A Guide for Health Professionals

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EXECUTIVE SUMMARY

Manipulating medicines to deliver appropriate, reproducible doses to paediatric patients where no suitable product is available at the point of care: a guideline for Healthcare Professionals

Background

A lack of authorised, commercially available, age-appropriate formulations makes it difficult to administer medicines to babies and children. Many pharmaceutical dosage forms are designed for adults and a proportion of the available dose may therefore be required for administration to paediatric patients. This can lead to manipulation of the medicine at the point of care, in an attempt to deliver the prescribed dose. Little is known about the potential risks to the product or to the operator or recipient. In 2007, legislation was introduced in Europe to drive the development of appropriate medicines for children, but it will be some years before the benefits of this legislation are realized. Even where age-appropriate formulations are marketed, the need for manipulation will probably remain as drug development is unlikely to take account of drivers like patient preference. The development of this guideline has been informed by a series of work streams conducted as part of the MODRIC (Manipulation of Drugs in Children) research.

Target audience

The guideline is intended for use by healthcare professionals working in UK hospitals in neonatal and paediatric (birth to 18 years) in-patient settings.

Guideline development

A guideline development group consisting of healthcare professionals, research, academic, and formulation experts, pharmaceutical quality control professionals and parent representatives reviewed the presented evidence and developed this guideline.

Definition of Manipulation

A manipulation is defined as the physical alteration of a pharmaceutical drug dosage form for the purposes of extracting and administering the required proportion of the drug dose. In this context it does not include the manipulation of a medicine solely for the purpose of ease of administration. Examples of the types of manipulation include:

Tablets: split/broken/cut and a segment given, crushed and a proportion of the powder given, dispersed in liquid and a portion of the liquid given.

Transdermal Patches: patch cut and a portion of patch uncovered and applied.

Guideline

This guideline presents the available evidence on manipulation of medicines to achieve a proportional dose and aims to describe interventions that may avoid the need to manipulate medicines. Where manipulation is considered necessary this guideline aims to provide accessible, dosage form specific guidance, for undertaking manipulations and provides guidance on avoiding manipulations (where possible) and medicines that should not be manipulated.

This guideline recognizes the risk that may be associated with manipulations and highlights where advice should be sought prior to undertaking any manipulation.

Summary of Recommendations

Recommendations for healthcare professionals prior to undertaking any manipulation:

- Avoid manipulating medicines wherever possible.
    - Procure dosage forms which are appropriate to the age and ability of the patient:
        - Of an appropriate strength where available.
        - These should be licensed products where possible, but it may be necessary to procure unlicensed special formulations or imported medicines.
    - Consult with the prescriber:
        - To check if a dosage range is applicable to the product and the patient's condition (amending the dose within this range could avoid the need for manipulation).
        - To consider rounding the dose to an available dosage form or convenient measurable volume, if appropriate.
        - To consider whether an alternative dosage form can be used (If this dosage form is intended for a different route of administration confirm whether the dose should be adjusted and whether excipients are safe).
        - To consider whether an alternative medicine within the same therapeutic class with an appropriate dosage form can be used; the prescriber and/or pharmacist should determine whether this can be done safely.
- Do not manipulate medicines with a narrow therapeutic index (e.g. digoxin, warfarin).

- Never manipulate hazardous medicines e.g. cytotoxic medicines, outside a controlled environment (cytotoxic containment cabinet).
- Do not manipulate medicines presented as modified release dosage forms (e.g. Controlled Release, Sustained Release, Modified Release) unless specific information from the manufacturer or pharmacist permits manipulation.
- If a manipulation is considered necessary, further information may be required to ensure this is carried out safely and as accurately as possible. Consult hospital/local guidelines/policies prior to undertaking any manipulation.
- Where appropriate consult a pharmacist for further information.
- If a manipulation is considered necessary this should be undertaken immediately prior to administration:
    - The effects of a manipulated product may differ from those described for the non-manipulated product; careful monitoring of the patient is recommended particularly after administration of the first dose.
- Ensure that all equipment used to manipulate dosage forms is maintained in accordance with hospital/local policies.
- Use the appropriate sized syringe for the volume of solution to be measured.
- In some instances failure to administer any medicine to the patient may be more harmful than administering a dose which has been manipulated without supporting evidence.

Further information including the full guideline and recommendations are available from Alder Hey Children's NHS Foundation Trust website, http://www.alderhey.nhs.uk/departments/pharmacy/

1. INTRODUCTION

1.1. DEFINITION OF MANIPULATION

A manipulation is defined as the physical alteration of a drug dosage form for the purpose of extracting and administering the required proportion of the drug dose.

Examples of the types of manipulation that may be applied to the different dosage forms are described in the following table.

Drug dosage form	Manipulations	Drug dosage form	Manipulations
Tablet	split/broken/cut and a segment given crushed and a proportion of the powder given dispersed in liquid and a portion of the liquid given	**Intravenous injection**	reconstituted or ready prepared solution, further diluted to allow a smaller dose to be measured, volume of fluid removed from IV container, drug added (to obtain accurate concentration for infusion) drug added to infusion bag, portion with smaller dose removed and infused
Capsule	opened, dispersed in liquid and a proportion of the liquid given opened and a proportion of the powder given	**Suppository**	cut/split and a segment given
Sachet	opened, dispersed in liquid and a proportion of the liquid given opened and a proportion of the powder given	**Enema**	proportion of sachet/unit given (the remainder then discarded) proportion of contents removed and the remainder given
Nebuliser Solution	proportion given diluted and a proportion given	**Transdermal Patch**	patch cut and a portion applied portion of patch uncovered and applied

1.2. BACKGROUND

The Pharmaceutical industry invests considerable time and financial resource in the development of products designed for accurate and appropriate drug delivery. Legislation, in the form of the European Union Paediatric Regulation (2007) [http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf, http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf, http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf] was established to drive the development of appropriately licensed and formulated medicines for

children, through a system of requirements and incentives. Simultaneously the World Health Organisation (WHO) [http://www.who.int/childmedicines/en/] spearheaded a global campaign to raise awareness and accelerate action to address the need for improved availability and access to safe, child-specific medicines for all children under 12 years of age.

However, it will be some time before the influence of this legislation and campaign strategy is realized and suitably formulated medicines are made available for children. Even when age-appropriate formulations are marketed, the need for manipulations will remain as drug development is not able to take account of all the possible circumstances of drug administration.

Currently in neonatal and paediatric practice, where products may be used outside the terms of their licence ('off-label') and suitable formulations are lacking, healthcare professionals may be required to manipulate medicines in order to deliver the intended dose. Although this is perceived to be an established practice, the extent of this practice, and the precise methods used to manipulate medicines have not been defined. Manipulation of dosage forms, to achieve a suitable neonatal or paediatric dose, may occur because of the lack of available products in an appropriate paediatric dosage form and strength, or because patients express a preference for a formulation type, which is not accommodated by the available commercial products. Dosage forms may also be altered using similar methods where the administration of solid dosage forms is difficult.

The evidence base supporting the manipulation of medicines for the purposes of achieving the required dose is lacking. There are no evidence-based guidelines available which consider the manipulation of medicines to obtain the required dose for use in neonatal and paediatric clinical practice.

The development of this guideline was undertaken as part of the Manipulation of Drugs Required in Children (MODRIC) project. MODRIC aims to establish the nature, frequency and risk of drug manipulations made at the point of administration by healthcare professionals for the purpose of obtaining required drug doses for administration to neonates and children.

1.3. CLINICAL QUESTION

- How can healthcare professionals manipulate medicines to deliver appropriate and reproducible doses where no suitable dosage form exists at the point of care?

1.4. AIMS AND OBJECTIVES OF THE GUIDELINE (See Appendix 1):

- To describe options available to avoid manipulation of medicines.
- Where manipulation is necessary, to provide readily accessible, easy to read guidance for delivering appropriate and reproducible medicine doses to neonatal and paediatric patients

where no suitable medicinal product is available at the point of care.

- To reduce risk to the product functionality, patient, person undertaking the manipulation and environment.
- To inform healthcare professionals of best practice and potential risk associated with manipulation of medicines.
- To raise awareness amongst regulators, advisory bodies (such as WHO) and the pharmaceutical industry that manipulations occur but that carers would not have to manipulate if age-appropriate dosage forms were more generally available.

1.5. PATIENTS TO WHOM THE GUIDELINE IS INTENDED TO APPLY

- UK hospital neonatal and paediatric in-patients (birth to 18 years of age).

1.6. TARGET USERS OF THE GUIDELINE

- Healthcare professionals working in neonatal and paediatric healthcare settings in the UK.

1.7. APPLYING CLINICAL JUDGEMENT

Healthcare professionals must use their judgement, supported by guidelines and other available information, to make decisions about medicines manipulation. This guideline cannot take account of all possible clinical and social circumstances and should be used with the best interests of the patient in mind. If in doubt, seek advice from an experienced practitioner. This guideline is not a recommendation for the use of products for unlicensed indications or populations. It should be recognized that when products are used outside the terms of their licence, a greater liability rests with the individual prescriber and the person responsible for the provision and administration of the product. Refer to relevant professional bodies for further advice.

