

Pediatric Dosage Form Development: Challenges and Opportunities

A Cambrex webinar overview



Pediatric drug development offers advantages to younger patients through the availability of newly developed medicine forms. It also offers advantages to the sponsor pharmaceutical companies through extended exclusivity for their marketed product. As a result of this, the number of pediatric drug approvals has increased five-fold over the last 20 years, rising from 10-20 approvals per year to 50-60 approvals annually today.

Pediatric patients, which includes infants, children and adolescents, require different oral dosage forms from adults due to differences in swallowing abilities, taste preferences and dosage requirements. In general, this pediatric population is not homogeneous and requires different formulations depending on the age, developmental and clinical state of the patients. Oral pediatric formulation designs are therefore primarily focused on the patient age, body size, and the swallowing capability of the target population.

This webinar will:

- Provide an overview of the pediatric market and present potential growth areas
- Consider the challenges and opportunities of pediatric formulations
- Review several pediatric formulation dosage forms including liquid dosage forms and solid dosage forms (mini-tablets, orodispersible tablets (ODT) and chewable formulation)
- Conclude with an overview of the regulatory considerations for new pediatric formulations

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Dr. Qu joined Cambrex after the company's acquisition of Halo Pharma in September 2018. Previously, Dr. Qu was Group Director of Product Development at Patheon and led and directed a group of 100+ scientific staff developing projects (NDA, 505(B)(2), ANDA) for various clients and different phases. Dr. Qu earned his PhD in Pharmacology from the University of Toronto, Canada and has subsequently worked for around 30 years in the pharmaceutical industry.

Opportunities in the pediatric market

The global pediatric dosage form market is expected to reach \$110 billion in 2019.¹ This represents around 5% year on year growth from three years ago, when the market was valued at \$95 billion. The US represents approximately 44% of this \$110 billion, EMEA 33%, and APAC 22%. Whilst some areas of the market are expected to grow slightly more than 5%, some areas will grow just under 5%, with the average being approximately 5%. This market presents great growth opportunities and is expected to remain at this rate until 2021.

In the last 20 years pediatric drug approvals increased five-fold, with an average of 10-20 approvals per year to 50-60 approvals annually today.

There are three pathways to pediatric drug product approval:

1. Original Approval

Original approvals for pediatric use through either 505(b)(1)/new molecular entity or 505(b)(2)/typically new dosage form submissions.

2. Pediatric Exclusivity (PE)

FDA requests pediatric study on an existing adult product which, if successful, results in a label change and pediatric exclusivity which, if granted, adds 6 months market exclusivity. PE in general applies to products that have patent life or exclusivity remaining.

3. Supplementary Approvals (SA)

Drugs originally approved for treating adults can have labelling change or labelling extension for their use in children.

Pediatric applications and challenges

Oncology, central nervous system (CNS), and infectious disease applications are three areas which lead the pediatric dosage trends in clinical trials, and of more than 1,000 pediatric trials currently ongoing, half of them are small molecules.

From the pediatric patient perspective, this group is unique. People often assume that pediatric dosing is straightforward and that the adult formulation is suitable, however this is not the case. For example, with an adult dosage tablet, it is not as simple as cutting the dose into a smaller size for a pediatric patient. In addition to the different age/dosage correlation, consideration must be given to the difference in preferences, abilities and body weights, making their pharmacokinetic profiles different.

In the case of very young children, for example a 1-year old patient who is unable to swallow solids such as tablets and capsules, a liquid dosage form may be appropriate. Children over the age of 7 can often take a tablet or capsule but there will be a subset of this group that may still prefer a liquid solution or suspension.

Such factors, such as the ease of swallowing the drug and the better taste sensation, can have a big impact on the success or failure of its clinical trial.

It is also important to note that new formulations are not only for pediatric patients – and they could also be appropriate for other patient groups that have swallowing issues; such as the elderly, patients who have had a stroke, or patients with long-term diseases such as Parkinson's or Alzheimer's Disease.

