Position statement 2020-01
Choosing an Oral Liquid Medicine for Children

Take Home Summary

Pharmacists have a professional responsibility to ensure any medicine is suitable for the patient. If the pharmacist has concerns as to the appropriateness of a particular product, they should discuss these with the prescriber. This is especially true for unlicensed medicines, medicines used "off-label" and those prepared extemporaneously. It may be necessary to review the formulation of different products to ensure that the most suitable one is supplied.

When choosing an oral liquid medicine for a child, the following must be considered:

1. Excipient content, including quantity and suitability.
2. Cumulative daily excipient intake from all products being taken.
3. Potential adverse effects due to excipients.
4. The risk-benefit analysis of using an unlicensed product vs. a licensed product
5. The concentration of the product and the dose volume. Ideally the dosing volume should not be less than 0.2mL or more than 10mL, though it may be necessary to administer smaller volumes within neonatal critical care. Where smaller volumes are required, consideration should be given to how these can be safely administered to minimise the potential for error.
6. Any local agreement on use of standard concentrations, in both Primary and Secondary care.

Excipients

Excipients are a necessary component of almost all medicines, but they may be present in quantities which are potentially harmful to babies and children. Excipients can rarely be completely avoided, and professional judgment is required to balance competing risks. A product containing a small amount of ethanol, for example, may be preferable to an ethanol-free product that is less suitable in other ways (e.g. lower assurance of quality, a large quantity of sorbitol or other problem excipient, or concentration.)

Advice on specific excipients is given in Table 1, and worked examples of how to calculate and evaluate excipient contents of liquid medicines are presented on page 5. However, it should be noted that safe limits are not always described for children and so some data has been extrapolated from food standards or adult limits. Alternatively, European Medicines Agency (EMA) recommendations for labelling limits may have been used as an indicator of safety (where safety studies may not have been formally conducted). The STEP Database provides a comprehensive summary of the published literature on a range of pharmaceutical excipients.

Consideration should also be given to the carbohydrate content of medicines in patients who have been diagnosed with congenital metabolic disorders or who are on a ketogenic diet.

Table 1: Recommendations on Specific Excipients *(see also notes below table).*

<table>
<tr><th>Excipient</th><th>Examples of Potential Effects</th><th>Recommendation</th></tr>
<tr><td>Propylene Glycol

(see also notes below).</td><td>CNS depression, especially in neonates and young children. Hyperosmolality, metabolic acidosis and renal impairment[1,2].</td><td>
<table>
<tr><th>Age</th><th>Max. daily dose[1,2]</th></tr>
<tr><td>≤ 28 days (or 44 weeks post-menstrual age)</td><td>1mg/kg</td></tr>
<tr><td>1 month – 4 years</td><td>50mg/kg</td></tr>
<tr><td>5 – 17 years</td><td>500mg/kg</td></tr>
</table>
</td></tr>
<tr><td>Ethanol

