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Review

Preparation of medicines for children – A hierarchy of classification

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This paper is dedicated to the memory of the late John Hempenstall (formerly of GlaxoSmithKline).

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ABSTRACT

There is some confusion about the types of paediatric pharmaceutical preparation (in a regulatory and pharmaceutical development context) that are acceptable for approval by medicines regulators. Some of the confusion relates to terminology which may mean different things to different stakeholders.

It may not always be possible to provide authorised, commercially manufactured, age appropriate, ready-to-administer preparations. In terms of assurance of quality and bioavailability there is a continuum from this ideal through intermediate products through authorised compounding and manipulation of commercial dosage forms to ad hoc compounding using only the skills and experience of the individual pharmacist. Additionally, it is widely known that caregivers may manipulate medicines at home, for example by segmenting tablets and by addition to foods or liquids.

The first intent of the manufacturer should be to provide for children an age appropriate, ready-to-administer preparation which is commercially manufactured and approved by the competent authorities. However, there will still be a place for providing other age appropriate preparations such as approved products that are 'intermediates' requiring reconstitution before use, or instructions for compounding or manipulation of a dosage form. If compounding or manipulation is likely to be required it is preferable that data are generated by Industry, approved by the competent authorities and provided in the Summary of Product Characteristics (SmPC). It is acknowledged however, that ad hoc compounding or manipulation may also take place in certain circumstances such as logistical difficulties or to satisfy the needs of the child who does not find the authorised product to be 'age appropriate'.

This paper explores compounding and manipulation of medicines in relation to approval by medicines regulators and non-approved preparation to fulfil the needs of the individual patient. Definitions are proposed to provide a hierarchical classification based on assurances of quality and bioavailability.

Contents

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1. Introduction

For many years children have been described as 'therapeutic orphans' (Shirkey, 1968) to indicate that medicines research, regulation and formulation development has mainly focused on disease in adults. Consequently, there has been significant 'off-label' use of medicines (Mason et al., 2011) frequently meaning that dosage forms designed for adults have had to be modified for administration to children – by pharmacists preparing a suitable unlicensed medicine or by manipulation of the dosage form at the point of administration e.g. segmenting tablets; cutting transdermal patches (Nunn, 2003).

In January 2007 the European paediatric regulation (EMA, 2007), came into force, requiring (and rewarding) manufacturers to study their medicines in children along agreed timelines if they were also seeking Marketing Authorisation (MA) for that particular medicine in the adult population. A Paediatric Investigation Plan (PIP) must be agreed with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) describing the clinical studies that will be undertaken and including information on formulation development indicating suitability for children.

For new drugs or MA variations there is an opportunity to apply modern formulation technology to ensure that all relevant ages can receive a commercially manufactured, authorised dosage form – whilst traditional tablets and liquids will be suitable in some cases, oro-dispersible and dispersible tablets, coated granules, mini-tablets and multi-particulates offer other opportunities which may be more acceptable in others. Traditional manufacturing methods for less stable drugs desired to be administered in liquid form may be utilised to manufacture granules or a powder containing taste-masking agents and other excipients to be reconstituted before use. Such dosage form design, also offers an opportunity to manufacture an appropriate medicine rather than relying on ad hoc adaptation of an authorised dosage form by the dispensing pharmacist or care giver.

The European Paediatric Formulations Initiative (EuPFI; www.eupfi.org), a group consisting of paediatric formulation experts from industry, academia and clinical pharmacy, was founded in 2007 with the aim of raising awareness of paediatric formulation issues. The current focus areas of the group include excipients, taste (masking and testing), age-appropriate formulations, delivery devices for the administration of medicines, and extemporaneous or compounded preparations.

This reflection paper highlights on behalf of this group some of the challenges associated with the terminology used in the manufacture and preparation of medicines for children. Importantly a proposal is made to distinguish in terms of product quality and clinical preference between authorised and non-authorised compounding or manipulation to produce a suitable paediatric medicine, demonstrated to be capable of delivering the correct dose.

