Table 2
Factors to consider in the choice of excipients.

- Safety profile of the excipient for children of the intended age group(s)
- Route of administration
- Single and daily dose of the excipient
- Duration of the treatment
- Acceptability for the intended paediatric population
- Potential alternatives
- Regulatory status in the intended market

for the choice of excipients. In the formulation of paediatric medicines, the number of excipients and their level in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations to support quality.

Potential alternatives to excipients posing a significant risk should always be considered. Another formulation or even route of administration might be necessary to avoid significant risk. In addition, alternative excipients may need to be considered because of different cultural or religious reasons, e.g. the use of gelatin may not be acceptable for all patients.

General guidance regarding safety of some types of excipients are included in the "points to consider" document, namely coloring agents, antimicrobial preservatives, sweetening agents, taste masking agents and solubility enhancers.

Quality attributes of paediatric medicines do not differ from those of adult medicines. The WHO guidance document makes therefore reference to current quality guidelines and pharmacopoeias, for example ICH guidelines on the acceptable level of impurities in APIs and degradation products in finished dosage forms. The WHO's experts' viewpoint is that safety margins established during toxicological studies apply to both adults and children; although a child would receive a lesser dose, the exposure per kg is likely to be similar. Term and pre-term neonates have however to be considered specifically. With regard to dissolution testing, dissolution media prescribed or recommended in pharmacopoeias should be carefully re-considered in view of the different gastric pH of the child.

Container-closure systems for paediatric medicines are designed and constructed of materials meeting relevant regulatory requirements and taking into account the stability of the medicines during storage, transport and use. In addition, they are designed with a view to accurate dosing and convenient administration, robust and convenient for the supply chain and tailored to the target age group. The packaging should provide information on the use of the medicine as adequate information about the medicine and its use, are highly important. Drawings or pictograms showing time, method and route of administration are strongly recommended. In cases where the paediatric medicine is significantly different from a similar adult medicine, it would be important to have the product packaging be noticeably different between the two products.

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International initiatives on extemporaneous dispensing☆

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Extemporaneous compounding is important to paediatric practice to allow the provision of age-appropriate dosage forms when appropriate authorised medicines are not available. In resource-poor countries even common medicines such as oral paracetamol liquid may be compounded because access to priority medicines from the WHO Essential Medicines List for children is not assured. The process of compounding is not without danger and there may be alternative strategies such as dose-rounding, therapeutic substitution or manipulation of 'adult' dosage forms so that compounding is a last resort. WHO has commissioned literature review and guidance to better inform practitioners on the risks and the alternatives. The preparation of the guidance is briefly reviewed and recommendations for further action are presented.

Extemporaneous dispensing or compounding is considered an important practice by paediatric pharmacists in Europe and North America which enables the provision of age-appropriate formulations (often oral liquids) when no authorised preparation is available. Pharmaceutical manufacturers have an interest in the practice to substitute for manufactured products in clinical trials or when manufacturing is difficult or costly. Regulators have concerns about the quality of product produced by extemporaneous dispensing and with bioavailability. There are few standards for extemporaneous dispensing in European countries but, with a recent resolution, the European Council will seek to avoid quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial scale (Committee of Ministers, 2011).

Many resource-poor countries will use the World Health Organization (WHO) Essential Medicines List for children as the starting point for a national list of medicines to be made available. Additional information on the drugs, doses and dosage forms is provided in the WHO Model Formulary for Children (WHO, 2010) but not all age-appropriate dosage forms are listed and many will only be available in certain countries. Little is known about extemporaneous dispensing in resource-poor countries but there is evidence of lack of access to many essential medicines especially age-appropriate preparations for children (Robertson et al., 2009). 70% of 475 information requests concerning compounded preparations concerned medicines available in other markets with Quinine, prednisone and rifampin the most frequently requested specific drugs (Woods, 2010). A meeting of WHO representatives from Anglophone African countries identified extemporaneous dispens-

☆ *Disclaimer*: Views expressed are those of the authors and not of their employers or organisations mentioned in this paper.

ing as an important practice (WHO, 2009) and a survey by the Commonwealth Pharmacy Association (Farwell; personal communication) suggested that the practice is extensive and that many of the medicines prepared (55% of the 60 preparations identified) are commonly available as authorised age-appropriate preparations in Europe (e.g. ciprofloxacin, digoxin, furosemide, paracetamol oral liquids), but that many priority medicines e.g. for tuberculosis and malaria (isoniazid, quinine oral liquids) are also prepared extemporaneously. There is literature evidence of medication error during extemporaneous dispensing or small scale batch preparation which has resulted in the deaths and injury of many children (Choonara, 2008). During the H1N1 pandemic of 2009/10 it was noted that most resource-poor countries would not have access to the ingredients to prepare an extemporaneous preparation of oseltamivir oral liquid as approved in the label or marketing authorisation of Tamiflu™ (Roche).

