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A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – An application for paediatric dosage form selection

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ABSTRACT

The design and selection of new pharmaceutical dosage forms involves the careful consideration and balancing of a quality target product profile against technical challenges and development feasibility. Paediatric dosage forms present particular complexity due to the diverse patient population, patient compliance challenges and safety considerations of this vulnerable population.

This paper presents a structured framework for assessing the comparative benefits and risks of different pharmaceutical design options against pre-determined criteria relating to (1) efficacy, (2) safety and (3) patient access. This benefit/risk framework has then been applied to three hypothetical, but realistic, scenarios for paediatric dosage forms in order to explore its utility in guiding dosage form design and formulation selection. The approach allows a rigorous, systematic and qualitative assessment of the merits and disadvantages of each dosage form option and helps identify mitigating strategies to modify risk.

The application of a weighting and scoring system to the criteria depending on the specific case could further refine the analysis and aid decision-making. In this paper, one case study is scored for illustrative purposes. However, it is acknowledged that in real development scenarios, the generation of actual data considering the very specific situation for the patient/product/developer would come into play to drive decisions on the most appropriate dosage form strategy.

1. Introduction

1.1. Dosage form selection as part of modern pharmaceutical development

Selecting and designing an appropriate dosage form for the paediatric population is particularly challenging. In addition to those challenges usually encountered when developing adult dosage forms; developing a dosage form for children poses other challenges such as the diversity of the patient population both in terms of size and physiological and biological maturation; specific patient compliance challenges such as swallowing difficulties and low tolerance to unacceptable taste; and specific safety concerns associated with the required excipients (Bowles et al., 2010; Ernest et al., 2007; Kaye, 2011).

As with adult patients, the oral route of drug administration is the most commonly used for paediatric patients. This poses the additional challenges of developing dosage forms that are easily swallowed and have acceptable palatability. Many oral dosage forms are available, each with their advantages and disadvantages, which formulators will take into account when assessing the strategy for developing a paediatric product for a specific situation. See Table 1 for a summary of the situation for oral dosage forms. Other factors to be considered are related to ease of development, manufacturability, transport, storage and dispensing. Formulation developers need flexibility in the choice of dosage form and excipients to develop formulations that meet the needs of the patient, whilst also accommodating the properties of the drug.

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Table 1
Potential advantages and disadvantages for the paediatric patient associated with the different types of oral dosage forms.

Type of oral dosage form	Potential advantages	Potential disadvantages
Tablet (non dispersible) OR Capsule	• Solid state stability • Development strategy similar to adult dosage form • Convenience for patient in terms of pack, transport and usage • Modified release opportunities • Taste masking by tablet coat • Range of shapes, sizes (e.g. minitablets) and colours available for identification • Single or multiple use packs	• May be difficult for young children to swallow (depending on tablet or capsule size and age of child) • Crushing or breaking of tablet to assist administration may be undesirable e.g. in case of functional coat, etc. • Limited dose flexibility
Tablet (dispersible and/or fast disintegrating and/or melt)	• Overcomes issues associated with swallowing difficulties in younger children • Convenience for patient in terms of pack, transport and usage • Single or multiple use packs • Solid state stability • May provide convenience for patient in terms of pack, transport and usage	• Less stable than 'standard' tablets • May require sophisticated pack • IP rights/costs for some technologies • Taste masking needed (palatability) • Limited opportunity to modify drug release • Limited freedom to operate (intellectual property) • Limited dose flexibility
Oral granules/sprinkles/powders for reconstitution/multi-particulate preparations/minitablets	• Solid state stability • Can be mixed with food or beverage • Dose flexibility	• Development of non-lockable capsule, sachet or bottle with measuring system • Need to verify compatibility with food or beverages • Need for diluent/suspending agent (Note potable water may not be available) • May require taste masking (avoid risk of causing aversion to food) • Limited control over dose intake
Oral solution/syrup/drops	• Maximum dose flexibility • Ease of swallowing • Opportunity to flavour as required • Single or multiple use packs	• Limited by solubility (requiring pH buffers, use of co-solvents etc.) • Chemical, physical and/or microbiological stability issues • Limited shelf life • Taste masking; flavours and/or sweeteners likely to be required • Use of preservative in case of multiple use • Limited control over dose intake • Limited opportunity to modify drug release
Oral Suspension	• As for 'Oral Solution' but potentially less likely to require taste masking	• As for 'Oral Solution' but likely to be less physically stable