Many medicines can be manufactured as ready-to-administer, age-appropriate preparations for children and will be acceptable for authorisation by medicines regulators. There are also a number of examples of 'intermediate' age-appropriate preparations that require a simple reconstitution step before administration, such as many antibiotics suspensions. However, there may be technical reasons why it is not possible to manufacture a ready-to-administer dosage form or there may be situations that dictate a different approach e.g. in logistical emergencies such as pandemic influenza; or when the number of patients is very small. In addition, many care givers are aware of children that refuse an authorised preparation considered to be 'age-appropriate'; for example, a child may have developmental delay so that the 'age-appropriate', authorised dosage form is not suitable or have complicating needs such as the presence of enteral feeding tubes. Often a pragmatic approach has been taken with the ad hoc preparation of a suitable medicine by the pharmacist (by *extemporaneous preparation or compounding*) or modification of a dosage form by the care giver to provide a smaller dose or to make it easier to administer, typically by addition to food or liquid (by *manipulation*).

In many parts of the world extemporaneous dispensing or preparation is known as compounding. It may involve the bench top modification and incorporation of an 'adult' dosage form (e.g. tablets) or an active ingredient, with other ingredients, to produce an age-appropriate paediatric formulation such as an oral liquid. Few European countries have standards for the preparation of compounded preparations with the result that reproducibility and safety are potential issues (Standing and Tuleu, 2005; Raine, 2009).

Some formulations and/or performance standards for compounded preparations have been included in pharmacopoeias or investigated by staff in hospitals or academia and published in peer-reviewed journals or formularies. These can assist the dispensing pharmacist by providing greater assurances over quality of the medicine prepared and are preferable to ad hoc approaches but rarely will bioavailability have been studied. It is possible however to investigate such extemporaneous preparation or compounding and provide both pharmaceutical and clinical assurances of the quality of the preparation to the satisfaction of the regulator for inclusion of instructions in the Summary of Product Characteristics (SmPC; EU) or product label (USA).

Thus, provision of age-appropriate preparations acceptable to all children may involve a continuum of sophisticated, manufactured, ready-to-administer dosage forms through authorised '*intermediate*' products requiring minimal processing during dispensing to authorised preparation of a medicine by the pharmacist to preparation of unlicensed medicines using published information to ad hoc compounding. Similarly manipulations of dosage forms to achieve administration may be authorised, supported by published evidence or ad hoc (refer to Fig. 1).

The preparations used to treat patients should be of agreed quality and safety such that bioavailability of the active and safety and efficacy are assured. This is hard to achieve if individual pharmacists formulate and produce compounded medicines and may be difficult to achieve by simply publishing a formula or even quality performance standards. Standardised and verified methods of preparation with suitable instructions are required.

If compounded preparation or manipulation is proposed, PIP applicants should be expected to demonstrate that quality; safety and bioavailability of a preparation are assured by minimising variability in the method of preparation and recommending methods of quality assurance. It will be helpful to manufacturers if more information becomes available on what constitutes reasonable steps to produce age-appropriate formulations for children (taking into account technical challenges and patient numbers) and

