 Pharmacopeial requirements and challenges

USP and European Pharmacopoeia standards include requirements for dose uniformity, but very small doses, small dosage units, and products containing multiple units can be difficult to control. Extemporaneously prepared medicines may add further variability. Meeting finished-product tests alone cannot compensate for inconsistent manufacturing, so processes and sampling should be controlled throughout production.

### 12.3 Ways to improve uniformity

Dose consistency can be supported by controlling particle size and powder flow, using suitable mixing and filling methods, and checking quality during production. Unit-dose packaging may reduce errors. For multiparticulates, consistent coating and representative batch sampling are also important.

Packaging, measuring or counting tools, and caregiver instructions should be designed alongside the formulation. Testing how the medicine is prepared and given in realistic conditions can reveal whether the child receives the intended full dose.

## 13. STABILITY

### 13.1 Types of stability

Medicine stability includes maintaining the drug's effectiveness, the product's physical properties, and protection from microbial growth. These concerns are especially important for water-based medicines. Quality must be maintained during transport, home storage, repeated opening, and after reconstitution.

Packaging should protect against moisture, light, air, and contamination while remaining easy to use. Labels should give practical instructions on storage, shaking, keeping the medicine in its original container, and when to discard it.

### 13.2 Factors affecting stability

Temperature, humidity, light, oxygen, pH, water content, packaging, and interactions between ingredients can affect a medicine's stability. Adding water to a dry product may make it more vulnerable to microbial growth, degradation, settling, or changes in thickness, so reconstituted medicines often have a limited use period.

Storage instructions should reflect conditions families can realistically maintain. If a medicine requires difficult storage conditions, developers may need to improve the packaging or choose a more stable formulation.

### 13.3 Improving stability

Dry products and single-dose packaging can reduce exposure to water and contamination. Preservatives may be needed for some multidose liquids, but their use should be justified and appropriate for the child's age and treatment.

Stability testing should cover transport, home storage, repeated opening, and use after reconstitution. Clear, practical labels can help caregivers store, shake, and discard medicines correctly.

## 14. PATIENT AND CAREGIVER ACCEPTABILITY

### 14.1 What acceptability includes

Acceptability involves more than taste. It includes swallowing, preparation and administration, dose frequency, product size, and whether the child is willing to take the medicine. Caregivers' ability to prepare and give it also matters. A medicine that works well in a study with healthy children may be harder to give during illness or long-term treatment. (27, 56)

### 14.2 Assessing acceptability

Researchers can observe whether children take the full dose, spit it out, chew it, or need a long time to take it. They can also gather age-appropriate feedback from children and reports from caregivers. Together, these methods can help identify whether difficulties come from taste, texture, dose volume, anxiety, or the dosing device.

Acceptance can change as a child grows or treatment continues. Follow-up may reveal new challenges or declining willingness to take a medicine.

### 14.3 Comparing dosage forms

Liquid medicines are not always the most acceptable option. Some children can take mini-tablets, although studies suggest ease of swallowing varies with age, tablet size, formulation, and experience. Mini-tablets have been accepted by some infants and young children, but may be harder to swallow than liquids or fine granules in some groups. (6–8.) (30, 31, 33, 34)

Study results should be interpreted in light of the children's health, how the medicine was given, and the setting.

### 14.4 Practical and psychosocial factors

Caregivers may need to measure, mix, prepare, and give several doses each day. Easy-to-use packaging and dosing devices can reduce the burden and help prevent errors. Medicines given at school should be portable, simple, discreet, and safe to use.

Considering children's and caregivers' experiences can help identify practical barriers and guide the choice or improvement of a dosage form.

## 15. REGULATORY CONSIDERATIONS

### 15.1 Pediatric regulation

The EU Pediatric Regulation (EC) No. 1901/2006 and 1902/2006 aims to support the development and availability of medicines for children. Developers should

show that each formulation, strength, excipient, package, and dosing device is suitable for its intended age group. (2) (3, 4, 20)

### 15.2 Pediatric Investigation Plans

Formulation needs for different pediatric age groups should be considered in the Pediatric Investigation Plan, not left until late in development. Early discussions with regulators can help identify the need for different strengths or forms, acceptability and bridging studies, and additional child-specific evidence. (3, 15)

### 15.3 EMA pharmaceutical development guidance

EMA guidance covers medicines for children from birth to 18 years. It calls for justification of the dosage form and route, dose range, excipients, administration devices, stability, dosing-error risks, and acceptability. Submissions should connect the proposed use and age group to the formulation choices and supporting evidence. (3.) (3)

### 15.4 Further guidance

The EMA's reflection paper on pediatric formulations and the WHO technology landscape offer additional guidance on suitable dosage forms and delivery approaches. (4, 15.)