1.2. Factors influencing the selection of an appropriate dosage form

The criteria of an appropriate dosage form are as follows:

(i) The medication is efficacious and easy to use.
(ii) The medication is safe for the patient.
(iii) The patient has access to the medication.

Every dosage form should balance these 3 criteria as is illustrated in Fig. 1.

Factors associated with efficacy and ease of use include dose flexibility; and acceptability of dose size or dose volume. The paediatric product should provide suitable dose flexibility to enable accurate dose administration across the defined paediatric age range ideally without the need to manipulate the product.

The dosage form must also be designed to ensure patient compliance. This may be achieved by being designed to have a minimal impact on lifestyle and of appropriate appearance e.g. colour and palatability.

Acceptable palatability of oral medicines, especially for oral liquids and powders, is vital to facilitate paediatric patient compliance (Cram et al., 2009). The taste of the drug substance may provide justification for the dosage form to be selected and will determine if taste improvement is needed.

As with developing any pharmaceutical dosage form, patient safety is of paramount importance. Patient safety includes many aspects including acceptable and consistent bioavailability of the

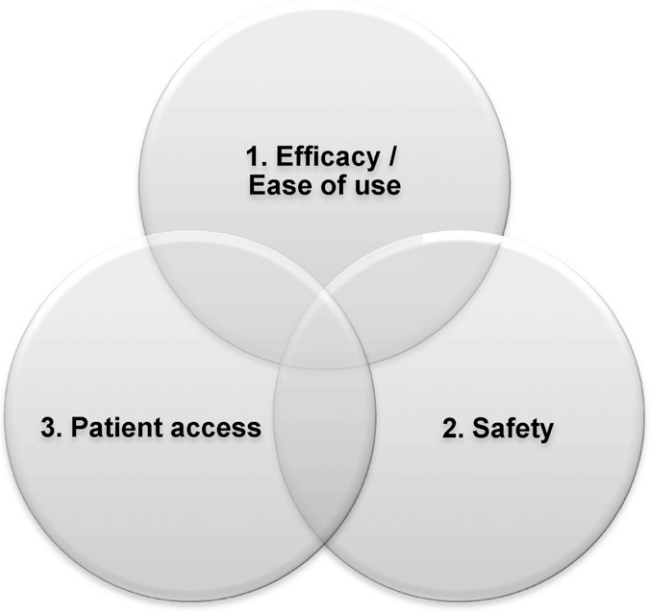

Fig. 1. Criteria influencing the selection of an appropriate dosage form.

Table 2
Selection of the most appropriate drug product for the patient based on benefit/risk using efficacy, safety and access criteria.