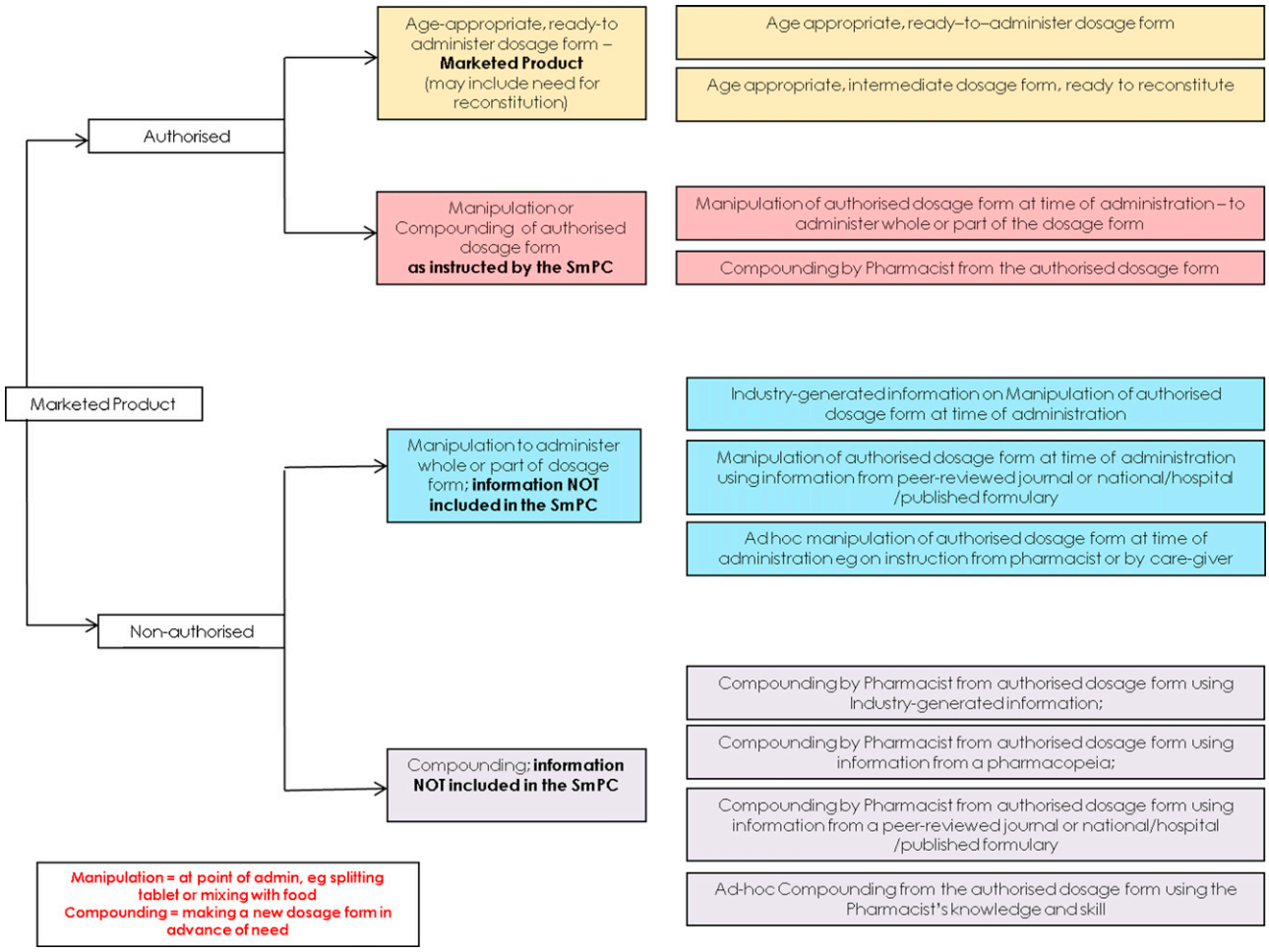

Fig. 1. Definitions associated with the use of marketed medicinal products.

how intermediate and industry-generated information on compounding or manipulation can be utilised. The requirement for a detailed evaluation of formulation development plans, the place of industry-verified preparations or manipulations in the drug development life cycle and the experience gained by regulators could be communicated.

The terminology associated with such manufacture, preparation and manipulation is poorly defined and may be misunderstood in discussions between manufacturers, regulators and practitioners.

2. Context and terminology

Children should have access to authorised, ready-to-administer, age-appropriate preparations of medicines. Nothing in this document should detract from this objective.

All reasonable efforts should be made by the pharmaceutical industry to develop age-appropriate formulations which can be manufactured to ensure safety, efficacy and quality and this should always be the first intent.

Fig. 1 illustrates the suggested terminology for various types of preparation that might be used as authorised products and situations in which compounding or manipulation of a dosage form would be considered 'non-authorised'. The definitions only refer to compounding or manipulation with products available commercially and not to preparation with actives and individual excipients.

Fig. 2 illustrates the suggested terminology associated with the types of preparations that may be considered for use in use paediatric clinical studies.

2.1. Preparations used in commercial clinical studies

Products that are intended to be used in commercial clinical studies undergo rigorous development and regulatory scrutiny prior to clinical application approval (e.g. PIP submission and agreement; Investigational New Drug Request, Clinical Trials Authorisation) or will be agreed with the regulator under provisions in the Clinical Trials Directive. Such medicines must be of assured quality, meeting all appropriate pre-defined pharmacopoeial and associated specifications. Where required, bioavailability of the formulation will be confirmed with PK studies. All medicines used in clinical trials can therefore be considered 'authorised' (authorised for use in a clinical trial as opposed to an authorised marketed formulation).