Age and dose-appropriate delivery dosage form consideration

Table 1: Age-appropriate oral delivery

	Preterm newborn	Term newborn	Infants & toddlers	Preschool children	School children	Adolescent
Solution	2	4	5	5	4	4
Suspension	2	3	4	5	4	4
Capsules	1	1	1	2	4	5
Tablets	1	1	1	3	4	4
Chewable tablet	1	1	1	3	5	5
Mini-tablet	1	2	2	4	4	5

1 = Not applicable/the dosage form cannot be given to patients

2 = The form is applicable but may present issues

3 = Likely acceptable but not preferred

4 & 5 = Typically presents no issues

Table 1 highlights which dosage form is acceptable for a range of ages. As children grow beyond 7 years of age, they can usually take any of the dosage forms available. This table can be used as guidance when designing formulation dosage forms for different pediatric patient populations.

Unique oral delivery dosage forms

When considering the unique nature of pediatric formulations, it is also important to review the types of formulations on the market, including:

Oral liquid formulations

Oral liquid formulations include solutions, syrups and suspensions. The advantage of these formulations is their suitability for patients who have trouble swallowing. They also allow for flexible dosing by simply adding more or less liquid, and are typically absorbed faster than solid dosage forms. On the flip side, these formulations typically need to be refrigerated in between use and have a shorter shelf life. This can make stability an issue as certain APIs may not be stable in a liquid form, even though they may be efficacious in a solid dose. Accurate dosing is another problem due to the range of domestic spoon sizes, so it is important to follow dosing standards strictly.

Oral solid formulations

Solid oral dosage formulations, tablets and capsules present many advantages. They are well-established technologies that have stable, long-term shelf lives, are pre-measured for dosing, and can be coated to mask taste or added to food. Conversely, some patients such as infants have trouble swallowing, and certain types of formulations are hydroscopic and require special packaging and storage in a dry place.

Fast-dissolving tablets are another example of an oral solid formulation and dissolve in the mouth within 60 seconds. In this type of formulation the product is required to be dosed in strength under 20mg and requires high solubility in water or saliva to partition into the epithelium of the upper gastrointestinal tract. Alternatively, if the drug half-life is short or requires sustained or controlled release, then fast-dissolve tablets are not suitable.

Chewable tablets are another suitable oral solid dose formulation for pediatric patients as children generally have the ability to bite and chew. These formulations typically benefit from enhanced bioavailability and are convenient as water is not required for consumption and absorption is typically fast. However, chewable tablets can contain sorbitol, which potentially can cause side effects such as diarrhea, and if the product requires an excessive amount of chewing this can lead to facial pain. It is also important to consider a number of other factors such as material flow, type of lubricants, the disintegration acceptance, taste, compressibility and stability.

Multi-particulate formulations

An example of a multi-particulate formulation is a mini-tablet, which are small tablets approximately 1.5-3.0mm that are able to be filled into a capsule or compressed into a larger tablet. They can also be filled into a sachet or stick-pack, and offer flexible dosing based on the number of mini-tablets used.

Another benefit is the relative ease of mixing the immediate and sustained release mini-tablets together if required. In addition, mini-tablets facilitate the formulation of fixed dose combinations products (a combination of either two or three different APIs). Combination formulations are increasing in popularity for a variety of pharmaceutical companies due to the 505(b)(2) approval pathways. Finally, mini-tablets typically have consistent pharmacokinetic profiles, are easy to swallow and taste is easily masked due to the small size.

Mini-tablets require specialized design but offer flexibility in dosing; for example, an increased dose strength can be achieved by filling more mini-tablets into the same stick pack. In Table 2: each mini-tablet with 5mg weight contains 20% active drug load equating to 1mg strength. Therefore, filling a stick-pack with 10 mini-tablets results in a 10mg stick-pack. The administrator can adjust the number of mini-tablets in the stick-pack to meet the clinical dosage requirement. The strength can also be doubled or tripled, by increasing two times or three times the active drug load in tablet weight.