Benefit/risk	Criterion for drug product	Definition	Additional explanation
1. Efficacy/ease of use	**1.1 Dosage:**	**Size, frequency, and number of doses. A dose is a quantity to be administered at one time.**	
	– Dose flexibility	The capability of a drug product to be subdivided without impact on the product's safety or efficacy.	Dose flexibility may allow more appropriate dosing (e.g. mg drug kg body weight) to be administered to the patient.
	– Acceptability of dose size/dose volume	Dimensions or volumes that allow reliable administration and good patient compliance.	Acceptable dose size/dose volume will facilitate compliance and ease of handling and administration.
	1.2 Dose preparation and administration:	**Dose preparation is the handling and manipulation of the dose prior to administration, where needed and directed.**	
	– Easy and convenient handling	The required preparatory handling can be performed in a simple, non-complex and robust way.	Easy handling prior to administration, e.g. dispersion, dilution, facilitates correct dosing.
	– Correct use	Use of the drug product as prescribed and intended in the labelling.	Impact of incorrect use needs to be considered.
	1.3 Compliance:	**The degree to which a patient correctly adheres to the prescribed medication.**	
	– Minimal impact on lifestyle	To have as little as possible influence on the habits, attitudes, tastes, cultural norms etc., that together constitute the patient's way of living.	Consider convenience of handling, transport and administration in relation to patient lifestyle and condition.
	– Acceptable appearance (including colour) and taste	Colour and taste are acceptable from a compliance point of view.	Unacceptable colour or taste may have an adverse impact on patient compliance.
	– Minimal administration frequency	Administration frequency is the number of doses administered in a day.	Low frequency of administration may be more convenient to the patient/carer and thus assist in patient compliance.
2. Patient safety	**2.1 Drug substance/drug product:**	**Drug product is defined as the combination of drug substance, excipients and packaging.**	
	– Acceptable and consistent bioavailability	The extent that the formulation is capable of delivering acceptable plasma concentration time profiles and levels.	Drug substance and, formulation may affect bioavailability.
	2.2 Excipients:	**Substances within the formulation other than the drug substance. Excipients can: (1) aid in the processing of the drug delivery system during its manufacture, (2) protect, support or enhance stability, bioavailability or patient acceptability, (3) assist in product identification, or (4) enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. [IPEC Excipient composition guide 2009]**	
	– Minimal number and levels needed for acceptable formulation	The lowest number and quantities of excipients required to serve well-defined and essential process or product functions.	For each excipient justification for its inclusion and its level should be provided.
	– Acceptable tolerability and safety	A physiologically tolerable excipient is an excipient that causes no adverse effects in the target population. A safe excipient is an excipient that does not lead to acute toxicity, organ toxicity, GI side-effects, or local tolerability (e.g.: s.c., i.v.).	Age of patients, condition to be treated and duration of use should be considered when assessing if excipients have acceptable tolerability and safety.
	2.3 Stability:	**The degree to which the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. It encompasses chemical/physical/microbial stability.**	
	– Stable during shelf life	Stability of the drug product should be established for an entire shelf-life of sufficient duration.	The suitability of the product to be used or appropriately stored in various climatic regions must be considered.
	– Stable in-use	In-use stability is the stability of the drug product after (re)constitution or dilution of the preparation at the specified storage condition and in-use period.	Consideration must be given where doses of product are administered from a multi-dose container.
	2.4 Medication error:	**Any preventable event that may cause or lead to inappropriate medication use or patient harm.**	
	– Minimal risk of dosing error	Minimal risk of administration of the incorrect dose.	In general, a dosing error can be defined as any dose deviating more than 10 percent of the recommended dose. The range can be broader or smaller depending upon the drug's therapeutic index.

Table 2 (*Continued*)

Benefit/risk	Criterion for drug product	Definition	Additional explanation
3. Patient Access	**3.1 Manufacturability:**	**The extent to which a drug product of acceptable quality can be manufactured routinely at reasonable cost.**	
	– Robust manufacturing process	A robust manufacturing process is one that routinely delivers products of consistent acceptable quality at commercial scale.	The lack of a robust manufacturing process may lead to supply issues and increased cost of goods.
	– Commercial viability	A medicinal product is commercially viable if the company is likely to make an adequate return on its investment in the development of the product.	Commercial viability can be a prerequisite for commercial availability and supply.
	3.2 Affordable:	**A medicine is considered affordable when the local income/economy, the cost to the patient or healthcare provider is reasonable with respect to its benefit.**	
	– Acceptable cost to patient or health care provider	Acceptable cost refers to cost relative to income or budget availability, or to alternative similar products available on the market.	Patients may get access to expensive medicines via special programs.
	– Easily transported and stored	Ease of transport and storage refers to the need to take measures to maintain integrity and stability of the drug product.	Access to medicines can be compromised due to difficulty in transportation, such as controlled temperature supply chain.
	– Low environmental impact	Environmental impact concerns the indirect and direct consequences of use of the product (e.g. disposal of packaging) on the natural environment.	
	3.3 Speed:	**Speed refers to the duration of time that is needed to make the drug product available to the patient, encompassing development, registration, distribution, etc.**	
	– Easily developed and produced	No major hurdles in development and production.	Ease of development may be influenced by the knowledge, capabilities and resources of the company.

drug substance but also must consider the safety of excipients in the product.