Remember that in some instances failure to administer any medicine to the patient may be more harmful than administering a dose which has been manipulated without supporting evidence – the balance of risk to the patient must be taken into account.

Palatability and compliance may be affected by manipulating products for oral administration.

Biological medicines (such as insulin, erythropoietin) may be more problematic to manipulate due to minor changes in formulation possibly having major effects on the integrity/function of the active drug. Consult a pharmacist if manipulation of a biological medicine is required.

This guideline can be used to further inform and/or help the development of local policy.

1.8. GUIDELINE DEVELOPMENT

Several approaches were used to obtain or generate evidence to inform the guideline:

- A systematic review of studies investigating the effects of drug manipulation on dose accuracy, palatability of the drug, safety of the recipient and person carrying out the manipulation, bioavailability and stability of the drug.
- An observational study which identified and observed manipulations in selected paediatric wards at a large regional paediatric hospital, a district general hospital and a large regional neonatal unit (see Appendix 5 for further details).
- A quantitative review of all prescriptions over a 5-day period completed in the same clinical areas as above.
- A survey of paediatric nurses throughout the UK that included an assessment of the number and type of drug manipulations undertaken by survey participants over the previous (see Appendix 6 for further details)
- Consideration of potential risks

The work described above has been published elsewhere. See Section 4.1 for further details.

The collected data were analysed, presented and discussed by the Guideline Development Group (for composition see Appendix 2). This guideline group included representatives from healthcare professionals, guideline experts, formulations experts, parents and quality control professionals. A writing group from the MODRIC (Manipulations of Drugs Required in Children) Steering Committee drafted the initial Guideline and the recommendations. These drafts were discussed and further developed by the guideline development group which also reviewed and agreed the final guideline and recommendations.

Four main databases were searched for the systematic review; International Pharmaceutical Abstracts (IPA), PubMed, CINAHL and EMBASE. The reference lists of included papers were also screened and experts in the area were contacted and asked to provide details of any unpublished work in this area.

1.9. GUIDELINE FORMAT

This guideline summarises the evidence from the systematic review alongside the findings from the observational study of manipulations in neonatal and paediatric practice and a survey questionnaire administered to a sample of children's nurses throughout the UK. This evidence was discussed by the guideline group and recommendations drafted, revised and reviewed.

2. DOSAGE FORMS

The evidence generated from the systematic review, survey and observational study is presented below together with the resultant recommendations for each dosage form. The quality of evidence identified in the systematic review has been rated as high (++), moderate (+) or low (-) as per the table below.

Quality level	Criteria
++	Included studies where the reported methods and subsequent results and conclusions could be considered (with reasonable confidence) not to be biased. The process of the drug manipulations was at least adequately described.
+	Included studies where there were some concerns about the reported study methods or the methods were not reported with enough detail to permit sufficient assessment
-	Included studies where there were considerable concerns about the reported methods or there was insufficient reporting of the methods for them to be assessed

2.1. QUALITY ASSESSMENT

Fifty studies were included and quality-assessed using criteria from validated checklists used for systematic reviews, where studies in which laboratory based quality criteria from standardized tests and acceptance limits were used. Additionally, specific criteria were developed for this study.

The quality ratings and the country of origin of the reported studies are described below

Ref	Quality	Country	Ref	Quality	Country	Ref	Quality	Country
1	+	UK	18	+	USA	35	+	UK
2	+	UK	19	+	USA	36	+	UK
3	++	USA	20	+	Canada	37	-	Sweden
4	++	USA	21	++	Rwanda / Belgium	38	-	UK
5	+	USA	22	+	UK	39	+	Malawi / USA
6	+	USA	23	+	USA	40	+	USA
7	+	USA	24	++	USA	41	+	USA
8	+	UK / France	25	+	USA	42	+	USA
9	++	Palestine	26	+	USA	43	+	USA
10	+	USA	27	+	Belgium	44	+	USA
11	++	Jordan	28	-	USA	45	+	USA
12	++	Egypt	29	-	Belgium	46	-	USA
13	+	Bosnia Herzegovina	30	++	Netherlands	47	-	Netherlands
14	+	Portugal	31	++	Saudi Arabia	48	-	USA
15	+	Belgium / Italy	32	++	USA	49	++	Australia
16	+	Switzerland / Germany	33	++	USA	50	-	USA
17	+	USA	3	+	Australia			

2.2. TABLETS

2.2.1 *Systematic review evidence*

Forty nine studies that met the inclusion criteria were identified. They involved tablets that were crushed, split or dispersed. These included 24 studies that had outcomes that included an assessment of the weight of split portions and/or their drug content and 10 studies that compared different methods of manipulation.

2.2.1.1 Weight and/or drug content outcomes

There were 24 studies that assessed the physical characteristics of halved tablets; 18 studies halved tablets and used adapted pharmacopoeial criteria for assessment including the United States Pharmacopoeia (USP), the British Pharmacopoeia (BP) or the European Pharmacopoeia (Ph Eur). When many of these studies were undertaken the relevant pharmacopoeia criteria did not have specifications for subdivided tablets; adaptations were made based on the whole tablet requirements. It might be assumed that any split fragment of a tablet will contain the fraction of the initial content proportional to the ratio of the fragment weight: whole tablet weight. Analysis of mercaptopurine tablets showed this to be the case since the expected contents of fragments did not significantly differ to those predicted from the fragment: tablet weight ratios [1]. However analysis of fragments from levodopa tablets [2] showed a highly significant difference in the variation of percentage of drug content between quarters and tablets. Most studies do not make an assessment of the uniformity of drug distribution in tablet fragments.

Table 1: Studies which halved or quartered tablets and used pharmacopoeia-based outcomes for weight and/or drug content uniformity

Drugs	Outcomes summary	Ref
Mercaptopurine 10mg, unscored Mercaptopurine 50mg, scored	Halved tablets from both scored and unscored products did not meet the uniformity of weight specification (BP).	1
Warfarin sodium 5mg, oblong, non-coated, scored Simvastatin 80mg, oval, film-coated, unscored Metoprolol succinate 200mg, oval, film-coated, unscored Citalopram 40mg, oblong, non-coated, scored Metoprolol tartrate 25mg, circular, non-coated, scored Lisinopril 40mg, oval, non-coated, unscored	Overall 43/180 (23.9%) of half tablets were outside of USP specification for drug content [warfarin (36.7%), metoprolol succinate (33%), lisinopril (33%), citalopram (16.7%), metoprolol tartrate (13.3%), simvastatin (10%)] Overall 23/180 (12.8%) of half tablets were outside USP specification for weight; warfarin (33.3%), metoprolol succinate (20%), lisinopril (23.3%) 22.2% (20/90) of scored tablets were outside the USP specification for drug content compared with 25.6% (23/90) unscored tablets 11.1% (10/90) of scored tablets were outside the USP specification for weight compared with 14.4% (13/90) unscored tablets	3