The products to be investigated are likely to be age appropriate but may also be 'clinical-phase appropriate' in terms of dosage form design, as opposed to being the final commercial presentation. This will clearly depend on the clinical stage associated with the new chemical entity. For example, an early PK study in children may not utilise the definitive commercial dosage form presentation, but a Phase III study where the required dose is known and which uses the potential commercial dosage form is likely to avoid the need for bridging studies (terminology: *age-appropriate, ready-to-administer dosage form – intended future commercial presentation*). It may be technically difficult and take considerable time to produce elegant age-appropriate products especially for new chemical entities early in their development program. Developing sophisticated dosage forms for early paediatric trials could

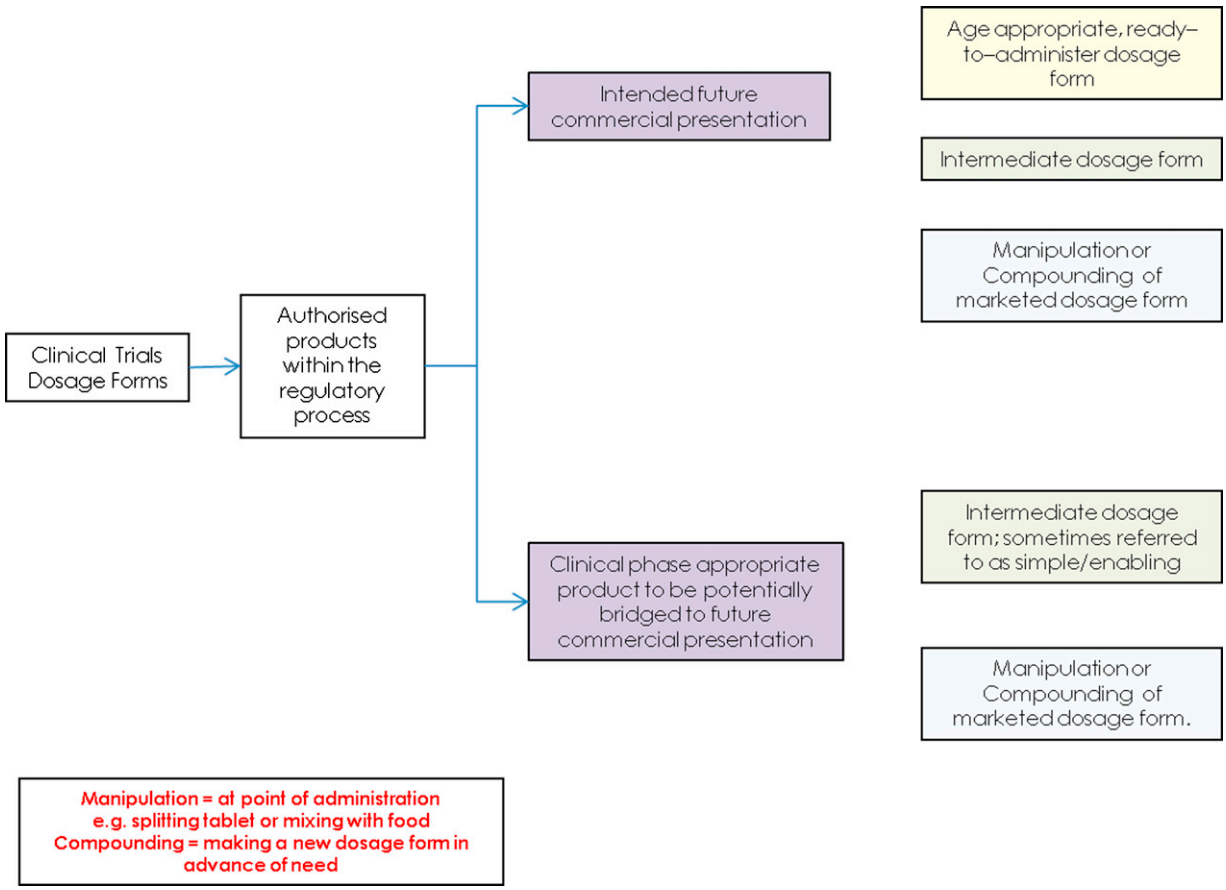

Fig. 2. Definitions associated with clinical trials dosage forms.