As for adult medicines, the use of excipients in paediatric products is driven by functional requirements and should be justified through a risk-based assessment taking into account, amongst others, the route of administration, the frequency of dosing and the duration of use. The added challenge for paediatric medicines is that excipients may lead to adverse events in children, especially neonates and infants, that are not experienced in adults, or not seen to the same extent. The WHO Points to Consider document (World Health Organization, 2010), the EMA Reflection Paper (European Medicines Agency, 2006), and the new draft EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use (European Medicines Agency, 2011) list known concerns about the use of excipients in paediatric patients.

Clearly, an overly conservative approach to the inclusion of specific excipients or classes of excipients will limit and hinder the development of dosage forms that have the appropriate pharmaceutical quality and meet patient needs. For instance, the use of a preservative in a liquid multi-dose drug product may be acceptable when compared to the risk of microbiological contamination or the potential negative impact on access to patients globally (due to for example issues with packaging, shipment, storage, unit cost and disposal) that can be associated with single use presentations. In addition to the excipients needed to develop a physically and chemically stable dosage form, there may be a need to include other excipients such as flavourings, colourings or sweeteners to aid patient compliance, with appropriate justification.

Both the medication stability and risk of medication error must also be considered as these also have a significant impact on patient safety.

For paediatric medicines in particular, patient access is a vital consideration. Patient access includes aspects associated with manufacturability, affordability and speed. A state of the art paediatric dosage form that meets efficacy and safety criteria is of little use if the manufacturability is non robust or too expensive as the medicine will not reach the targeted paediatric patient population. The paediatric dosage form should be designed to enable global access to the product at appropriate cost with low environmental impact.

2. Materials and methods

2.1. A generic framework for establishing the relative benefit/risk of a dosage form

A structured framework that can be used for assessing the comparative benefits and risks of different pharmaceutical design options against the factors outlined above (drug product criteria) has been developed.

The criteria and their definitions are provided in Table 2.

It is proposed that potential drug product options should be assessed for each criterion and then compared against each other. Strategies for mitigating against any risks identified may also be considered as part of the framework, for example the use of a specific delivery device to ensure measurement and administration of the correct dose or instructions in the product labelling.

Product options may be prioritised by adopting a scoring system, and here a variety of approaches could be used. One approach is to define scales for scoring the differences for the various criteria in the range from equal to extremely different, followed by a weak point and sensitivity analysis. It should be emphasised that the framework should be used on a case-by-case basis and consider the specific product characteristics and medical need.

Table 3
Case study 3: multiple dose oral liquid containing preservative versus a single unit dose non-preserved oral liquid (treatment group 2–6 years).