Atorvastatin 40mg, oval, unscored Citalopram 40mg, oval, scored Furosemide 40mg, round, scored Glipizide 10mg, round, scored Lisinopril 40mg, trapezoid, unscored Lovastatin 40mg, octagon, unscored Metoprolol tartarte 50mg, oblong, scored Paroxetine 40mg, oval, unscored Sertraline 100mg, oblong, scored Simvastatin 20mg shield-like, unscored Rofecoxib 25mg, round/spherical, unscored Warfarin 5mg, round, scored.	8/12 halved products passed adapted USP weight uniformity test; citalopram, warfarin, furosemide, glipizide, atorvastatin, metoprolol, paroxetine, sertraline; 6 out of 8 of the products were scored. Warfarin and furosemide were tested in two orientations relative to the cutter. 4/12 did not pass adapted USP uniformity test; lovastatin, Lisinopril (2 orientations used), rofecoxib, simvastatin; Each of these 4 products were unscored and lisinopril was tested in two orientations relative to the cutter.	4
Paroxetine 20mg, scored on one side Paroxetine 40mg, unscored Risperidone 2mg, unscored Risperidone 4mg, unscored Sertraline 100mg, scored on one side	Halved tablets Met the USP weight specification - paroxetine 20mg Did not meet the weight specification - paroxetine 40mg, risperidone 2mg, risperidone 4mg, sertraline 100mg	5
Buspirone 5mg, ovoid-rectangular, scored Captopril 6.25mg, capsule-shaped, scored Donepezil 5mg, round, unscored Doxazosin 0.5mg, round, scored Doxazosin 2mg, oblong, scored Fluvoxamine 50mg, elliptical, scored Glipizide 2.5mg, round, scored Hydrochlorothiazide 12.5mg, round, scored Metoprolol tartrate 25mg, capsule-shaped, scored Metoprolol tartrate 25mg, round, scored Metoprolol succinate 50mg, biconvex, scored, extended-release Oxybutynin 2.5mg, round, scored Paroxetine 10mg, modified-oval, scored Risperidone 0.25mg, oblong, unscored Risperidone 1mg, oblong, unscored Sertraline 25mg, capsule-shaped, scored Sertraline 50mg, capsule-shaped, scored (A) Sertraline 50mg, capsule-shaped, scored (B) Trazodone 25mg, round, scored (one brand) Trazodone 25mg, round, scored (second brand) Venlafaxine 25mg, shield-shaped, scored Warfarin 0.5mg, round, scored	Halved tablets. Met the USP weight specification; doxazosin 2mg, fluvoxamine 50mg, hydrochlorothiazide 12.5mg, metoprolol succinate 50mg (extended-release), paroxetine 10mg, risperidone 0.25mg, trazodone 25mg (second brand). 6/7 scored and 1/7 unscored products Did not meet the USP weight specification; buspirone 5mg, captopril 6.25mg, donepezil 5mg, doxazosin 0.5mg, glipizide 2.5mg, metoprolol tartarte 25mg (both), oxybutynin 2.5mg, risperidone 1mg, sertraline 25mg & 50mg (both A & B), trazodone 25mg (one brand), venlafaxine 25mg, warfarin 0.5mg. 13/15 scored and 2/15 unscored products	6
Atorvastatin 20mg, oval, not flat, unscored Atorvastatin 40mg, oval, not flat, unscored Glyburide 5mg, not oval, not flat, scored Hydrochlorothiazide 50mg, not oval or flat, scored Hydrochlorothiazide 50mg, not oval, flat, scored Hydrochlorothiazide 25mg, not oval or flat, unscored Lisinopril 40mg, not oval or flat, unscored Metformin 850mg, not oval or flat, unscored Paroxetine 40mg, oval, not flat, unscored Sertraline 100mg, oval, not flat, scored Sildenafil 50mg, not oval or flat, unscored	Halved tablets. Met the USP weight variation specification; Lisinopril 40mg, paroxetine 40mg, sertraline 100mg.: 1/3 scored, 2/3 oval Did not meet USP weight variation specification; atorvastatin 20mg, atorvastatin 40mg, glyburide 5mg, hydrochlorothiazide 50mg (both products), hydrochlorothiazide 25mg, metformin 80mg, sildenafil 50mg: 3/8 scored, 2/8 oval	7

Nifedipine 10mg, round unscored, sustained-release	38/40 tablet halves deviated from the percentage deviation allowed (European Pharmacopoeia for uncoated or film-coated tablets of ≤80mg). There was wide variability for half and quarter tablet weights Halves and quarters had similar dissolution profiles, both released the drug slightly faster than whole tablets	8
All tablets scored Atorvastatin 20mg, film coated, oblong Atorvastatin 10mg, film coated, oblong Amlodipine besylate 5 mg, oblong Captopril 25mg, round Enalapril maleate 5mg, round Atenolol 100mg, round Amiloride hydrochloride 5mg and hydrochlorothiazide 50 mg, round Enalapril maleate 10mg, round Losartan 50mg, round Amlodipine 5mg oblong Enalapril maleate 20mg round Atenolol 100mg round Enalapril maleate 5mg round Propranolol 10mg round	Halved tablets Only the film coated, oblong Atorvastatin 20mg product met the European Pharmacopoeia specification for weight uniformity of scored tablets. All of the thirteen other tablets , following splitting had fragments outside of the 85-115% range of the average mass Only four tablets following splitting (Atorvastatin 10mg, film coated, oblong; Amlodipine besylate 5 mg, oblong; Captopril 25mg, round; Enalapril maleate 5mg, round) had no fragments outside of the 75-125% range of the average mass	9

Table 2: One study halved and quartered tablets and used pharmacopoeia based outcomes for weight and/or drug content uniformity to compare tablet cutters.

Drugs	Outcomes summary	Ref
Clonidine 0.1mg (brand and generic), scored Captopril 12.5mg, scored Amlodipine 5mg, not scored Atenolol 25mg, not scored Sertraline 50mg, scored Carbamazepine 100mg, scored	First cutter; % halves weighing within ±15%, USP specification, (3 lots of each used, range across these lots); clonidine (brand) 52.5-100%, clonidine (generic) 47.5-70%, captopril 58.3-95% amlodipine 77.5-85.7%, atenolol 62.5-95% sertraline 100%, carbamazepine 87.5-92.5% % quarters weighing within ±15%; clonidine (brand) 43.8-60%, clonidine (generic) 37.5-45%, captopril 37.5-55% Second cutter; % halves weighing within ±15%; clonidine (brand) 85-90%, clonidine (generic) 30-78.9%, captopril 95-100% amlodipine 76.9-90.5%, atenolol 27.5-35%, sertraline 90-100%, carbamazepine 60-80% % quarters weighing within ±15%; clonidine (brand) 57.5-71.3% clonidine (generic) 25.0-48.8%, captopril 26.3-36.1%	10

The presence of a score line does not guarantee an equal subdivision of tablets [1,3,4,5,6,7,9,10]. (Tables 1 and 2). Uniform splitting was related to the hardness, friability and shape of tablets [9]. Splitting was also related to tablet shape, size & hardness and the depth of score lines (Table 3)

Table 3: Studies relating uniformity of splitting to tablet shape, size, hardness and depth of score lines [11,12]

Drugs	Outcomes summary	Ref
Warfarin 5 mg (deep score), Digoxin 0.25 mg (scored), Phenobarbital 30 mg (Unscored), Prednisolone 5 mg (Scored)	Tablets split with knife and resulting half-tablets were weighed and evaluated for weight uniformity using adapted USP method. Splitting warfarin tablets produces weight-uniform half-tablets possibly attributed to hardness and presence of deep score line. Digoxin, phenobarbital, and prednisolone tablet splitting produces highly weight variable half tablets.	11
Mirtazapine 30 mg, Bromazepam 3mg, Oxcarbazepin 150 mg, Sertraline 50 mg, Carvedilol 25 mg, Bisoprolol fumarate 10 mg, Losartan 50 mg, Digoxin 0.25 mg, Amiodarone HCl 200 mg, Metformin HCl 1g, Glimepiride 4 mg, Montelukast 10 mg, Ibuprofen 600 mg, Celecoxib 200 mg, Meloxicam 15 mg, Sildenafil citrate 50 mg	Investigated the effect of tablet characteristics on weight and content uniformity of half tablets, resulting from splitting 16 commonly used medications with a knife. Dose variation exceeded a proxy USP specification for more than one-third of sampled half tablets of bromazepam, carvedilol, bisoprolol, and digoxin. Drug content variation in half tablets appeared to be attributed to weight variation due to fragment or powder loss during the splitting process. Tablet size, shape, hardness and presence of score lines were important variables. Provides recommendations and decision tree for safe tablet-splitting prescribing practices.	12

Two studies have applied specifications, other than those weight related, to whole tablets to halved or quartered tablets (Table 4)

Table 4: Studies considering the physical parameters of whole halved and quartered tablets.

Drugs	Outcomes summary	Ref
Lisinopril 5mg, 10mg, 20mg, scored Lisinopril/hydrochlorothiazide 20/12.5mg, scored	Ph Eur adapted specification, all whole and halved tablets met the specification for crushing strength, friability, disintegration time and mass uniformity	13
Captopril (1) 25mg, circular, uncoated Captopril (2) 25mg, circular, uncoated Captopril (3) 25mg, square, coated	Whole halved and quartered tablets were studied The hardness of the tablets ranked as whole > halves > quarters for each of the three products The friability ranked as whole < halves < quarters for each of the three products	14

A variety of studies has extended splitting to include quartered tablets (Table 1 ref [8], Table 2 ref [10], Tables 5, 6)

Table 5: One study applied Pharmacopoeia specifications to examine deviations from the theoretical weights of halved and quartered tablets

Drugs	Outcomes summary	Ref
Captopril (1) 25mg, circular, uncoated Captopril (2) 25mg, circular, uncoated Captopril (3) 25mg, square, coated Captopril 1 and 2 had differing diameters and thicknesses All had two crossed grooves on one of the faces	Half tablet weight variations from theoretical weight higher than the divisibility limit value (Portuguese Pharmacopoeia VI), 25% (captopril 1), 10% (captopril 2) and 32.5% (captopril 3) Quarter tablet weight variations higher than the divisibility assay limit, 42.2% (captopril 1), 37.5% (captopril 2) and 58.8% (captopril 3) – of these 13.8% (captopril 1), 75% (captopril 2) and 26.3% (captopril 3) had values more than double the limit Dissolution profiles and parameters of halved tablets met the specification, quartered tablets did not	14

Table 6: One study quartered tablets and considered them not to be of acceptable weight standards

Drugs	Outcome summary	Ref
Levodopa 500mg (x3 brands: A, B C Sulphamethoxypyridazine 500mg (multiple scored tablets)	Levodopa A and B; No significant difference in weight variation between whole tablets and quarters. Levodopa C and Sulphamethoxypyridazine: significant difference in weight variation between whole tablets and quarters. Levodopa A: significant difference in % content between tablets and quarters implying less homogeneity of drug distribution in un-quartered tablets Levodopa B & C and Sulphamethoxypyridazine; No significant difference in % content between tablets and quarters	2

In addition, a commercial controlled release isorbide-5-mononitrate tablet of 60 mg is scored to allow division into 20mg and 40 mg segments [15]. Splitting tablets into two or three parts was reproducible with relative standard deviations of 0.8 – 1.5 %.