potentially delay these trials. As an alternative, it may be appropriate to manufacture a 'simple' or 'enabling' preparation – often an '*intermediate for reconstitution*' – which might enable shorter timelines for overall development. Examples of such preparations may be powder mixes or simple granules in bottles, which might be measured directly to obtain a dose or reconstituted like many antibiotic preparations. Using phase-appropriate preparations, with potential bridging studies to the commercial dosage form as more information becomes available, could thus enable easier achievement of acceptable timelines for paediatric clinical studies (terminology: *Clinical phase-appropriate product to be bridged to future commercial presentation – Intermediate dosage form*).

However, whilst detailed consideration of formulation development plans will be required in a PIP application, this could also enable the provision of appropriate paediatric formulation information at the time of PIP submission and expedite the overall development of a commercial paediatric product. These clinical phase appropriate products may require few if any excipients and could be accompanied with verified instructions for taste-masking by addition to suitable food or liquid or by adding appropriate excipients at the time of dispensing or administration if this facilitates stability or acceptability. Hence these formulations can be seen as potentially an important contribution to the drug development strategy.

On some occasions it may be acceptable to provide manipulation or compounding instructions for the marketed dosage form, either for early clinical studies in paediatrics or, more rarely, as the intended future commercial presentation.

In considering formulation development challenges such as aqueous stability, intermediate preparations for reconstitution may also be justifiable as viable commercial formulations in certain circumstances thus negating the need to develop more sophisticated formulations that require no such reconstitution (terminology: *intermediate dosage form – intended future commercial presentation*).

In addition to new products being developed by the industry, there are many off-patent medicines that are already licensed for adults but still require clinical data to be generated in paediatric populations. In these cases clinical phase appropriate/intermediate preparations may have utility to generate clinical data in a more timely and cost-effective way compared to the manufacture of specific and sophisticated medicines.

2.2. Compounding and manipulation

The EMA reflection paper on 'Formulations of choice for the paediatric population' summarises much of the background to the issues of access to age-appropriate preparations (EMA, 2006). Whilst stating that 'the manipulation of adult medicinal products for paediatric use should be the last resort' it also states that 'at the same time it is recognised as an unavoidable and necessary operation in many cases'. The reflection paper encourages manufacturers to produce and provide relevant data and information to practitioners. The paper goes on to state that 'in essence, the pharmaceutical industry should be aware that an 'adult' formulation may be manipulated for paediatric use and provide any such information about the product that would allow the pharmacist to design a satisfactory formulation. Depending on the evaluation of such data by the competent authorities, validated formulations for extemporaneous dispensing may be considered acceptable for inclusion in the

SmPC and package leaflet'. *Note: The reflection paper uses the term 'manipulation' to include compounding by the pharmacist.*

It is to be anticipated that the majority of new medicines developed through the PIP process will have age-appropriate formulations manufactured so that the need for compounding or manipulation is minimal. However, many older medicines (often 'adult' medicines used off-label) may never have suitable commercial dosage forms made for children and it remains likely that caregivers will continue to manipulate medicines at the point of administration to cope with the abilities and preferences of children and in some cases it will be preferable for the pharmacist to produce a medicine that the child finds acceptable. It is important that the regulatory agencies, academia and industry work together to enable provision of data supporting these activities.

Typically, any kind of modification or manipulation of a drug product prior to administration has been termed 'extemporaneous'. However, the term is loosely defined and is therefore a potential source of confusion as it could mean different things in different sectors involved with medicines for children. Similarly 'compounding' or 'manipulation' may be used to describe a variety of processes applied to dosage forms. (The terms 'compounded', 'pharmacy-compounded' and 'extemporaneous' are each used within the UK SmPC for Tamiflu®).