Across development, decisions and evidence should be documented clearly. Any remaining limitations should be disclosed, along with plans to manage them, such as age restrictions, additional labeling, or post-approval studies.

## 16. EMERGING TECHNOLOGIES AND FUTURE PERSPECTIVES

### 16.1 3D printing and digital health

3D printing may enable child-specific doses, complex release patterns, and combinations of medicines in one product. Linking digital prescribing and dose calculations with manufacturing could support personalized production. Safe use will require reliable quality controls, clinical evidence, regulatory guidance, data protection, and trained staff. (10, 12, 13)

### 16.2 Smart packaging and connected devices

Electronic dose monitors and connected devices may remind families when medicine is due and track missed doses. They are useful only if families can use and afford them, and if they improve health outcomes. Implementation should account for privacy, training, quality, and supply.

### 16.3 New technologies

New materials and methods including advanced polymers, nanotechnology, microfluidics, prilling, and vibration technologies may improve dosing, taste, solubility, and manufacturing flexibility. (10). These approaches need to work safely and reliably in everyday care. Developers should also consider affordability and access, since specialized technology may not be practical in every setting. (10, 64, 65, 68)

### 16.4 Research priorities

Research should improve pediatric-relevant dissolution tests, predictions of how medicines behave in children, knowledge of long-term excipient exposure, and methods for measuring acceptability. It should also study real-world adherence, food mixing, dosing devices, and scalable personalized manufacturing. (14, 60, 61, 62)

Consistent study methods and clear reporting would make findings easier to compare. New technologies should demonstrate practical benefits for children while meeting quality and data-protection needs and remaining accessible across different healthcare settings.

## CONCLUSION

### 17.1 Summary of key messages

Pediatric dosage-form optimization is a complex process that involves many areas of medicine development. These include children's changing physiology, pharmacokinetics, formulation technology, excipient safety, taste, acceptability, quality control, drug-release behavior, stability, and regulatory requirements. Developing a suitable medicine for children requires consideration of all these factors together so as to enable all groups of pediatric get their doses according to

their needs and at the accurate measurement with standard formulation.

Evidence suggests that pediatric medicines should not depend only on liquid formulations. Although liquids remain useful in many situations, other dosage forms such as mini-tablets, multiparticulates, and orally disintegrating products can also be suitable for children. Mini-tablets are an important example because studies have shown that properly designed, small units can be accepted and swallowed by some infants and young children. (1, 15, 16)

Age appropriateness is not determined by only one feature, such as a small tablet size, a pleasant taste, or a dose calculated from body weight. It depends on the complete medicine system. The formulation, packaging, dosing device, instructions, and expected place of use must all work together to ensure that the correct dose can be given repeatedly and safely without placing too much burden on the child or caregiver.

The best development decisions consider several perspectives at the same time. These include the child's clinical needs, pharmaceutical quality, ease of use, safety, and the ability to manufacture the product consistently. Early collaboration between healthcare professionals, formulation scientists, manufacturers, regulators, caregivers, and patients can help identify challenges and trade-offs before they become difficult to solve.

Pediatric formulations should also be viewed as products that can improve over time rather than as fixed versions of adult medicines. As new knowledge becomes available about children's physiology, medicine acceptability, materials, and administration practices, it should be used to improve product design and long-term management. This continuous learning approach can support safer, easier-to-use, and more effective medicines for children in different healthcare settings.

### 17.2 Clinical and formulation implications

The most suitable pediatric dosage form should not be chosen based on age alone. It should be selected using evidence about the child's dose requirement, ability to swallow, the properties of the active drug, taste, excipient exposure, stability, administration conditions, and the needs of caregivers. A medicine may be scientifically well designed but still fail in practice if children cannot take it properly or if caregivers find it difficult to prepare and administer.

Age appropriateness is therefore a property of the complete medicine system. It cannot be judged only by tablet size, flavor, or body weight-based dosing. The formulation, packaging, dosing device, instructions, and expected setting of use must work together to ensure that the intended dose can be given safely, accurately, and repeatedly without creating unnecessary difficulty for children or caregivers.

Strong pediatric formulation decisions should consider clinical need, product quality, usability, safety, and manufacturing feasibility at the same time. Early collaboration among formulation scientists, clinicians, caregivers, patients, manufacturers, and regulators helps identify important trade-offs before the product is finalized. This approach supports the development of medicines that perform well in laboratory and clinical testing while also being practical for everyday use.

Pediatric formulations should also be continuously improved as new information becomes available. Evidence about child physiology, medicine acceptability, excipients, materials, and administration practices should be used to guide future product design and lifecycle decisions. Viewing pediatric medicines as evolving products rather than simple adaptations of adult formulations can lead to safer, more effective, and easier-to-use treatments for children.

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