One further study (Table 7) assessed the divisibility of scored antihypertensive tablets to achieve dose accuracy.

Table 7: One study split 34 brands of antihypertensive scored tablets, grouping the halved tablets into categories dependent on the weight deviation from the theoretical weight of halved tablets

Drugs	Outcomes Summary	Ref
Acebutolol (400mg) / Mefruside (20mg). Acebutolol (400mg). Amiloride (5mg) / Hydrochlorothiazide (50mg). Atenolol (100mg) / Chlorthalidone (25mg) Atenolol (100mg). Catopril (25mg). Chlorthalidone (100mg). Clopamide (20mg). Dihydralazine (25mg). Diltiazem (60mg). Frusemide (40mg). Guanfacine (2mg). Hydrochlorothiazide (25mg). Methyldopa (500mg) [two batches]. Metolazone (5mg). Metoprolol (200mg) / Chlorthalidone (25 mg). Metoprolol (100mg) / Hydrochlorothiazide (12.5mg) / Hydralazine (25mg). Metoprolol (100mg) / Hydrochlorothiazide (12.5mg). Metoprolol (200mg). Metoprolol (100mg). Nadolol (120mg). Oxprenolol (160mg). Penbutolol (40mg). Pindolol (10mg) / Clopamide (5mg). Pindolol (10mg). Prazosin (5mg). Prazosin (1mg). Propranolol (40mg). Propranolol (80mg). Sotalol (320mg). Sotalol (160mg) / Hydrochlorothiazide (25mg). Timolol (100mg) / Hydrochlorothiazide (250mg) / Amiloride (2.5mg). Timolol (10mg).	Weight deviation based on theoretical weight of half tablets 7 Excellent divisibility: Acebutolol (400mg), Methyldopa (500mg), Metoprolol (200mg) / Chlorthalidone (25 mg), Metoprolol (200mg), Oxprenolol (160mg), Penbutolol (40mg), Timolol (10mg). 11 Good divisibility: Acebutolol (400mg) / Mefruside (20mg), Catopril (25mg), Clopamide (20mg), Frusemide (40mg), Metolazone (5mg), Nadolol (120mg), Pindolol (10mg) / Clopamide (5mg), Prazosin (5mg), Prazosin (1mg), Sotaolol (160mg) / Hydrochlorothiazide (25mg), Timolol (100mg) / Hydrochlorothiazide (250mg) / Amiloride (2.5mg). 10 Moderate divisibility: Amiloride (5mg) / Hydrochlorothiazide (50mg), Chlorthalidone (100mg), Diltiazem (60mg), Guanfacine (2mg), Hydrochlorothiazide (25mg), Methyldopa (500mg), Metoprolol (100mg) / Hydrochlorothiazide (12.5mg), Metoprolol (100mg), Pindolol (10mg), Propranolol (40mg). 6 Poor divisibility: Atenolol (100mg) / Chlorthalidone (25mg), Atenolol (100mg), Dihydralazine (25mg), Metoprolol (100mg) / Hydrochlorothiazide (12.5mg) / Hydralazine (25mg), Propranolol (80mg), Sotalol (320mg).	16

Eight studies used dissolution profiles to assess halved or segmented tablets (Table 8). Each study identified differences in dissolution profiles between halved and intact tablets and with the exception of refs [14,21] considered tablets with a modified-release mechanism.

Table 8: Studies which halved tablets and used dissolution profile outcomes

Drugs	Outcomes summary	Ref
Nifedipine 10mg modified release	USP 1 dissolution method: crushed tablets had the fastest dissolution profile. Tablets cut into halves or quarters had slower profiles which were still faster than intact tablets	8
Captopril (1) 25mg, circular, uncoated Captopril (2) 25mg, circular, uncoated Captopril (3) 25mg, square, coated	The three formulations released similar amounts of drug after 20 minutes. The coated product (3) gave a slower dissolution profile due to its film coat. Halving and quartering increased the speed of dissolution for the three products and obviated any retarding effect of the film in product (3)	14
Isorbide-5-mononitrate 60mg	Dissolution profiles of tablet fragments differed by 10% or less relative to the intact tablet	15
Methylphenidate 20mg, generic and brand named, extended release	Mean cumulative dissolution profiles (USP method) showed significant differences between halved and whole tablets from the same manufacturers and between halved brand and whole generic tablets	17
Aspirin 800mg, sustained-release Aspirin 325mg Aspirin 650mg, extended-release, microencapsulated particles	The dissolution rate of the split tablets of the 800mg tablets was significantly higher than that for whole tablets. The other tablets had similar drug release profiles over time with whole and split tablets	18
Theophylline 300mg controlled-release (8 different brands)	USP dissolution methods: 7 brands with simulated gastric fluid (SGF) and 6 brands with simulated intestinal fluid (SIF) had significant differences in dissolution profiles between whole and half tablets	19
Sustained release theophylline 100mg tablets	USP 2 dissolution method: dissolution from halved tablets was significantly higher than from whole tablets	20
A novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine,	Tablets were developed for paediatric HIV patients to allow easy breaking into a maximum of 8 subunits. The intact tablets and their subunits disintegrated within 20 s and in dissolution tests, > 95% of each drug was released after 30 min via USP 2 dissolution method	21

Apart from splitting tablets, dispersing tablets in water and taking an aliquot of the resulting suspension is used clinically to obtain reduced doses. Two studies assessed this practice using prior crushing and dispersion [8] or dispersing dispersible tablets [21] (Table 9)

Table 9: Studies dispersing tablets and taking aliquots equivalent to a dose

Drugs	Outcome summary	Ref
Nifedipine 10mg modified release	10mg crushed nifedepine tablets were suspended in 10ml water. Samples were extracted using 1 or 5ml oral syringes. Doses ranging from 2.9 to 5,7mg and 0,6 to 1.5mg were obtained using 5ml and 1 ml syringes respectively compared to theoretical doses of 5 and 1mg.	8
Aspirin 75mg, dispersible	Irrespective of dispersion time the samples taken from the base of the container were consistently closest to the intended dose, with a trend for the aspirin dose to decrease as the dose withdrawal zones ascended up the beaker	22

Weight and/or drug content evidence summary statements
• One study [3] considered six drug products with 12.8% of halves outside the weight specification and 23.9% outside the drug content specification • Seven studies [1,4,5,6,7,8,9] identified that for halved tablets 33.3% (4/12 products), 68.2% (15/22 products), 70% (7/10 products), 80% (4/5 products), 95% (1 product), 100% (2/2 products) and 93% (13/14) did not meet the pharmacopeia based weight specification • Dose variation exceeded a proxy USP specification for more than one-third of sampled half tablets of four drugs [12]. Variation of dug quantity half tablets was attributed to weight variation due to fragment or powder loss during splitting. • Three studies [8,10,14] (12 products) halved and quartered tablets; there were higher percentages of quartered tablets outside the specification than there were with halved tablets • One study [2] found no significant difference in weight variation between whole tablets and quarters for two products but significant differences for two other products. For one of the former products there was significant variation between whole tablets and quarters in % content implying poorer homogeneity of drug distribution • Five studies [817,18,19,20] (seven products) halved sustained-release tablets and used dissolution profiles, all showed significant differences in dissolution profiles between halved and intact tablets • One study (+) used deviations from the theoretical weight of halved and quartered tablets, finding that 10-32.5% of halves and 37.5-58.8% of quarters were outside the weight limit [14]. • One study quartered tablets and considered them not to be of acceptable weight standards [2]. • One study showed considerable variation in the intended dose following tablet crushing and subsequent dispersion [8]. • One study [22] (1 product) dispersed tablets; irrespective of dispersion time samples taken from the base of the container were closest to the intended dose

2.2.1.2. Methods of manipulation outcomes

Twelve of the studies compared methods of manipulating tablets.