Benefit/risk	Criterion for drug product	Liquid solution (2–6 years)	Non dispersible tablet (6–12 years)	Sprinkle (2–12 years)
1. Efficacy/ease of use	**1.1 Dosage:** – Dose flexibility – Acceptable dose size/dose volume	High dose flexibility provided by volume administered	Minimal dose flexibility, but a range of unit doses could be prepared	Moderate dose flexibility but a range of unit doses could be prepared. Or the quantity of sprinkle administered could be adjusted according to the dose required **Risk mitigation** A dispensing device would be required to enable sprinkles to be 'sub dispensed' by volume according to dose required
	1.2 Dose preparation and administration: – Easy and convenient handling – Correct use		Portable A breakline could be used	Portable
	1.3 Compliance: – Minimal impact on life style – Acceptable colour and taste – Minimal administration frequency	Taste masking/flavouring of solution may be required	Tablet would need to be suitably small to avoid swallowing difficulties in the age group	Mouthfeel would need to be considered but taste per se could be masked by administering with food for example or by coating
2. Patient Safety	**2.1 Drug substance/drug product**: – Acceptable and consistent bioavailability	Potential for precipitation upon administration or increased exposure to be considered **Risk mitigation** A relative bioavailability study may need to be considered if significantly different formulations are to be used across age groups	Acceptable biorelevant dissolution profile required	Acceptable biorelevant dissolution profile required. If taken with food the impact of the food on bioavailability would need to be considered **Risk mitigation** Testing with food might need to be conducted
	2.2 Excipients: – Minimal number and levels needed for acceptable formulation – Acceptable tolerability and safety	Solubility enhancing, flavouring or sweetening excipients may be required **Risk mitigation** Paed tolerability of such excipients would need to be considered		
	2.3 Stability: (chemical/physical/microbial stability in the relevant environments and climates) – Stable during shelf life – Stable in use	Preservatives may be required for long term storage **Risk mitigation** Single use or multi use packs of solution could be prepared		Foodstuff could impact drug product or API stability **Risk mitigation** Stability/compatibility of drug product in a range of foodstuffs would need to be considered
	2.4 Dosing precision and accuracy: – Minimal risk of medication error/dosing error – Minimal manipulation by health professionals or caregivers prior to use	A suitable device for dose measurement required		If sprinkled on food all food would need to be consumed for complete dose to be administered
3. Patient Access	**3.1 Manufacturability:** – Robust manufacturing process – Commercial viability	Conventional manufacturing process	Conventional manufacturing process	Sachet packs would be least conventional but still viable.
	3.2 Affordable: – Acceptable cost to patient or health care provider – Easily transported and stored e.g. need for cold chain – low environmental impact e.g. consider packaging and disposal costs	May require specialized storage conditions if preservatives are not used. May require 'clean' manufacturing conditions if non preserved		Sachet packaging costs could be high.
	3.3 Speed: – Easily developed and produced	Depends on need for solubility enhancement and taste masking. Could be complex development	Could be derived from adult dosage form if available	Fastest approach as only one dosage form is required. However taste masking efforts may be required. Sprinkle formulation could be derived from adult dosage form if available. Requires specialized manufacturing

Table 4
Case study 2: oral tablet with blue colourant E132 in coat versus oral tablet uncoloured (treatment of adolescents).

Benefit/risk	Criterion for drug product	Oral tablet with blue colourant (E132)	Oral tablet with white colourant (titanium dioxide)
1. Efficacy/ease of use	**1.1 Dosage:** – Dose flexibility – Acceptable dose size/dose volume	No difference	No difference
	1.2 Dose preparation and administration: – Easy and convenient handling – Correct use	No difference	No difference
	1.3 Compliance: – Minimal impact on life style – Acceptable colour and taste – Minimal administration frequency	Colour could enhance patient acceptance	
2. Patient Safety	**2.1 Drug substance/drug product:** – Acceptable and consistent bioavailability	No difference	No difference
	2.2 Excipients: – Minimal number and levels needed for acceptable formulation – Acceptable tolerability and safety	E132 may lead to hypersensitivity in "adolescents **Mitigation**: Warning in labeling on potential hypersensitivity	Titanium dioxide has GRAS status
	2.3 Stability: (Chemical/physical/microbial stability in the relevant environments and climates) – Stable during shelf life – Stable in use	No difference	No difference
	2.4 Dosing precision and accuracy: – Minimal risk of medication error/dosing error – Minimal manipulation by health professionals or caregivers prior to use	The colour could help to avoid dispensing and patient medication errors (1)	**Mitigation:** Use of printing, packaging and labeling to avoid confusion with other medication
3. Patient access	**3.1 Manufacturability:** – Robust manufacturing process – Commercial viability	Colour ensures correct orientation of tablet for printing and consequently results in less waste	
	3.2 Affordable: – Acceptable cost to patient or health care provider – Easily transported and stored e.g. need for cold chain – low environmental impact e.g. consider packaging and disposal costs	No difference	No difference
	3.3 Speed: – Easily developed and produced	The product with blue colourant is commercially available and can be supplied immediately at lower cost	