Table 2: Mini-tablets flexible dose*

Mini-tabs per stick	Dose strength (mg)
10	10
20	20
30	30
50	50
70	70

*Example of mini-tablet with 5mg weight containing 20% active drug load.

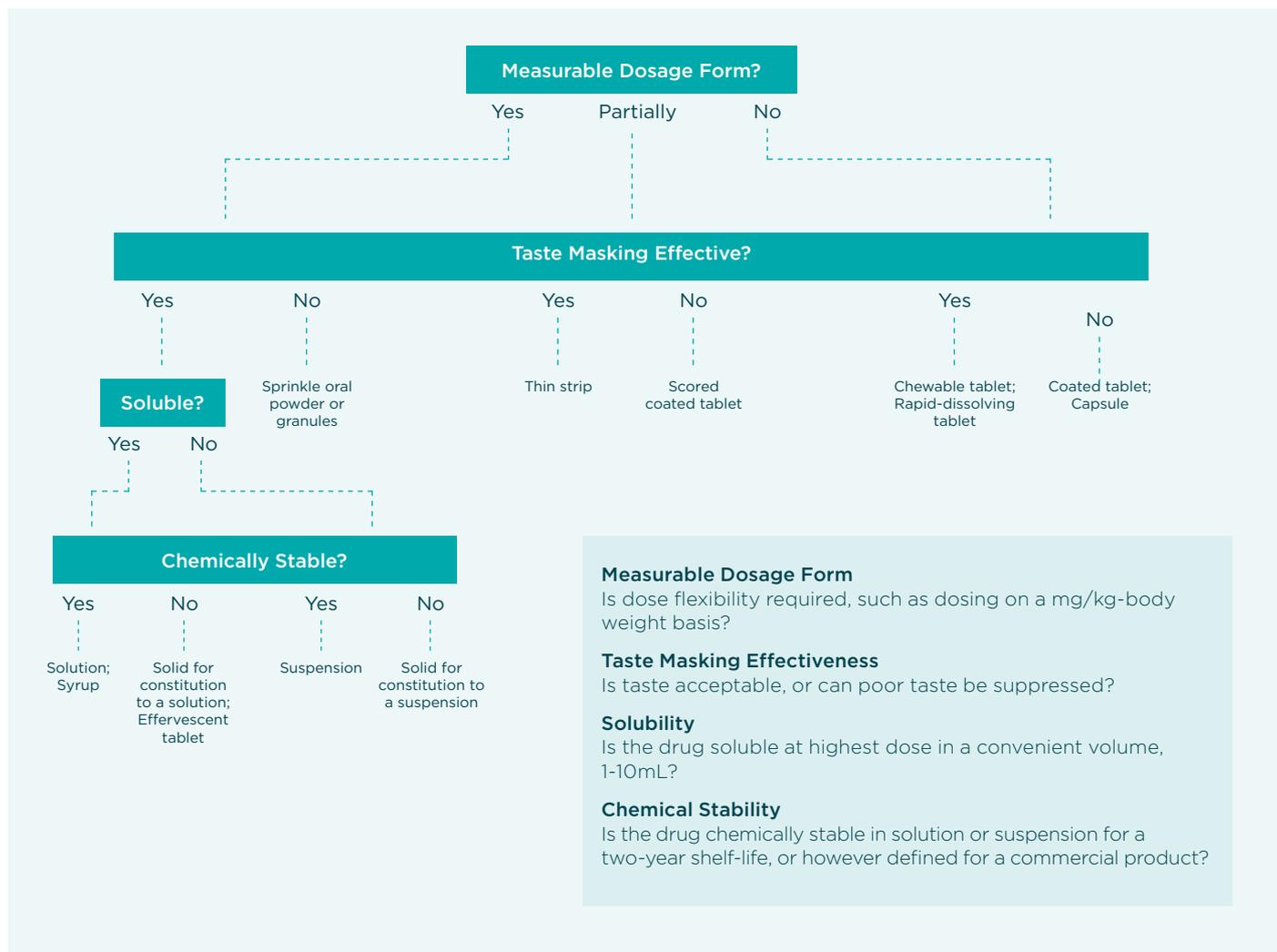
Alternative oral delivery pathways

In addition to the different formulations, there are similarly a number of different delivery pathways. For example, the Medibottle has the appearance of a bottle but works in combination with a syringe that delivers a drug into the infant's milk or liquid drink. Another example is dose sipping technology, in which medicine is loaded into straws and mixes with the child's drink.

Pediatric oral formulations

When considering the appropriate formulation design to use it is important to ask four questions using the formulation decision tree shown in Figure 1.

Figure 1: Pediatric oral formulation decision tree²



The questions you should ask include:

1. What measurable dose form is required based on mg/kg-body weight?
2. Does the API formulation have a bad taste? And if so, can this taste be suppressed or masked?
3. Is the API soluble or not soluble? Taste should also be considered at this stage.
4. Is the formulation stable or not stable? If yes, a solution, such as a syrup and solution can be made. If the formulation is not stable, it will have to be a solid form.

Manufacturing technologies

Different types of manufacturing technologies can be applied based on the resulting drug product.

Direct compression represents the simplest and the most cost-effective manufacturing process of mixing the API with the excipients and compressing them using a tablet press. Wet granulation adds a liquid to a powder to mix the API and the excipients. The liquid can be aqueous, but can also be a solvent, and during the mixing process the liquid is removed.

Roller compaction is a technique that has three units, starting with a feeding unit at the top where powder and API are fed into the roller. This follows with a compacting unit where the powder is compacted between two counter-rotating rollers to force this powder to form a ribbon (also referred to as an envelope), and a size reduction unit for milling that cuts the ribbon into the desired particle size.

Finally, hot melt extrusion applies heat and pressure to overcome bioavailability challenges by melting a polymer and forcing the API through an orifice so that it can pre-dissolve.