Table 10: Studies which considered different methods of tablet manipulation

Methods of manipulation – outcome summary	Ref
4 products were examined (Levodopa 500mg (x3 brands: A, B C) & Sulphamethoxypyridazine 500mg which were multiple scored tablets allowing halving and quartering. Using a blade based cutting apparatus resulted in quarters where a large proportion were outside acceptable limits for uniformity of weight; with tablets broken by hand non-uniformity was more marked.	2
11 drugs halved with a razor blade, 3 passed USP uniformity of weight specification (2 unscored tablets, 1 scored tablets) and 8 failed uniformity specification; (5 unscored tablets, 3 scored tablets). 3 of the scored drugs, all of which had failed the uniformity specification when split with a razor blade, were also failed when split by hand	7
Two commercial cutters were examined for halving and quartering tablets of captopril, clonidine, amlodipine, atenolol, carbamazepine and sertraline. Neither cutter yielded consistent results for tablet quarters or halves. Statistical analysis to determine the superiority of either cutter was not conducted because of the lack of reproducibility of weights	10
No significant difference between 100 unscored tablets halved with a tablet splitter and 25 tablets of the same drug which were split by hand	23
45 round, film coated, unscored tablets from the same lot number, halved with a tablet splitter. 16% had a deviation of >15% from the theoretical weight compared with 58% of 45 tablets which were split with a kitchen knife	24
33% of manually halved round, scored tablets were within 5% of the ideal weight, 40.2% of tablet splitter halved tablets were within 5% of the ideal weight	25
2 methods of crushing whole tablets for nasogastric tube administration (pestle/mortar and between medicine cups) and dispersing whole tablets showed significant differences in the amount of drug delivered – dispersing was the closest to the intended dose	26

8 drugs, halved and quartered, scored and unscored tablets. Those split with a tablet splitter had significantly lower deviation from theoretical weight and significantly less weight loss than those split by scissors (unscored)/hand (scored) or with a kitchen knife. For theoretical weight there was no significant difference between the scissors/hand and the kitchen knife and for weight loss there was significantly less weight loss with the scissors/hand than with the kitchen knife	27
24 round, unscored tablets quartered with a tablet splitter or manually cut with a razor blade found no significant difference in mean fragment weight and a significantly greater variance within the group for the tablet splitter than with the manually split tablets. This study also found significant differences in the drug content in different fragment weight groups	28
Flat, round, cross-scored tablets were manually halved and quartered, using four different methods (30 tablets per method), and split using a knife. Using USP criteria Half tablets; the score-up break had the lowest residual variance, the score-down break and the score-up knife had the lowest person variability. Quarter tablets; score-down break had significantly higher variability than for score-up break or score-up knife	29
Paracetamol tablets (round, flat, uncoated, 500 mg, scoring not stated) divided by hand or using 6 different proprietary tablet splitters or a kitchen knife. The intra and inter device accuracy, precision and sustainability were investigated. Compliance to (adapted Ph Eur) regulatory requirements was also investigated. Only hand splitting produced half-tablets complying with regulations.	30
Salbutamol 4 mg scored tablets were split by hand or tablet cutter and weight and drug content variability compared against USP specification. Drug content variation in half-tablets appeared to be attributable to weight variation occurring during the splitting process. The tablet cutter was superior to manual splitting,	31

Methods of manipulation evidence summary statements

- One study [2] (4 products) found the use of a blade-based cutting apparatus resulted in quarters where a large proportion were outside acceptable limits for uniformity of weight; non-uniformity was more marked with tablets broken by hand
- One study [7] (11 products) considered tablets halved with a razor blade; 8/11 failed the uniformity specification (3 of these were scored and when split manually again failed the specification)
- One study [10] (6 products) used 2 cutters to half and quarter tablets but neither cutter yielded consistent results
- One study [23] (1 product) found no significant difference in weight variation between unscored tablets halved with a tablet splitter or by hand
- One study [24] (1 product) using film coated, unscored tablets found 16% had a deviation of >15% when using a tablet splitter and 58% when using a kitchen knife from the theoretical tablet weight
- One study [25] (1 product) found 33% of manually halved tablets were within 5% of the ideal weight compared to 40.2% of tablets halved with a splitter
- One study [27] (eight products) considered tablets halved and quartered with a tablet splitter, a kitchen knife and scissors/manually. The tablet splitter was significantly more accurate and had less weight loss than the other methods
- One study [26] (one product) considered two methods of crushing and dispersing; dispersing the tablets provided the closest dose to the intended dose
- One study [28] (one product) considered tablet halved with a splitter or manually cut; there was no difference in mean fragment weight (there was greater variance with the tablet splitter)
- One study [29] (one product) considered tablets halved and quartered using four methods manually and with a kitchen knife; lowest loss found with two of the manual methods
- One study [30] found that manual halving of paracetamol tablets produced half tablets complying with regulation whilst tablet splitters or a knife did not. The study acknowledged ‘ideal’ tablet and conditions used for manual splitting.
- One study [31] (1 product) found drug content variation in half-tablets was superior when halved with a tablet cutter compared to manual splitting

2.2.1.3 Tablet shape Outcomes

There were five studies [3,4,6,7,12,27] that included tablets which were not flat and round but were alternatively shaped (e.g., trapezoid, octagon, shield-shaped, ovoid-rectangular). Halves of these tablets did not meet the specified USP weight specification. Another study [9] showed that of 4 products examined, only 1 film-coated oblong shaped tablet passed the EP specification for weight uniformity of scored tablets whereas 3 other oblong-shaped tablets (one film-coated) did not. A square captopril product,[14] subdivided into halves and quarters, met weight variation limits whereas two circular tablets did not, despite all three products having crossed grooves on one of their faces.

Tablet shape evidence summary statement
• Eight studies [3,4,6,7,9,12,14,27] indicated that halved irregularly shaped tablets did not meet the specified weight criteria • One study [9] showed that only 1 of 4 oblong shaped tablets met the specified weight criteria. • One study [14] demonstrated that square-shaped tablets met the specified weight criteria on halving and quartering in contrast to round tablets

A novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine, was developed for paediatric HIV patients [21]. The tablet was rectangular in shape (22.4 mm long, 11.2 mm wide) with multiple score lines (depth 0.89 mm, angle 100º) to allow easy breaking into a maximum of 8 subunits. The tablets were subdivided along the score lines into 1/2 (along shortest axis of the tablet), 1/4 (along shortest axis), 3/4 (along shortest axis) and 1/8 tablet. The average weights of the smallest pieces (1/8 of a tablet) were within the 85–115% range of the average mass limits as required by the EP.

2.2.1.4 Scored versus unscored tablet outcomes

Studies [1,3,4,5,6,7,10,11,12] describing outcomes from scored and unscored tablet from the studies using pharmacopoeia specifications are in Tables 1 to 5. One additional study [23] which used weight variance reported on differences between scored and unscored tablets. 125 unscored tablets split with either a tablet splitter or by hand had significantly higher weight variance than 30 tablets of a scored control of a different drug.

Scored, unscored tablets evidence summary statements
• Overall outcomes from studies which compared scored and unscored halved tablets indicated that scored tablets may split more accurately than unscored tablets. • Five [3,4,1,5,6] studies which halved tablets and used pharmacopeia based specifications (40 products) found that both scored and unscored tablets did not meet the specified criteria • One study [23] (two products) found significantly higher weight variance with unscored tablets than with a scored control (+ quality level) • One study [3] (six products) found higher percentages of unscored tablets outside the specifications for weight and drug content than the scored tablets • One study[7] (4 scored products) found only 1 product, when halved, met the USP weight variation specification • One study[10] (5 products, three lots of each) demonstrated that the quality of halves and quarters, depended on the batch and the cutter used. • One study[11] (3 scored products) showed that one deep scored product produced weight-uniform half-tablets whereas two other scored products did not.

2.2.1.5 Bioavailability outcomes

There were no studies identified which met the definition of a manipulation of tablets to obtain the required dose i.e. obtained and administered a proportion of the original dosage form. All of the studies administered the whole dose e.g. by halving a tablet and then giving both halves to study participants. However, a number of studies investigated the splitting or crushing of sustained-release or enteric-coated tablets and therefore although the whole dose was administered the outcomes were considered relevant. Nine of these studies were included, all of which involved adult participants.

Table 11: Bioavailability studies on crushed modified-release tablets

Drug	Outcomes summary	Adverse effects	Ref
Pentoxifylline 400mg & 600mg (extended-release, Trental)	Crushing the tablets did not significantly change the relative bioavailability. Cmax significantly greater and tmax significantly shorter for crushed versus intact tablets	Crushed tablets – nausea (3 mild, 7 moderate & dizziness), 1/10 diaphoresis, headache, vomiting. None with intact tablets	32
Pantoprazole 40mg (enteric coated, Protonix)	Suspension of the crushed tablet 25% less bioavailable than the whole tablet	Both treatments well tolerated 1 anorexia, 1 rhinitis (study included NG tube insertion when the suspension was being administered)	33
Theophylline 300mg (sustained- release, Theo-Dur)	No significant difference in AUC to 24hour and serum concentration at 12 or 24hour, intact tablets took a significantly longer time to peak concentration	Not reported	34

There were six studies identified which split tablets; four compared halved and whole tablets, one compared halved tablets with whole tablets and an elixir and one compared tablets split into thirds and whole tablets.