Following a meeting between representatives of WHO and UNICEF and invited experts to review the situation, WHO commissioned a literature review and development of a guideline on extemporaneous dispensing in resource-poor countries (UNICEF, 2010). A draft of the information was considered by the WHO Essential Medicines Committee (WHO, 2011c) and concern was expressed about

- risks of inappropriate preparations
- risks of diverting efforts aimed at the development of age-appropriate dosage forms for children (and indicated that WHO endorsement of extemporaneous use should not be seen as indicating a lack of need for commercially available paediatric dosage forms)
- potentially conflicting signals arising from a WHO publication that might appear to endorse wider use of manipulation of adult dosage forms for children.

Notwithstanding these concerns the Committee agreed 'that the document should be finalised for publication as a time-limited guidance that addresses the current need for advice'. The Committee recommended that the final document be considered by the WHO Expert Committee on the Specification of Pharmaceuticals. A 'final draft' was first considered by a WHO informal consultation on paediatrics and generics guidelines development and the guidance was retitled to reflect a lack of consensus on the meaning of 'extemporaneous dispensing' and the nature of the document being 'points to consider' rather than 'guidelines' (WHO, 2011a). The literature review was developed as a resource to support the 'points to consider' document and to provide illustrative scenarios to assist in understanding how 'extemporaneous' dispensing might be avoided WHO, 2011b). Relevant documents have been made available for consultation on the WHO website until September 2011.

The main theme of the 'points to consider' document and the literature review is that extemporaneous dispensing or compounding should be undertaken as a last resort. The practice can be avoided if health professionals work together to ensure that commercial age-appropriate dosage forms are available whenever possible, that prescribers are aware of the dosage forms available locally, that prescribing is rationalised and therapeutic substitution and dose rounding take place as necessary. Pragmatically however, it is recognised that for many years this 'ideal' situation will not be achieved and that advice and education on manipulation of dosage forms to provide accurate (smaller) doses for children and on compounding will be required. The pharmaceutical industry can assist by providing affordable paediatric dosage forms but also by validating manipulation and compounding from their 'adult' dosage forms if appropriate. Ideally formulations using suspending agents that can be readily sourced locally should be investigated and further research is required to produce an affordable, generic suspending base that could be used with the majority of essential medicines. If this could be produced in dry powder form shipping costs could be reduced and it might be reconstituted locally. In reviewing the literature and developing their guidance the authors produced a series of recommendations shown in Table 1.

As the Essential Medicines Committee rightly pointed out, the main requirement is for the pharmaceutical industry to produce, authorise and make available firstly medicines on the WHO list of priority medicines for mothers and children (WHO, 2011d) and then to address the essential medicines list for children. In many so-called westernised countries children continue to be 'therapeutic orphans' (Shirkey, 1968) because age-appropriate dosage forms authorised for age and indication are still not available. US and EU legislation is beginning to address the issue but in many resource poor countries we still fail to make available even basic, life-saving medicines in forms that children can take.

Table 1
Recommendations.

Recommendation:
Organisations such as WHO and UNICEF have an important role to play in helping ensure that medicines on the paediatric priority list are available at affordable prices in all countries and that information is provided on the availability and price of all age-appropriate dosage forms on the Essential Medicines List for Children.
There should be a systematic review of drugs and dosage forms and guidance prepared on common therapeutic substitutions that might be investigated for children.
WHO should ensure that the model formulary for children contains information on those drugs for which dose rounding may be appropriate and educates practitioners.
WHO should encourage manufacturers to investigate and provide information on all paediatric uses of medicines whether authorised or not.
WHO should encourage paediatric centres to establish links and share relevant information.
WHO should review the guidance to be published by the MODRIC research group on manipulation of dosage forms and consider adding it to this guideline.
WHO/UNICEF should consider which tablets are most frequently manipulated to achieve accurate, smaller doses for children and seek assurances from manufacturers.
Information should be generated on medicines that can or cannot be dispersed in liquid so that an accurate dose can be obtained by measuring a proportion. Such information should be included in the model formulary for children.
WHO should seek to produce a list of excipients and safe exposure limits for babies, infants and children and a list of extemporaneous formulations of common medicines that contain a minimum of excipients.
WHO should take steps to standardise common extemporaneous preparations to formulae for which there is good quality, efficacy and stability data and promote this information to improve current practice.
Minimum pharmaceutical standards for extemporaneous dispensing should be produced.
Awareness of the potential problems when extemporaneously dispensing should be promoted and education and training arranged so that risk can be reduced.
Development and supply of a universal generic suspending base similar to the large scale bases already available should be promoted.
Stability studies in the above base should be commissioned with a focus on medicines most frequently required in developing countries.
A dry powder or granule suspending agent that can easily be mixed with good quality water to provide a palatable suspension of a range of commonly used medicines should be developed.
An educational package on medicines administration for children and the use of age appropriate formulations, including preparation principles and basic GMP should be developed. The package should be delivered via a range of formats from hard copy to an e-Learning module on the internet.
This training package should be aimed at a multidisciplinary audience (physicians, nurses, pharmacists) and focus on safe and effective strategies in the preparation and administration of medicines for children.
The development of an international question and answer database and responsive information service on formulation, administration and related issues which will promote the sharing of information, problem solving, best practice and educational awareness. This will also help to identify research projects that can be directed toward academia and industry.