Case study 1: Mini-tablets in capsules

A client requested a formulation with three API's, however one of the API's was not compatible with the other two. After reviewing the API's physical and chemical properties, and factoring in the different age populations, a mini-tablet approach was selected. The two compatible API's were compressed into one mini-tablet, and the third incompatible API was compressed into a separate mini-tablet. Both of the mini-tablets were then filled into a capsule.

Case study 2: Mini-tablets in stick-packs

One client was working to a limited budget and requested a single formulation to cover an age range from 1 to 17 years and in doing so would avoid the issue of multiple formulations, multiple registration batches and stability studies. After reviewing the physical and chemical properties of the API, a mini-tablet approach was selected which provided a rapid solution allowing a range of quantities of mini-tablets to be filled into a stick-pack to accommodate each age range.

Regulatory considerations

With growing interest and opportunities around pediatric dose formulations, the regulatory landscape has also increased. The Pediatric Research Equity Act (PREA) requires pediatric studies for drugs and biological products that will be used in younger populations, with specific guidance on formulation by age. It also covers specific labeling of these products to ensure that they are administered for the correct indications, in the correct dosage form and dosing regimens.

Conclusion

In conclusion, pediatric formulation development requires an experienced CDMO with specialist pediatric expertise. Such CDMOs will be able to provide guidance and develop the right formulation that considers patient age, different dosage forms and taste preferences, in addition to paying attention to regulatory approval early on in the development process.

The team at Cambrex is the right partner to help you develop safe, fast and cost-effective solutions for pediatric drug products that meet and exceed regulatory standards and get your product faster to market.

References

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- 2 Robert G. Strickley et. al, J. Pharm. Sci. 2008;97;5:1731-1774.

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