Extemporaneous or magistral products are produced for an individual patient to the specific order of a clinician by a pharmacist (Brion et al., 2003). Whilst 'extemporaneous' is frequently used in guidance the term has not been specifically defined and is taken by some to include, for example, the reconstitution of a preparation according to directions given in the SmPC. In discussing extemporaneous preparation in European hospitals, Brion et al. suggested that 'Extemporaneous or magistral preparation describes the manipulation by pharmacists of various drug and chemical ingredients using traditional compounding techniques to produce suitable medicines when no commercial form is available'. However, this definition does not distinguish between ad hoc preparation by the pharmacist using his knowledge and experience and preparation according to a manufacturer's instructions which may have been approved by the regulator and included in the SmPC.

In many parts of the world extemporaneous dispensing or preparation is known as compounding. It may involve the bench top modification and incorporation of an 'adult' dosage form (e.g. tablets) or an active ingredient, with other ingredients, to produce an age-appropriate paediatric formulation such as an oral liquid. Because the term extemporaneous is poorly defined, the term '*compounding*' should be used for the process undertaken by the individual pharmacist who creates a medicine from active drug substance and excipients or from an authorised dosage form and excipients when no suitable paediatric dosage form is commercially or locally available.

Few European countries have standards for the preparation of compounded preparations with the result that reproducibility and safety are potential issues (Standing and Tuleu, 2005; Raine, 2009). Sometimes compounded preparations are used on a large scale and may be prepared in larger quantities (batches), usually from actives and excipients. Exemptions in medicines legislation may allow this to be classed as 'dispensing' (with little quality assurance) but commercial or health service units may also produce such unlicensed preparations to GMP standard. In the UK such medicines are known as 'specials' but when requesting a product there is often confusion as to what standard has been used in their preparation (Gross, 2005). Although aspects of quality may be assured, there may be inconsistency between producers with bioavailability differences, colour, taste and strength variation.

'Manipulation' has been described as the physical alteration of a dosage form to achieve administration of that dosage form usually, for children, in a smaller age/weight-related dosage than in the original dosage form. This is usually undertaken by the carer at the time of administration and may also include modification of the dosage form for addition to food or liquid to facilitate administration. Segmenting of tablets is the most common manipulation of a dosage form but dispersion or dissolution of tablets or capsule in liquid and proportional dosing; mini-tablets in capsules for adults, to be counted for different ages of children or reducing the size of a suppository by cutting might also be considered.

The term 'industry-verified' has been used to describe preparations and methods of preparation verified by approved manufacturers based on supportive scientific data (pharmaceutical and sometimes clinical), which can provide a much higher degree of control and assurance than traditional compounded preparations.

Where compounded or manipulated preparations are proposed for paediatric use authorised by the regulatory authority, it is expected that the manufacturer will have investigated appropriate pharmaceutical and bioavailability aspects of the products paying particular attention to accuracy of dose delivery, bioavailability and uniformity of preparation. Pharmacopoeial and other tests and standards applied must be described and justified in the PIP as part of formulation development. It is preferable that such industry-generated data are reviewed and approved by the competent authority and included in the approved SmPC.

2.3. Authorised products

2.3.1. Age-appropriate, ready-to-administer dosage forms

Many commercially manufactured, authorised products are ready-to-administer directly to the child and have been shown to be appropriate to administer to the target age group e.g. proprietary paracetamol suspension (terminology: *age-appropriate, ready-to-administer dosage form – marketed product*).

2.3.2. Age-appropriate, intermediate dosage forms

However, it is common for unstable products to be manufactured as dry powders (with excipients) to be reconstituted (by the pharmacist or, in some countries, by the patient) with water before administration e.g. antibiotic preparations.

It may also be appropriate to provide a measured unit of dry active with a separate, more complex, manufactured vehicle or diluent containing excipients to be added to the powder or vice versa e.g. the kit for COZAAR® 2.5 mg/ml losartan potassium powder and solvent for oral suspension (Anonymous, 2011a). Such a manufactured product has been through the regulatory assessment process and is included in the MA. It is unnecessary, therefore, to refer to these authorised products as 'industry-verified' (terminology: *age-appropriate, intermediate dosage form – marketed product*).