3. Results

3.1. Qualitative side-by-side comparison of dosage forms. A general comparison of several oral dosage forms

Three generic case studies illustrating the framework described above are provided below and demonstrate how the framework may be applied. Although the case studies are based on examples of oral dosage forms, the framework may also be used for dosage forms intended for other routes of delivery. The tool should be used on an individual case-by-case basis and the assessment of each criterion will depend upon the product characteristics and specific medical need, for example indication, patient population, frequency and duration of use.

The criteria have not been weighted or scored in case studies 1 and 2. However, a scoring system has been applied for case study 3 in order to illustrate how this may be done, although it is recognised that other approaches could be used. Each case study is described in further detail below.

3.2. Case study 1

The first example is derived from the scenario whereby an oral paediatric product is required for children in the age range 2–12 years. Oral liquids tend to be preferred by young children. However, children from the age of approximately 6 years can usually take tablets and indeed tablets are generally preferred by adolescents (European Medicines Agency, 2006). Therefore, it is challenging to develop one dosage form that will meet all the patients' needs.

The drug product options are required to meet the following criteria:

- Age of patients is 2–12 years.
- Once daily dosing for the treatment of a chronic condition.
- 14 days supply of medication required.

The product options are the development of two dosage forms; an oral liquid solution (for 2–6 years age group) and a non-dispersible tablet (for 6–12 years age group), or development of one dosage form; a sprinkle, for the entire specified age range (2–12 years) (see Table 3).

3.3. Case study 2

The second example is derived from the scenario whereby an already developed adult immediate release tablet formulation, is to be used for the treatment of adolescents. The adult product contains a film coat with a blue colourant (indigo carmine, E132) and the example evaluates the use of this tablet coating with one containing titanium dioxide (white pigment) (see Table 4)

The drug product is required to meet the following criteria:

- An immediate release tablet to be taken twice a day for the treatment of a chronic condition.
- Age of patients is 12–18 years.
- Same unit dose required for whole age range.

Table 5
Case study 1: two dosage forms versus one dosage form covering the age range 2–12 years.

Benefit/risk	Criterion for drug product	Multiple dose oral liquid containing preservative (150 ml bottle plus syringe)	Single unit dose non-preserved oral liquid (5 ml sachets)
1. Efficacy/ease of use	**1.1 Dosage:** – Dose flexibility – Acceptable dose size/dose volume	Contents sufficient to provide a range of doses	Use of multiple units provides only limited dose flexibility
	1.2 Dose preparation and administration: – Easy and convenient handling – Correct use	Requires use of measuring device	No measuring of dose required by patient–take whole contents of pack
	1.3 **Compliance:** – Minimal impact on life style – Acceptable colour and taste – Minimal administration frequency		Sachet is easily portable
2. Patient Safety	**2.1 Drug substance/drug product:** – Acceptable and consistent bioavailability	No difference	No difference
	2.2 Excipients: – Minimal number and levels needed for acceptable formulation – Acceptable tolerability and safety	Preservative may cause hypersensitivity **Mitigation**: Use minimum amount of preservative required as validated by development studies	
	2.3 Stability: (Chemical/physical/microbial stability in the relevant environments and climates) – Stable during shelf life – Stable in use	Packaging offers protection in case of inappropriate storage by patient.	
	2.4 Dosing precision and accuracy: – Minimal risk of medication error/dosing error – Minimal manipulation by health professionals or caregivers prior to use	Potential for inaccurate measuring of required dose **Mitigation**: Provision of appropriate delivery device and clear instructions in PIL/label	Potential for part of dose to be left in container (especially, if viscous) **Mitigation**: Development work conducted to assess residual volume.
3. Patient Access	**3.1 Manufacturability:** – Robust manufacturing process – Commercial viability	Conventional filling process. Primary pack components are low cost and readily available.	"Clean" manufacture is needed. Specialised sachet filling line is required. High cost may compromise commercial viability.
	3.2 Affordable: – Acceptable cost to patient or health care provider – Easily transported and stored e.g. need for cold chain – Low environmental impact e.g. consider packaging and disposal costs	Glass bottle presentation does not impact significantly on cost to patient. Glass can be readily recycled.	Sachet presentation increases cost to patient. Environmental impact of disposing multiple sachets.
	3.3 Speed: – Easily developed and produced	Depends upon companies experience and facilities	