Table 12: Bioavailability studies on split modified-release tablets

Drug	Outcomes summary	Adverse effects	Ref
Isosorbide-5-mononitrate 60mg (controlled-release, Monoket Multitab)	AUC unaffected by splitting, C_{max} 10% higher, C_{min} 19% lower for trisected tablet	2 dropped out with severe headache (split tablets), 4 low severity headache not related to a particular treatment	15
Theophylline 100mg (sustained-release, Theo- Dur)	No significant difference in AUC, mean absorption times, mean theophylline half-life values and total body clearance of theophylline	Not reported	20
Verapamil 240mg (sustained-release; Securon SR)	No significant difference in mean plasma concentration and mean time to peak plasma levels between halved and whole tablets	Tolerability considered excellent 1 withdrawn with heartblock (treatment not specified)	35
Theophylline 400mg (slow-release, Uniphyllin)	AUC_{12} and peak plasma levels significantly higher with halved compared with intact tablets,	6 slight tremor, jitteriness, nausea, headache with both treatments – occurred earlier with split tablets	36
Theophylline 300mg (sustained-release, Theo-Dur)	Mean bioavailability similar for halved and whole tablets, sustained action was maintained after splitting	Not reported	37
Verapamil 240mg (sustained-release, Isoptin SR, Securon SR)	Mean peak plasma level, T_{max} and AUC, NS difference between halved and whole tablets	Not reported	38

Bioavailability evidence summary statements

- In two studies [32, 35] whole sustained-release tablets were crushed and administered. There were no significant changes in bioavailability outcomes, though the time taken to reach peak concentrations was significantly longer for intact tablets.
- In four studies [20,35,37,38] whole sustained-release tablets were split and administered. There were no significant changes in bioavailability outcomes.
- In two studies [15,36] whole sustained-release tablets were split and administered. Higher peak plasma concentration levels were found with split compared with intact tablets.
- In one study [33] whole enteric-coated tablets were crushed and administered. The crushed tablet was 25% less bioavailable than the intact tablet.

Two other studies were identified. No significant difference in pharmacokinetic parameters in bioavailability in adults between Duovir® and a novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine, intended for paediatric HIV patients was reported [21]. No significant differences in pharmacokinetics in HIV-infected children were noted between quartered, halved or three quartered generic tablets containing multiples of lamivudine 300mg, stavudine 80 mg and nevirapine 400 mg and liquid formulations containing the individual drugs.

2.2.1.6 Additional outcomes

Nine additional studies had outcomes relating to indicators of effectiveness or patient experience of manipulating tablets or adherence/compliance.

Table 13: Effectiveness, patient experience and adherence/compliance

Drugs	Outcomes summary	Ref
Atorvastatin Simvastatin Pravastatin	Lipid profiles: No significant difference in total cholesterol, HDL, LDL or triglycerides between baseline levels and post splitting levels Adherence unchanged prior to and post tablet splitting Survey: overall respondents did not find splitting tablets had affected their willingness to take their medication or that tablets had to be discarded due to splitting-related problems	40
Fosinopril sodium 20mg	No significant difference in compliance between whole and halved tablet groups Survey: overall tablet splitter not detrimental to compliance and did not result in any more missed doses than whole tablets	41
Lisinopril 16 mg (mean daily dose)	No significant difference in mean systolic and mean diastolic blood pressure with tablet splitting Survey: overall tablet splitting 'not bothersome', for 57% there were more than 2 pieces after splitting either some of the time or most of the time	42
Risperidone, scored	Adherence (by medication possession ratios) increased significantly from pre to post splitting No change in psychiatric or non-psychiatric admission rate from pre to post splitting	43
Lovastatin 40mg	Survey: overall majority of respondents found tablet splitters easy to use, did not waste medication and did not hinder compliance	44
Simvastatin Atorvastatin (tablet dose not specified)	Overall – significant decreases in total cholesterol and LDL pre and post splitting. Half tablet dosing as affective as whole tablet taking.	45
Atorvastatin Lovastatin Simvastatin	No significant difference in total cholesterol and triglycerides pre and post tablet splitting, significant small increases in HDL, AST and ALT and decreases in LDL Survey: overall – tablet splitter was not considered difficult to use and did not affect compliance, 46% found it easier to take medications when they did not have to split tablets	46
Prednisolone 1mg/kg	Taste scores were significantly better for oral solution than for crushed tablets 9 (23%) children withdrew with repeated vomiting from the crushed tablet group No significant difference in dyspnoea between groups	47
Simvastatin 5,10,20,40mg	No significant difference in LDL between whole and halved tablets Medication compliance: NS difference between whole and halved tablet groups	48

Adherence/compliance evidence summary statements

- Six studies considered adherence/compliance: Five studies [40,41,44,46,47] found that splitting tablets did not affect adherence/compliance but one study [45] showed improved compliance

Clinical/ biochemical outcomes evidence summary statements

- Six studies considered clinical or biochemical outcomes. Five studies [40,42,43,46,48] found that splitting tablets did not influence clinical or biochemical outcomes but one study[45] showed improved clinical performance.

Patient experience summary statements

- Four survey based studies [40,42,44,46] found that patients did not consider tablet splitting difficult

Palatability summary statements

- One study [47] reported that children taste-scored an oral solution significantly better than crushed tablets

2.2.2 *Questionnaire*

59/153 (38.6%) of questionnaire respondents reported the manipulation of tablets. (See Appendix 4; Richey, Shah et al, BMC Pediatrics 2013 13:81 doi:10.1186/1471-2431-13-81). These

respondents identified 86 manipulations. These included situations where different methods of manipulation were reported for the same drug e.g., the same drug could have been reported as halved by one respondent and dispersed by another and where different proportions of the original dose were required e.g. a drug was reported as halved by one respondent and quartered by another. These manipulations involved 30 different drugs (acyclovir, allopurinol, aspirin, atenolol, baclofen, captopril, clobazam, codeine, cyclizine, diazepam, diclofenac, domperidone, folic acid, gabapentin, glycopyrronium bromide, hydrocortisone, ibuprofen, levomepromazine, Lisinopril, metronidazole, nifedipine, omeprazole, paracetamol, phenobarbitone, potassium chloride, prednisolone, ranitidine, sildenafil, thyroxine, topirimate).

The types of tablet manipulations reported were:

- Tablet dispersed, proportion given: 46/86 (53.5%)
- Tablet cut, proportion given: 31/86 (36.0%)
- Tablet crushed, proportion given: 9/86 (10.5%)

The percentage of the original tablet dose required in the 86 manipulations was identified in the questionnaire: 35/86 (40.7%) required halving the tablet dose, 12/86 (13.8%) required quartering to give a quarter or three-quarters of the tablet dose.

Table 14: Percentage of original tablet dose required

Percentage of original tablet dose required	Frequency identified
7%	1
19%	1
20%	2
25%	8
40%	6
50%	35
60%	8
65%	1
66%	1
75%	4
80%	4
90%	1
Missing or obscure	14

Respondents to the questionnaire were asked to report the equipment that they used to split tablets. Almost two thirds of respondents (98/153, 64.1%) use tablet splitters, 11.8% (18/153) use tablet splitters or break the tablets by hand, 2.6% (4/153) break by hand, 2% (3/153) use a stitch

splitter/blade, 1.3% (2/153) use tablet splitters, knives or break the tablets by hand.

Questionnaire summary:
• 61.8% of tablet manipulations identified in the questionnaire required a half or a quarter of the original tablet dose. • In 53.5% of reported tablet manipulations the tablets were dispersed and a proportion of the dose administered. • The predominant method used by respondents to split tablets was with a tablet splitter.

2.2.3 *Observational study*

There were 191 manipulations of 27 drugs which aimed to achieve the required dose involving tablets. Of these, 40 manipulations were observed, 25 where tablets were split, 12 where tablets were dispersed, one where a tablet was broken by hand, one where a tablet was crushed and one where two manipulations (splitting and dispersing) were required to get the prescribed dose. These observed manipulations involved 17 drugs (Amitryptiline, Aspirin, Diclofenac, Digoxin, Furosemide, glycopyrronium bromide, hydralazine, hydrocortisone, levothyroxine, omeprazole, paracetamol, phosphate Sandoz, prednisolone, tetrabenazine, tramadol, warfarin, zinc sulphate). Of the 40 manipulations observed: 29/40 (72.5%) required halving the tablet dose, 6/40 (15%) required quartering the tablet dose to take a quarter or a three-quarters of the tablet dose.

Table 15: Percentage of original tablet dose in observed manipulations

Percentage of original tablet dose required	Frequency observed
25%	6
30%	1
31.6%	1
40%	1
50%	29
60%	1
75%	1

Of the 26 tablets which were observed being split (25 solely split, one initially split to get half and dispersed to get a quarter), all were split using a tablet splitter. Of the tablets halved or quartered, the resultant segments were considered to be visibly unequal in size in eight (30.8%) cases and visible powder was generated or the tablet crumbled in nine (34.6%) cases. Three (11.5%) manipulations were repeated; in two cases because the tablets crumbled on splitting and in the third case because the tablet did not split evenly (all of the manipulations which required repeating involved different drugs).

In all but one case where tablets were dispersed it appeared to observers that the tablet had fully

dispersed prior to a proportion being taken: in all cases the dispersed dose was drawn from the bottom of the container.

Two of the observed tablet manipulations were undertaken although there was an alternative dosage form available (oral liquid) which did not require manipulation. In both cases, the patient preference was for a solid dosage form which could only be provided as a half tablet.