(see also notes below).</td><td>Drowsiness, behavioural changes, impaired concentration, ataxia. Hypothermia and hypoglycaemia, especially in children[3,4].</td><td>
<table>
<tr><th>Ethanol Intake per dose of medicine</th><th>Recommendation[4]</th></tr>
<tr><td><15mg/kg/dose</td><td>Will not have noticeable effects; product safe to use.</td></tr>
<tr><td>15 – 75mg/kg/ dose</td><td>Unlikely to affect adults and adolescents. Effects in children unlikely to be noticeable, though more likely in younger children. Consider alternative licensed products to minimise exposure; use of an unlicensed product not justified.</td></tr>
<tr><td>> 75mg/kg/dose</td><td>Likely to affect children. Use an alternative licensed product to minimise exposure where available; or an unlicensed product if no suitable licensed alternative.</td></tr>
</table>
</td></tr>
<tr><td>Sorbitol</td><td>Osmotic diarrhoea, gastrointestinal discomfort. Reduction in absorption of other medicines administered orally concurrently[5].</td><td>Daily intake exceeding 140mg/kg/day is more likely to cause gastrointestinal symptoms[5].
Sorbitol is metabolised to fructose and is, therefore, unsuitable for patients with hereditary fructose intolerance[5].</td></tr>
<tr><td>Sucrose</td><td>Dental caries[6].</td><td>Hydrolysed in the intestine to fructose and glucose; avoid in hereditary fructose intolerance[6].
Short-term exposure via medicines (e.g. a 7-day antibiotic course) unlikely to be problematic in most cases. For long-term therapy sugar-free preparations are preferred.
In diabetic patients, ingestion of amounts under 5g per dose of medicine unlikely to affect blood sugar control significantly[7].</td></tr>
<tr><td rowspan="2">Aspartame and saccharin</td><td>Generally considered safe, but avoid aspartame in phenylketonuria (PKU)[8].</td><td>Acceptable intakes for the general population are 40mg/kg/day[8] for aspartame and 5mg/kg/day[9] for saccharin.</td></tr>
<tr><td colspan="2">Notes: 1) the limit for saccharin is extrapolated from the food industry as no pharmaceutical recommendations are available; 2) the stated limit for aspartame does not apply under 12 weeks of age – no recommendation can be made for this age group[8].</td></tr>
<tr><td>Parabens (methyl-, ethyl- and propyl-hydroxybenzoates)</td><td>Hypersensitivity reactions and hyperbilirubinaemia in neonates (most common with IV use). Oestrogenic and reproductive effects with propyl-hydroxybenzoates[10].</td><td>Acceptable daily combined intake for methyl- and ethy-hydroxybenzoates is 10mg/kg/day[11].
Maximum acceptable daily propyl-hydroxybenzoate intake is 2mg/kg/day[11].</td></tr>
<tr><td>Benzoic Acid / Benzoates</td><td>Displacement of bilirubin from albumin, leading to hyperbilirubinaemia, particularly in neonates[12].</td><td>Acceptable daily intake up to 5mg/kg for children over 4 weeks of age[13]. No recommendations have been found for neonates: though extreme caution advised, especially in known unconjugated hyperbilirubinaemia.</td></tr>
<tr><td>Azo Dyes</td><td colspan="2">Currently no Acceptable Daily Intakes (ADIs) or thresholds are stipulated for azo dyes (colourings) in medicines, however, ADIs are specified when used as food additives[14]. Allergic reactions to azo dyes can occur irrespective of the levels and so medicines containing azo dyes should be avoided in those with known allergies to these colourants. Examples include: Tartrazine (E 102); Sunset yellow FCF (E 110); Azorubine, carmoisine (E 122); Amaranth (E 123); Ponceau 4R, cochineal Red A (E 124); Brilliant black BN, black PN (E 151).</td></tr>
</table>

Notes: 1) in choosing a product, consider the cumulative daily excipient intake for **all** medicines taken by the patient;
2) both ethanol and propylene glycol are substrates of alcohol dehydrogenase, and so there is the potential for accumulation when both are ingested concurrently or repeatedly, especially in young children with low or immature metabolic capacity.

Professional Responsibility

Pharmacists have a professional responsibility to ensure the safety and quality of medicines supplied to patients under their care and that medicines are suitable for each patient[15]. This is clearly formalised in relation to unlicensed medicines and medicines used outside of their Marketing Authorisation[16, 17].

Excipients: Challenges and Considerations

Pharmaceutical excipients are required for a range of reasons including improving solubility, absorption and palatability, and the prolongation of product shelf-life. Whilst they are a necessary component of most medicines, they may be harmful to babies and children. In many cases liquids licensed for use only in adults are used off-label in children, and although safe maximum limits for excipients exist for adults, they may be higher than the recommended threshold for children. However, a paediatric licence does not always indicate suitability. There are examples of older products licensed specifically for children which are unsuitable for use in this population due to excipient content. Careful consideration of excipient content is therefore necessary when selecting an appropriate oral liquid product for neonates and children.

For some drugs, an unlicensed medicine may contain fewer undesirable excipients or excipients at lower levels than the licensed product. However, the quality, safety and efficacy of unlicensed medicines must be assessed by the purchaser and prescriber. In addition, unlicensed oral liquid medicines may not be available in standard concentrations, leading to the risk of confusion and dosing error. They can be challenging to obtain, especially in Primary Care, and tend to have shorter shelf lives and a higher acquisition cost than licensed products. Despite these issues, there will be occasions where the risk-benefit assessment suggests that an unlicensed medicine is the most appropriate choice for an individual patient, but the risks associated with this option need to be carefully balanced against those arising from exposure to excipients in licensed products. The Royal Pharmaceutical Society's *Professional Guidance for the Procurement and Supply of Specials* should be followed[16]. This clearly identifies the requirement to consider licensed alternatives before supplying an unlicensed medicine.