Reconstitution of authorised intermediate products should not be considered compounding and should be distinguished from 'manipulation'. The US Pharmacopeia has usefully defined which modifications of an authorised dosage form do not constitute compounding. These include mixing and reconstituting in accordance with agreed 'labelling'.

Account should be taken of different reconstitution practices in EU countries. In some it is common to have the carer instructed to reconstitute preparations rather than the dispensing pharmacist. Reconstitution should be evaluated in relevant situations. There should also be some means of defining which preparations can be prepared by adults, carers, parents and which need to be prepared by dispensing pharmacists. This will relate to the complexity of the method of preparation and nature of the medicine itself and guidance could be provided in the SmPC.

2.3.3. Authorised compounding or manipulation of an authorised dosage form

For a small number of medicines information has been agreed with the regulator in a MA or label application and considered appropriate to include instructions for compounding in product literature. For example:

> To cope with emergency situations both FDA and EMA have approved modifications to the label/SmPC for Tamiflu® to allow 'extemporaneous' preparation in the pharmacy and manipulation of capsule contents immediately before administration (Anonymous, 2011d). These modifications and manipulations are supported by published literature and manufacturer's data. The labels (authorisations) for lisinopril (Anonymous, 2011e) and losartan potassium in USA contain information on the compounded preparation of an 'industry-verified' suspension from the tablet dosage form (Thompson, 2010). In contrast, in Europe losartan potassium is supplied as an authorised 'intermediate' product of powder and vehicle (see above).

Industry-generated information of a compounded preparation with evidence approved by the regulator and included in the MA or label for the product can assure the consistent quality and bioavailability of a preparation and distinguishes it from ad hoc formulation and preparation by the individual pharmacist (terminology: *Compounding by pharmacist from the marketed dosage form; as instructed by SmPC*).

Industry-generated manipulation of authorised dosage forms to achieve accurate, smaller doses may be justifiable. Most examples involve breaking of tablets into segments (to be taken directly or added to food) to obtain the desired dose where tablet geometry may increase dosage accuracy (Kayitare et al., 2009) e.g. mefloquine hydrochloride (Lariam® (Anonymous, 2011b)), hydroxycarbamide, which can be divided into 4 segments (Siklos® (Anonymous, 2011c)). Instructions on manipulation contained in the SmPC must be supported by appropriate data and agreed with the regulator as part of the process of obtaining a MA (terminology: *Manipulation of marketed dosage form at time of administration; as instructed by SmPC – to administer part of the dosage form*).

It may also be appropriate for a dosage form with a MA to be manipulated immediately before dosing to facilitate administration of the whole of the dosage form. For example when swallowing a tablet is difficult it might be crushed or otherwise dispersed. This may form part of the product characteristics e.g. sodium valproate is available as crushable tablets (Epilim®) and didanosine (Videx®) and Lamotrigine (Lamictal®) are available as authorised chewable or dispersible tablets. Manipulation for convenience of administration may be supported by data (for example, on bioavailability when mixed with foods) submitted for MA and included in the SmPC (terminology: *Manipulation of marketed dosage form at time of administration; as instructed by SmPC – to administer the whole dosage form*).

2.4. Non-authorised products (information not included in SmPC)

2.4.1. Compounding

The quality of formulae for compounded preparations and of active and excipient ingredients may vary considerably. The formula or recipe may be published in a pharmacopoeia (officinal formula European Commission, 2001), journal or national/hospital/published formulary but may be based only on the knowledge and experience of the individual pharmacist. Formularies of compounded preparations have been published in an attempt to provide some guidance on the preparation and shelf life of paediatric formulations (Woods, 2011; Nahata and Hipple, 2000; Trissel, 2000; Jackson and Lowey, 2010).

There may or may not be appropriate information to support the quality of the formulation (e.g. stability or shelf life; taste acceptability (Glass and Haywood, 2006; Nahata and Allen, 2008) and only very rarely is bioavailability investigated (Abdel-Rahman et al., 2003; Christensen et al., 1998; Mulla et al., 2011).