Observational study summary
• 90% of the observed tablet manipulations required a half or a quarter of the original tablet dose. • In 5% of the observed tablet manipulations, the manipulation was undertaken because the patient did not want to take the oral liquid dosage form.

2.2.3.1 Observational study from the literature:

A study [49] was identified reporting observations of manipulation of solid oral dosage forms during medicine rounds in aged care facilities. From 160 observations across six medication rounds, 29 residents had a total of 75 medications modified by the nursing staff prior to administration, with 32% of these instances identified as inappropriate. Methods used for crushing and administration resulted in drug mixing, spillage and incomplete dosing. Staff reported adequate resources but a lack of knowledge on how to locate and use resources was evident. The pilot study concluded that improved staff training on how to use available resources was needed to reduce the observed high incidence of inappropriate crushing of medicines.

2.2.4 *Evidence to recommendations – tablets*

The group considered that where tablets are split, although there are limitations to the available evidence, the risk of this manipulation is increased if the properties of the tablet are altered (such as with sustained-release or enteric coated tablets) or if the tablet is an unusual shape. The risk may also be increased if the tablet is not scored.

The group considered that there was some evidence to support the use of tablet splitters for halving tablets which are of a uniform shape and that this method is the most likely to reduce the risk of not obtaining the intended dose.

The group discussed the theoretical risks of splitting or crushing tablets which have modified release mechanisms with the possibilities of altered dose release from manipulated tablets. The group agreed that tablets with this formulation should not be manipulated unless information from the manufacturer permits this or without specific discussion with prescribers and/or pharmacists.

The group considered that for dispersion of tablets for the purpose of taking a proportional dose, the method should not be undertaken unless the solubility of active ingredients is known.

The potential for confusion caused by the use of dose ranges was discussed and the group concluded that prescribers may consider dose rounding more acceptable. The group considered the need to include guidance around dose rounding and using a basis of pharmacopoeia limits for drug content, dose rounding (up or down) within 10% would be acceptable.

2.2.5 *Tablet recommendations*

- Where patient preference requires a tablet to be manipulated ensure that the implications of this are discussed with the patient/parents/carers
- Tablets should be split in preference to dispersing or crushing tablets and taking a proportion.
- Tablets should only be dispersed in liquid if there is knowledge of the dispersibility of products or solubility of active ingredients and of any special characteristics of the formulation (e.g. controlled release beads or enteric coated capsules and tablets). Insoluble material may remain after dispersion or dissolution of a drug which is known to be soluble due to the presence of insoluble excipients in the original product. Manufacturers and/or pharmacists should be consulted..
- Split tablets using a tablet splitter
- Clean and replace tablet splitters according to manufacturer and local recommendations
- Scored tablets should be split along the score line, with the score line uppermost
- Consult a pharmacist prior to splitting unscored tablets
- Do not split tablets into less than ¼ segments, unless specified by manufacturer. Visually assess the tablet segments to establish if they appear equal in size prior to administration
- Remaining segments of the tablet should be managed in accordance with local policy
- When crushing tablets add the water for dispersal to the container used for crushing so that loss through transfer of the crushed tablet is minimized

2.3 CAPSULES

2.3.1 Systematic review evidence

There were no studies identified through the systematic review which considered the manipulation of capsules.

2.3.2 Questionnaire evidence

13/153 (8.5%) of questionnaire respondents reported the manipulation of capsules. These respondents identified 15 manipulations of eight drugs (aprepitant, gabapentin, loperamide melatonin, nifedipine omeprazole, secobarbital, tacrolimus). These manipulations included liquid

filled capsules of one drug – nifedipine.

The percentage of the original capsule dose required in the 15 manipulations identified in the questionnaire: 5/15 (33.3%) required halving the capsule dose, 2/15 (13.3%) required quartering the capsule dose.

Table 16: Percentage of original capsule dose from the questionnaire

Percentage of original capsule dose required	Frequency identified
25%	1
31.25%	1
50%	5
60%	1
66%	1
75%	1
80%	1
85%	1
Missing	3

Questionnaire summary:

- 46.7% of capsule manipulations reported in the questionnaire required a half or a quarter of the original capsule dose.
- Liquid and solid dose form filled capsules were included in the capsule manipulations reported.

2.3.3 *Observational study*

The observational study identified four manipulations of capsule preparations for three drugs (loperamide, melatonin, oseltamivir). For these manipulations, two required half of the original capsule dose, one required a quarter of the original capsule dose and one required an eighth of the original dose. Where manipulations were observed, capsules were opened, the contents dispersed in water and a proportion taken for administration.

Observational study summary:

- Capsule manipulations required either half, a quarter or an eighth of the original capsule dose.

2.3.4 *Evidence to recommendations – capsules*

The group noted the lack of evidence available for capsule manipulations. The observational study and questionnaire did provide evidence that capsule manipulations are being undertaken in paediatric clinical practice. The group therefore considered and discussed the different types of capsule formulation and agreed that unless designed as a sprinkle formulation, capsules should not be opened to obtain a proportion of the drug contents. For liquid filled capsules the fill volume of the capsule should be known prior to obtaining a proportion of the drug dose. The group

discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.3.5 *Capsule recommendations*

- Unless a capsule is designed as a sprinkle formulation, do not open capsules and take a proportion of their contents without consulting a pharmacist.
- Do not disperse the contents of a capsule and take a proportion without knowledge of the solubility characteristics.
- The contents of capsules should only be dispersed in liquid if there is knowledge of the dispersibility of products or solubility of active ingredients and any special characteristics of the formulation (e.g. controlled release beads) or capsule (e.g. enteric coated). Manufacturers and/or pharmacists should be consulted.
- Avoid removing the contents of liquid-filled capsules where possible
- For liquid filled capsules, where the fill volume of the capsule is known, withdraw the required calculated volume into a syringe to measure the required dose
    - Note: as a needle will be required to extract the capsule contents an IV syringe will have to be used – to avoid the danger of inadvertent intravenous administration the required volume should be drawn up and administered in one operation without interruption. The needle should be removed and safely disposed of prior to administration.
- Discard the remaining portion of the capsule in accordance with local policy

2.4. SACHETS

2.4.1 *Systematic review evidence*

No studies were identified through the systematic review which considered the manipulation of sachets.

2.4.2 *Questionnaire*

2/153 (1.3%) of questionnaire respondents reported the manipulation of sachets; in both cases Gaviscon (compound alginate) was involved. One manipulation required a quarter of the sachet and the second manipulation reported that the dose required varied, dependent on feed volume.

Questionnaire summary:
• For one preparation, compound aliginate (Gaviscon Infant) where a quarter of the sachet was required this was reported as manipulated. (With Gaviscon Infant one 'dose' is half of a dual sachet. It was assumed that where respondents reported that half or a quarter of the dose was required that this was half of the assumed dose of half a dual sachet).

2.4.3 *Observational study*

There were 30 manipulations of four drugs (vigabatrin, morphine sulphate (MST), Gaviscon (compound alginate), Movicol (macrogol 3350)). For the 16 reported manipulations which were for Gaviscon (compound alginate), the dose required was not specified as it was related to the feed volume being used. For the others, six required half of the original sachet dose, three required 75%, three required 40% and one required 80% of the original sachet dose (one reported manipulation did not specify the dose required). Where manipulations were observed sachets were dispersed in water and a proportion taken for administration: in twelve observed sachet manipulations the sachet contents appeared fully dispersed prior to a proportion being taken. In all cases the dose was drawn from the bottom of the container.

Observational study summary:
• 30% of sachet manipulations identified in the observational study required a half or a quarter of the original sachet dose. • For all observed manipulations the sachet contents were dispersed in water and the dose drawn from the bottom of the container.

2.4.4 *Evidence to recommendations – sachets*

The group noted the lack of evidence available for sachet manipulations. The observational study and questionnaire provided evidence that sachet manipulations are being undertaken in paediatric clinical practice. The group discussed that sachet contents are designed to be dispersed to achieve administration of the whole dose. If the solubility characteristics of the drug are unknown it should not be dispersed and a proportion taken. If there is no other option it would be more accurate to weigh/measure the proportion of sachet required, then disperse in a suitable volume and administer the whole volume and wash down and administer any remaining solid in the dosing cup/device. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.4.5 *Sachet recommendations*

- Do not disperse the contents of a sachet and take a proportion without knowledge of the solubility characteristics of the drug
- Discard remaining portion in accordance with local policy

2.5 LIQUIDS FOR ORAL ADMINISTRATION

2.5.1 *Overall evidence*

There were no studies identified through the systematic review which considered the manipulation of liquids for oral administration. No manipulations of liquids for oral administration manipulations were identified in the observational study or reported by questionnaire respondents. The group discussed that whilst dilution of clear aqueous liquids may be straight forward, dilution and accurate dosing from viscous, non-aqueous liquids or suspensions may be more difficult. Factors such as viscosity, compatibility and miscibility of the liquid and diluent and additionally for suspensions the resuspendability of the diluted suspension should be taken into account. The group had no available evidence and used their expertise and informal discussion to develop the recommendations.