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Assessing taste without using humans: Rat brief access aversion model and electronic tongue

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There is a growing body of evidence to suggest that the organoleptic properties of a formulation (taste, smell, mouthfeel, etc.) are important determinants of patient concordance with treatment regimens (American Academy of Pediatrics, 2000; Griffith, 1990). Non concordance can have a significant effect on treatment outcomes since if a medicine is not taken it cannot exert its therapeutic effect.

The issue of unpleasant taste is particularly important for paediatric patients and for formulations where taste masking is difficult (or impossible) such as liquid dosage forms of highly soluble drug substances or those to be delivered via intra nasal or inhaled route. A survey on the burden of allergic rhinitis in American children (Meltzer et al., 2009) quotes poor taste as the second most commonly cited reason (43.7%) for patients ceasing to use their intranasal treatment for rhinitis. Similarly studies of patients using inhaled corticosteroid therapy showed that treatment compliance is often poor; poor taste affected 80% of the patients and that of all factors analysed, unpleasant taste score was most significantly different between patients of high adherence compared with medium and low adherence groups (Creer and Levstek, 1996; Harding and Modell, 1985; Milgrom et al., 1996). As well as an indirect effect on therapeutic efficacy via non compliance, there is some evidence (Shah et al., 2009) that cilia in the respiratory tract express bitterness receptors and beat faster in the presence of bitter compounds leading to faster clearance and hence a potential direct reduction in the therapeutic effect.

Generally poor taste does not become obvious until early clinical studies. If the taste is noticeable then it may unblind these studies, whilst if it is strongly aversive then it may be necessary to find a different salt of the API with better taste characteristics, or even to seek an alternative candidate. This will incur considerable delay in providing an improved treatment to patients, necessitate additional animal toxicology studies, and potentially add considerable cost to the developer.

Thus it would be very valuable to be able to screen molecules and/or salt forms early in development (preferably at the pre candidate stage) to enable the optimum molecule and/or form to be selected for further development. To undertake this in humans would require comprehensive toxicology cover, or microdosing at levels unrelated to final therapeutic doses and unlikely to yield any useful taste data. Obviously it would not be possible to perform such human studies early enough in development for them to be useful in selecting the candidate.

A number of methods have been proposed to screen the aversivness of API's and their formulations. Since these models require the compound to be in solution for testing they cannot address issues such as mouthfeel but can give valuable insights into other aspects of aversivness. These include in silico predictions (so far with limited success), in vitro methods (such as e-tongue), cell based assays (generally specific to bitterness rather than aversivness per se), isolated tongue models (limited life) and whole animal models (such as the rat brief access taste aversion [BATA] model). The presentation discusses the merits of each of these approaches concentrating on the e-tongue and rat models.

In order for the data from any of these methods to be helpful to the pharmaceutical scientist it is vital that they be predictive of the human taste response. We have undertaken a study to quantify the human, rat and e-tongue response to 9 compounds covering a wide range of chemical types and bitterness intensity. The compounds studied are presented in Table 1.

Each was assessed by a trained human sensory panel ($n = 15$ [2 males + 13 females, average age 45 years]) in a 'rinse and spit' study design at concentrations chosen to cover the expected range of bitterness from low/moderate to high at a range of molarities in quarter log steps. The panel scored the bitterness on an anchored 7 point scale. The bitterness was then converted to a % bitterness score. Samples were assessed during 9 sensory sessions. A single 'calibration' concentration of quinine was used in each session to ensure that data remained consistent between sessions.

The same compounds were also assessed using the BATA model and a new electronic tongue that is currently under development.

Table 1
Compounds studied and their use.

Compound	Use
Quinine HCl[a]	Anti malarial – bitterness standard
Chlorhexidine di gluconate	Antibacterial – mouthwash
Azelastine HCl	Rhinitis
Naratriptan HCl	Migraine headaches
Sumatriptan succinate	Migraine headaches
TegoBetaine	Surfactant – toothpaste ingredient
Caffeine	Stimulant – bitterness standard
Paracetamol	Analgesic/antipyretic
Potassium nitrate	Toothpaste ingredient

[a] A single concentration of 2.0×10^{-3} g/l defined as 'moderate bitterness' was used as a control to calibrate the panelist's responses in all studies.