3.4. Case study 3

The third example is derived from a scenario whereby a paediatric product is required for pre-school age children. It has been proposed to develop an oral liquid since this dosage form is acceptable for children in this age group (European Medicines Agency, 2006).

The drug product is required to meet the following criteria:

- An oral liquid formulation to be administered twice a day for the treatment of a chronic condition.
- Age of patients is 2–6 years.
- Volume per dose is 5 mL.
- 14 days supply of medication required.

The two product options under evaluation are a multiple dose oral liquid, which requires a preservative in the formulation to maintain microbiological quality, and a single unit dose oral liquid (in 5 mL sachets) (see Table 5).

A scoring system was applied to case study 3 for illustrative purposes only, in order to allow a more quantitative evaluation (see Table 6). In this example, the same weighting was applied to each of the criteria, such that access was scored equivalent to efficacy and safety.

In order for the scoring to be conducted, a number of assumptions were made which were based on previous experience. For dosage, although the proposed dose volume is 5 mL, it was considered that the multiple dose oral liquid would provide greater flexibility in dosing than the sachets. In addition, there is a risk of a residual volume of product being left in the sachet after dosing. However, the sachets were considered to be more convenient to use than the multiple dose product and also be slightly more favourable in terms of compliance in that they would be more portable thus improving patient convenience and adherence.

There was no difference between the products in terms of drug substance/drug product as it was assumed that there would be no difference in bioavailability between the two presentations. Importantly, it was assumed that suitable data was available demonstrating the preservative used in the multiple dose product was acceptable from a safety and tolerability perspective for this age range. It is considered from experience with oral liquids that stability and suitable shelf life can be more challenging when the product is packed into a sachet compared to a bottle and hence the multiple dose product scored slightly more favourably. Conversely, the single unit dose was more favourable from a medication error perspective as no measuring operation is required.

In terms of patient access, the multiple dose product was considered to be more favourable than the single unit dose. The filling of liquids into sachets is considered to be technically more difficult and specialised than filling into standard bottles resulting in higher costs. Furthermore, greater quantities of packaging materials are likely to be required, many of which may not be able to be re-cycled. Sachets may also be bulkier than multiple dose bottles and may thus be more difficult to distribute to patients and therefore have an impact on patient access.

Table 6
Score card to evaluate the most appropriate paediatric dosage form.