Where after due consideration, a decision has been made to use a product which will expose a patient to an excipient above recommended levels, the pharmacist must highlight this to the prescriber and agree with them the importance of regular review to ensure that any issues are promptly identified and appropriately managed.

The Medicines for Children website has a helpful patient information sheet entitled *Excipients in Children's Medicines*. The website also has a range of drug-specific patient information sheets, which may help provide further information.

Where to Find Information on the Excipient Content of Medicines

The Summary of Product Characteristics (SmPC) lists the excipients in each medicine although it is not always fully quantified. Patient Information Leaflets (PILs) and "product inserts" sometimes provide more detail of quantities, especially in relation to ethanol. SmPCs and PILs for most licensed products in the UK can be found in the Electronic Medicines Compendium (eMC) at: https://www.medicines.org.uk/emc . Where a licensed product is not listed on the eMC, it may be found on the Medicines and Healthcare Products Regulatory Agency (MHRA) website: https://products.mhra.gov.uk/.

If excipient quantities are not given in the SmPC or PIL, the manufacturer's Medicines Information (MI) Department may be consulted: contact details are available via the eMC and the British National Formulary. Alternatively, a local hospital MI department may give advice on suitable formulations.

Ethanol and propylene glycol are often components of flavouring agents. In general, where this is the ***only*** source of these excipients in a product, the quantities are not a concern. Equally, "Ethanol 96%" is sometimes listed as an excipient. This refers to the raw ingredient added rather than the quantity of ethanol in the final product, though the quantity of raw ingredient can still be significant and so further investigation is needed.

Using Standardised Concentrations of Active Ingredient(s)

Every year harm is caused by accidental under- and overdosing of medicines in children solely because the concentration of their liquid medicine changed when a new prescription or supply of medication was issued and the person administering the medicine did not realise the volume given needed to change. Standardising concentrations is key to preventing such incidents.

A study defined the most suitable concentration for 20 liquid special medications for children through expert Delphi review[18]. This concluded that dose volume should not be less than 0.2mL or more than 10mL. If these criteria cannot be met, dose volumes should be greater than 0.1mL but under 20mL. Smaller dose volumes may be necessary for inpatients in Neonatal Critical Care, but can usually be avoided once the patient is discharged.

General decisions about which products to use within a particular hospital or primary care setting should involve all relevant partner organisations so that practice is standardised across the locality. To ensure patient safety and continuity of care, use of a single concentration for each therapeutic agent across a healthcare system is advised wherever possible . A list of standard concentrations for selected unlicensed oral liquids has been published in the NPPG Position Statement *Using Standardised Concentrations of Unlicensed Liquid Medicines in Children*.

Special Considerations for Patients with Inherited Metabolic Disorders and those on a Ketogenic Diet

The carbohydrate content or calorific load arising from excipients in oral medicines can have a significant effect on patients with inherited metabolic diseases and those on a ketogenic diet[19]. This extends beyond simple sugars such as sucrose to include ethanol and artificial sweeteners such as sorbitol. Extra care is required for these patients, and consultation with a specialist Paediatric Pharmacist or NHS MI department is recommended.

Examples of how to Calculate the Amount of Ethanol a Patient would receive[20].

(Information on ethanol content of a medicine is usually expressed in terms of % v/v. This can be converted to % w/v using the specific gravity of ethanol, which is 0.789 [rounded to 0.8]).

1) Phenobarbital Elixir BP (15mg/5mL) contains 38% v/v ethanol. Using the specific gravity of ethanol, this corresponds to a concentration of around 30.4% w/v.

   The maintenance dose of phenobarbital is 2.5–4 mg/kg, once or twice a day for epilepsy in children aged 1 month - 11 years. Using the lowest dose, a 3 year old child weighing 14kg would receive 35mg of phenobarbital daily (11.7mL of Phenobarbital Elixir).

   With an ethanol concentration of 30.4% w/v, there is 30.4g of ethanol in 100mL of elixir.