The British Pharmacopoeia (BP) now has a chapter on unlicensed medicines and 36 performance monographs (The British Pharmacopoeia Commission, 2011). These monographs are available standards for medicinal products legally enforced by the UK Medicines Act 1968. Where a pharmacopoeial monograph exists, medicinal products sold or supplied in the UK must comply with that monograph. Hence it would be possible to create enforceable standards for finished product formulations of unlicensed (non-authorised) medicinal products by publication of monographs in the BP. This is part of an unlicensed medicines work programme which for the next two years will include more than 60 additional unlicensed products in the BP.

The United States Pharmacopeia also has information on compounded preparations (United States Pharmacopeial Convention, 2008). Again, assurances about quality are improved but not about bioavailability.

The pharmaceutical industry may investigate the quality (and sometimes bioavailability) of compounded preparations, perhaps in response to questions from practitioners or as part of product development but the information generated may not have been submitted for consideration by regulators. Such 'industry generated' information may be of high quality.

There is a continuum with additional assurances of quality (but rarely bioavailability) offered by 'industry generation' of data (but not evaluated by the regulator or published by the company in the SmPC), inclusion in a pharmacopoeia, publication and use of relevant information in peer-reviewed journals through formulations contained in local or national formularies investigated by staff using appropriate methodology to the ad hoc preparation by the individual pharmacist using only skill and experience. Such preparations are not authorised by the regulator and might be referred to respectively as:

- Compounding by Pharmacist from the authorised dosage form using industry-generated information; information **not** included in SmPC.
- Compounding by pharmacist from the authorised dosage form using information from a pharmacopoeia; information **not** included in SmPC.
- Compounding by pharmacist from the authorised dosage form using information from a peer-reviewed journal or national/hospital/published formulary; information **not** included in SmPC.
- 'Ad hoc' compounding from the authorised dosage form using the pharmacist's knowledge and skill.

2.4.2. Manipulation

Similarly, if manipulation of the dosage form has been verified by investigation by the manufacturer (e.g. in response to questions from patients or healthcare professionals) but data (for example, on accuracy, stability, compatibility with food or liquid) not yet included in the SmPC, it could be described as an '*industry generated' information on manipulation of authorised dosage form at time of administration; information **not** included in SmPC – to administer part or the whole of the dosage form* as appropriate and this would differentiate it from 'ad hoc' manipulation where no information to support the process may be available (terminology: *Ad hoc' manipulation of authorised dosage form at time of administration – to administer the whole* or *part of the dosage form*).

Again, a continuum exists with some information published in the peer-reviewed literature whose quality may give greater assurances than ad hoc manipulation (terminology: *manipulation of authorised dosage form at time of administration; using information from a peer-reviewed journal or national/hospital/published formulary; information **not** included in SmPC*).

3. Conclusion

Some manufacturers remain unsure of the type of pharmaceutical preparation that will meet with regulatory approval at different stages of the product life cycle. This paper has introduced terminology intended to clarify types of preparation in a regulatory and pharmaceutical development context. It is considered that the definitions proposed here could be globally applicable.

The first intent of pharmaceutical companies should be to provide manufactured, ready to administer, age appropriate dosage forms. Intermediate dosage forms appropriate to the phase of clinical trials should also be considered as part of the pharmaceutical development strategy.

The term "extemporaneous preparation" should be replaced by 'compounding' and the compounding described as ad hoc when the pharmacist improvises a medicine for individual patients by modifying dosage forms or active ingredients to produce an age-appropriate formulation. This non-authorised approach may enable the administration of medicines (which are unlicensed) to children but carries the risk of sub-optimal dosing and patient safety due to reduced quality of the formulation, uncertain stability and the potential for variable and modified bioavailability.

Greater assurances of quality may be available when formulations have been published and peer-reviewed but there is a need for standardisation and a mechanism for assuring practitioners of the quality of the formulation.

Whenever possible, compounding or manipulation should be developed under industry control using GMP processes, standards and quality assurance so that a robust product of known and reproducible bioavailability is delivered to the patient. Such preparations could be approved and included in the SmPC (where they become 'authorised') but as a last resort since there are many opportunities to manufacture age-appropriate intermediate products if sophisticated formulations are not appropriate. Adopting this approach can enable provision of safe and effective preparations of good quality for the paediatric patient.

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