Scale and criteria for selecting an appropriate drug product		**Score card to evaluate the most appropriate paediatric drug product** (Compound X, Children 2–6 years, chronic treatment at home, volume per dose 5 mL, 14 days supply of medication required)																
1 Equal	Two products contribute **equally** to the objective																	
3 Moderate	Experience and judgement **slightly favours** one product over the other																	
5 Strong	Experience and judgement **strongly favours** one product over the other																	
7 Very strong	One product is strongly favoured and its **dominance demonstrated** in practice	Multiple dose oral liquid containing preservative (150 mL bottle plus syringe)									Single unit dose non-preserved oral liquid (5 mL sachets)							
9 Extreme	The evidence favouring one product over the other is of the **highest possible order** of affirmation																	
2,4,6,8 Intermediate values – compromise is needed																		
Efficacy/ease of use	**Dosage** Dose flexibility Acceptability of dose size/dose volume	9	8	7	6	**5**	4	3	2	1	2	3	4	5	6	7	8	9
	Dose preparation & administration Easy and convenient handling Correct use	9	8	7	6	5	4	3	2	1	2	**3**	4	5	6	7	8	9
	Compliance Minimal impact on lifestyle Acceptable colour and taste Minimal administration frequency	9	8	7	6	5	4	3	2	1	**2**	3	4	5	6	7	8	9
Patient safety	**Drug substance/drug product** Acceptable and consistent bioavailability	9	8	7	6	5	4	3	2	**1**	2	3	4	5	6	7	8	9
	Excipients Minimal number & levels needed for acceptable formulation Acceptable tolerability & safety	9	8	7	6	5	4	3	2	1	2	**3**[a]	4	5	6	7	8	9
	Stability Stable during shelf life Stable in-use	9	8	7	6	5	4	**3**	2	1	2	3	4	5	6	7	8	9
	Medication errors Minimal risk of dosing error	9	8	7	6	5	4	3	2	1	**2**	3	4	5	6	7	8	9
Patient access	**Manufacturability** Robust manufacturing process Commercial viability	9	8	7	6	**5**	4	3	2	1	2	3	4	5	6	7	8	9
	Affordable Acceptable cost to patient or health care provider Easily transported and stored Low environmental impact	9	8	7	6	**5**	4	3	2	1	2	3	4	5	6	7	8	9
	Speed Easily developed and produced	9	8	7	6	5	4	3	**2**	1	2	3	4	5	6	7	8	9

Note: Scores are for illustrative purposes only. Scoring should be made on a case-by-case basis.

[a] Preservative selected considered acceptable for this age group.

It can be seen that multi criteria decision making in this specific setting shows a preference for the multiple dose oral liquid containing preservative. However, if the comparison had not considered patient access, a different outcome would have resulted.

Providing all the formulation and administration details in a real situation together with the clinical setting may well change single criteria as such or in combination which could change the overall calculation and therefore the decision.

4. Discussion

A major difficulty in decision making methods is the inability of the commonly used single attribute utility models to lead to an optimal choice between alternatives. The challenge is that decision alternatives usually differ in several criteria at the same time. Multi-criteria decision making based on pair-wise comparison, using for example an Analytical Hierarchy Process (AHP), is in principle more suitable (Saaty, 1990).

The design and development of dosage forms inevitably involve the balancing of multiple options and can arguably be influenced by specific perceptions and experiences which may favour a formulation strategy that is familiar to the formulator. The use of the pre-defined assessment framework presented in this paper may be helpful for an objective comparison of different formulation and dosage form options; their relative benefits, risks and possible mitigation strategies.

In each of the three theoretical case studies above, it was clear that no single dosage form option held an advantage over an alternative formulation approach for every criterion considered. Indeed, each of the dosage form approaches had their own advantages and disadvantages to consider.

Using case study 3, we illustrated the use of a comparative scoring system, to show how an objective, quantitative approach could be applied to determine a preferred formulation decision.

It is important to emphasise that the qualitative comparisons (and quantitative comparison in case study 3) of the different theoretical examples, does not indicate an outcome that would prevail in every real-life scenario. For example, readers should not draw the conclusion that a multi-use, preserved formulation would always be preferred over a single use, non-preserved presentation.

In a real research and development scenario, pharmaceutical development data, consultation of patients, clinicians, caregivers, pharmacists and regulators would all add valuable information to aid and support a formulation/dosage form choice. This additional information might impact the scoring and therefore also the weighting applied for different criteria and hence the outcome of the decision-making exercise.

5. Conclusion

In conclusion, the key value of this benefit/risk framework is that it enables a systematic, qualitative comparison of the advantages and disadvantages of different dosage form options using a holistic consideration of overall patient need. The exercise can encourage objective discussion and provide transparency to factors determining the selection of a particular formulation and dosage form above other possibilities.

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