   This is equivalent to 0.304g ethanol in 1mL, and 3.55g (3550mg) ethanol in 11.7mL of oral solution.

   This equates to 3550mg / 14kg = 254mg/kg of ethanol per 11.7mL dose.

   This is over the 75mg/mg/dose threshold, meaning that an alternative product must be used. For phenobarbital, there is no alternative licensed product, so use of an unlicensed medicine may be justified.

   As a result, recommended practice in the UK is to use an ethanol-free unlicensed 50mg in 5mL liquid for the oral administration of phenobarbital to children.

2) Furosemide Oral Solution (20mg/5mL and 50mg/5mL) contains 8% w/v ethanol.

   1 mg/kg twice daily is a typical maintenance dose for children under 6 months of age. For a 5kg child, this equates to 5mg twice daily.

   With an ethanol concentration of approximately 8% w/v, there is 8g of ethanol in 100mL of oral solution. This is equivalent to 0.08g (80mg) ethanol in 1mL of oral solution, independent of furosemide concentration.

   Using 1.25mL of 20mg/5mL liquid for the 5mg dose gives (1.25mL x 80mg / 5kg) = 20mg/kg ethanol per dose.

   Using 0.5mL of 50mg/5mL liquid for the 5mg dose gives (0.5mL x 80mg / 5kg) = 8mg/kg ethanol per dose.

   Ethanol exposure per dose using the 20mg in 5mL solution exceeds the 15mg/kg/dose threshold and so a licensed alternative should be considered. Using the 50mg in 5mL solution, the 15mg/kg/dose threshold is not breached; it may therefore be considered a suitable alternative licensed product.

Example of how to Calculate the Amount of Propylene Glycol (PG) a Patient would receive[20].

(*Where the manufacturer states the amount of PG in mL/mL of product (or % v/v), it is first necessary to convert to % w/v using the specific gravity of PG, which is 1.036 (i.e. 1mL weighs 1.036g).*

An amiloride 5mg/5mL oral solution contains 0.1mL PG per 5mL of solution = 2% v/v concentration. Using the specific gravity of PG, a concentration of 2% v/v corresponds to 2.07% w/v (2mL/100mL x 1.036 = 2.07g/100mL).

The dose of amiloride for a neonate is 100–200microgram/kg twice daily.

Using the lowest dose, a neonate weighing 3.5kg would receive 350 micrograms twice daily (i.e. 700 micrograms per day), which corresponds to 0.7mL of the oral solution daily.

With a PG concentration of 2.07% w/v, there is 2070mg PG in 100mL of the oral solution.

This is equivalent to 2.07mg PG in 0.1mL, and 14.49mg PG in 0.7mL of oral solution.

The patient's daily intake of PG would therefore be 14.49mg, or 4.14mg/kg.

This exceeds the maximum recommended dose of 1mg/kg/day of PG for a neonate, making the product unsuitable for this age group. An alternative formulation or drug (e.g. spironolactone) should be considered. However, the product may be suitable for a patient over 28 days (or 44 weeks post-menstrual age), due the higher maximum daily intake for this age group.

References:

1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Report published in support of the 'Questions and answers on propylene glycol used as an excipient in medicinal products for human use'(CHMP/704195/2013)"* (EMA/CHMP/334655/2013); October 2017. Available at: http://www.ema.europa.eu/en/documents/report/propylene-glycol-used-excipient-report-published-support-questions-answers-propylene-glycol-used_en.pdf .
2. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Background review for the excipient propylene glycol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medical products for human use'* (CPMP/463/00 Rev. 1) Draft; Nov 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177937.pdf .
3. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Questions and answers on ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medical products for human use'* (CPMP/463/00) Draft; Jan 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162033.pdf .
4. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use* (EMA/CHMP/43486/2018); September 2018. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-ethanol-used-excipient-medicinal-products-human-use_en.pdf .
5. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use* (EMA/CHMP/460886/2014); October 2017. Available at: https://www.ema.europa.eu/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products_en.pdf .
6. *Sucrose*. In: Sweetman S (ed). Martindale: The Complete Drug Reference London: The Royal Pharmaceutical Society, London. Available at: https://www.medicinescomplete.com/#/ (accessed Nov 2020).
7. Personal communication. Dr T Randell. Consultant Paediatric Endocrinologist. Nottingham University Hospitals NHS Trust. June 2020.
8. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Information for the package leaflet regarding aspartame and phenylalanine used as excipients in medicinal products for human use* (EMA/CHMP/134648/2015 corr. 1*); October 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-aspartame-phenylalanine-used-excipients-medicinal-products_en.pdf .
9. European Commission, Scientific Committee for Food: *Opinion on Saccharin and its sodium, potassium and calcium salts* (CS/ADD/EDUL/148-FINAL); February 1997. Available at: https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_7_out26_en.pdf .
10. *Hydroxybenzoates*. In: Sweetman S (ed). Martindale: The Complete Drug Reference London: The Royal Pharmaceutical Society, London. Available at: https://www.medicinescomplete.com/#/ (accessed Nov 2020).
11. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use* (EMA/CHMP/SWP/272921/2012); October 2015. Available at https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-use-methyl-propylparaben-excipients-human-medicinal-products-oral-use_en.pdf .
12. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use* (EMA/CHMP/508189/2013); October 2017. Available at: https://www.ema.europa.eu/documents/scientific-guideline/questions-answers-benzoic-acid-benzoates-used-excipients-medicinal-products-human-use_en.pdf .
13. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): *Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use* (EMA/CHMP/508188/2013); October 2017. Available at: https://www.ema.europa.eu/documents/scientific-guideline/questions-answers-benzyl-alcohol-used-excipient-medicinal-products-human-use_en.pdf .
14. European Commission. *Report from the commission on Dietary Food Additive Intake in the European Union; October* 2001. Available at: https://op.europa.eu/en/publication-detail/-/publication/26105dba-6d8f-4515-a641-0e43fe3f5498/language-en
15. General Pharmaceutical Council, UK. *What does a Pharmacist do?* https://www.pharmacyregulation.org/raising-concerns/raising-concerns-about-pharmacy-professional/what-expect-your-pharmacy/what-does-0 .
16. Royal Pharmaceutical Society, UK. *Professional Guidance for the Procurement and Supply of Specials*. December 2015. Available at: https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/toolkit/specials-professional-guidance.pdf
17. General Pharmaceutical Council, UK. *Guidance for registered pharmacies preparing unlicensed medicines.* August 2018. Available at: https://www.pharmacyregulation.org/sites/default/files/document/guidance_for_registered_pharmacies_preparing_unlicensed_medicines_august_2018_0.pdf .
18. Rawlence E et al. *Is the provision of paediatric oral liquid medicines safe?* Arch Dis Child Educ Pract Ed. 2018;103(6):310-3.
19. McArtney R et al. *What is a ketogenic diet and how does it affect the use of medicines?* Arch Dis Child Educ Pract Ed. 2017; 102:194-9.
20. Arthur S et al. *How to identify and manage 'problem' excipients in medicines for children*. Pharm J. 2017; 299 :42-45.

Disclaimer

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Appendix 1- Checklist for Assessing Suitability of a Product for Children

- ☑ Ideally the product concentration should not require families at home to measure dose volumes less than 0.2mL. Lower volumes may be unavoidable for inpatients, particularly in Neonatal Critical Care. Where smaller volumes are required, consideration should be given to how these can be safely administered to minimise the potential for error.

- ☑ Ideally the product concentration should result in a dose volume of 10mL or less, though up to 20mL may be necessary in some cases.

- ☑ Ideally the excipient intake should not exceed the limits stated in Table 1. This may require consideration of different products from a range of manufacturers. Alternative drugs which are available in a more suitable formulation should also be considered.

- ☑ Where it is not possible to avoid excipient quantities above the recommended maximum levels, the relevant members of the healthcare team need to be aware of the risks and review the patient should any issues arise.

- ☑ Using an unlicensed medicine to reduce excipient exposure must be balanced against the risks of using an unlicensed product. A decision to select an unlicensed product over a licensed product should be taken only after discussion with the prescriber and a specialist Children's Pharmacist.

- ☑ Continuity of product concentration for an individual patient should be maintained wherever possible in order to avoid potential confusion.

- ☑ Refer to local formularies where these exist.

- ☑ When making formulary decisions for a specific geographical area, a single concentration of medicine should be agreed wherever possible, liaising with partner organisations within the local healthcare system.