2.5.2 *Liquids for oral administration recommendations*

- Volumes of less than 5ml should be administered using an oral syringe
- If very small volumes of oral liquid medicines are required (less than 0.1 ml), they should be diluted to ensure that a volume can be measured accurately. Consult the pharmacist.
- If dilution is undertaken this should be on a dose by dose basis and diluted liquids should not be stored for future use.
- Ensure that the chosen diluent is compatible with the medicinal product

2.6 NEBULISER SOLUTIONS

2.6.1 *Systematic review evidence*

There were no studies identified through the systematic review which considered the manipulation of nebuliser solutions.

2.6.2 *Questionnaire evidence*

22/153 (14.4%) of questionnaire respondents reported the manipulation of nebuliser solutions, all of ipratropium bromide, 13/22 (59.1%) required half and 7/22 (31.8%) required a quarter of the

original dose (two reported manipulations did not specify the dose given).

Questionnaire summary:
• One drug (ipratropium bromide) where a half or a quarter of the original dose was required was reported as manipulated

2.6.3 *Observational study*

There were four manipulations identified, all of ipratropium bromide, which aimed to produce half of the dose from the commercially available product.

Observational study summary:
• One drug (ipratropium bromide) where half of the original dose was required was identified as manipulated.

2.6.4 *Evidence to recommendations – nebuliser solutions*

The group noted the lack of evidence available for nebuliser solution manipulations. The observational study and questionnaire provided evidence that nebuliser solution manipulations for ipratropium bromide are being undertaken in paediatric clinical practice. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.6.5 *Nebuliser solution recommendations*

- Withdraw the required dose volume from the vial into the syringe and add to the nebuliser chamber
    - Note: if a needle is required to extract the nebuliser contents an IV syringe will have to be used – ensure the syringe and unused contents are appropriately disposed of immediately
- To avoid the danger of inadvertent intravenous administration nebuliser solutions should be drawn up and added to the nebuliser chamber in one operation without interruption
- The recommended diluent should then be added to the nebuliser chamber and the solution mixed using a suitable, preferably sterile, device

2.7 INTRAVENOUS INJECTIONS

2.7.1 *Systematic review evidence*

There were no studies identified through the systematic review which considered the manipulation

of intravenous injections.

2.7.2 *Questionnaire evidence*

19/153 (12.4%) of questionnaire respondents reported the manipulation of intravenous drugs. These respondents identified 22 manipulations of 13 drugs (amoxicillin, clindamycin, dexamethasone, enoxaparin, gentamicin, midazolam, morphine, phenytoin, potassium, ranitidine, salbutamol, vancomycin, vitamin K,

The percentages of original intravenous doses required in the 22 manipulations identified in the questionnaire.

Table 17: Percentage of original intravenous dose from the questionnaire

Percentage of original intravenous dose required	Frequency identified
0.7%	1
1.2%	1
2%	3
3%	1
4.4%	1
5%	1
5.7%	2
6.4%	1
7%	1
7.7%	1
8.8%	2
11.2%	1
12%	1
19%	1
40%	1
50%	1
70%	1
Missing	1

Questionnaire summary
• 68.2% of the intravenous injection manipulations reported required <10% of the original dose

2.7.3 *Observational study*

There were 65 manipulations of 18 intravenous drugs (acyclovir, dinoprostone, fentanyl, hydrocortisone, indomethacin, insulin, liothyronine, midazolam, omeprazole, phenobarbitone, ranitidine, rifampicin, salbutamol, suxamethonium, teicoplanin, tetracosactide, vancomycin,

vecuronium). These manipulations required the further dilution of a reconstituted or ready prepared solution to achieve sufficient volume so that the required dose could be measured and administered.

2.7.4 *Evidence to recommendations – intravenous injections*

The group noted the lack of evidence available for intravenous injection manipulations. The observational study and questionnaire did provide evidence that intravenous injection manipulations are being undertaken in neonatal and paediatric clinical practice. The group discussed the intravenous injection manipulations which require further dilution to obtain the dose required. The potential for medication error due to the need for additional calculations and dose measurements was discussed and the importance of local/hospital guidelines to assist with this process was agreed. The volume of liquid in the hub of the syringe/needle could represent a substantial additional dose, particularly where there is small volume measurement of high strength products. To ensure that drug which is in the hub of the syringe is not erroneously administered the importance of adding the measured drug volume in one syringe to the separate syringe containing the diluent should be highlighted. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.7.5 *Intravenous injection recommendations*

- Note: a dilution or reconstitution in accordance with manufacturer instructions is not considered a manipulation in these guidelines
    - Note: The NPSA advises that certain injectable therapy manipulations are undertaken in pharmacy – see NPSA/2007/20: Promoting safer use of injectable medicines. http://www.nrls.npsa.nhs.uk/resources/?entryid45=59812
- Consult local/hospital IV guidelines prior to any manipulation of an intravenous preparation
- Ensure that the chosen diluent is compatible with the injectable product
- The measurement of volumes of less than 0.1ml should be avoided (with the exception of insulin because it is measured in insulin syringes). If a volume of less than 0.1ml must be obtained then the dose required should be measured after an appropriate dilution.
- When further diluting an intravenous injection preparation do not add the diluent to the syringe which contains the drug. Ensure that the drug is withdrawn into one syringe and added to the diluent which is in a separate syringe. Mix the active drug and diluent and withdraw the required volume into a separate syringe

2.8 INJECTIONS FOR SUBCUTANEOUS ADMINISTRATION

2.8.1 *Overall evidence*

There were no studies identified through the systematic review which considered the manipulation of injections for subcutaneous administration. No manipulations of injections for subcutaneous administration were identified in the observational study or reported by questionnaire respondents.

2.8.2 *Subcutaneous injection recommendations*

Note: dilution or reconstitution in accordance with manufacturer instructions is not considered a manipulation in these guidelines

- Consult local/hospital guidelines prior to any manipulation of a subcutaneous preparation
- Ensure that the chosen diluent is compatible with the injectable product
- The measurement of volumes of less than 0.1ml should be avoided (with the exception of insulin because it is measured in insulin syringes). If a volume of less than 0.1ml must be obtained then the dose required should be measured after an appropriate dilution.
- When further diluting a subcutaneous injection preparation do not add the diluent to the syringe which contains the drug. Ensure that the drug is withdrawn into one syringe and added to the diluent which is in a separate syringe. Mix the active drug and diluent and withdraw the required volume into a separate syringe

2.9 TRANSDERMAL PATCHES

2.9.1 *Systematic review evidence*

There were no studies identified through the systematic review which considered the manipulation of transdermal patches.

2.9.2 *Questionnaire*

20/153 (13.1%) of questionnaire respondents reported the manipulation of transdermal patches. These respondents identified 20 manipulations of two drugs (hyoscine hydrobromide and glyceryl trinitrate (GTN)). For hyoscine hydrobromide five manipulations required half of the original patch dose, nine manipulations required a quarter and two manipulations required three-quarters of the original patch dose (three reported manipulations did not specify the dose required). The one GTN patch manipulation which was reported in the questionnaire required an eighth of the original patch dose.

Within the questionnaire respondents were also asked about methods of manipulating transdermal

patches. 38/153 (24.8%) reported that this was not applicable as they do not manipulate transdermal patches. Of the 111 who did report manipulating transdermal patches, 73 (65.8%) cut the patch to obtain the required dose, 31 (27.9%) covered the unwanted segment of the patch and 7 (6.3%) either cut or covered the patch. 4/153 (2.6%) of respondents specified that they would retain unused portions of transdermal patches for future use.

Questionnaire summary
• 80% of transdermal patch manipulations reported in the questionnaire required a half or a quarter of the original patch dose.

Patches were reported as being manipulated both by cutting the required segment (65.8%) and covering the unwanted segment (27.9%).

2.9.3 *Observational study*

There were ten manipulations all of hyoscine hydrobromide transdermal patches. Of these manipulations, four required three-quarters and three required a quarter of the original patch dose (three of the reported manipulations did not specify the dose required). One transdermal patch was observed, the patch was cut with scissors, the required segment administered and the remaining segment was retained for future use.

Observational study summary:
• One drug (hyoscine hydrobromide) was identified where half, a quarter or three quarters of the original dose was required

2.9.4 *Evidence to recommendations – transdermal patches*

The group noted the lack of evidence available for transdermal patch manipulations. The observational study and questionnaire did provide evidence that transdermal patch manipulations (mainly of hyoscine hydrobromide) are being undertaken in paediatric clinical practice. The group discussed the different delivery mechanisms of transdermal patches and noted that the same drug can be delivered by different delivery mechanisms if patches are made by different manufacturers. It was agreed that reservoir patches should not be manipulated as this will permit leakage of drug from the cut area of the patch potentially leading to dose-dumping. The group considered that the size and shape of the patch must be taken into consideration prior to manipulation. The group agreed that division into more than 4 segments risks introducing further inaccuracies and should be avoided. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.9.5 *Transdermal patch recommendations*

Note: different brands of the same drug may have different delivery systems within the patch and may not be equivalent in the way or rate the drug is delivered

- Prior to any transdermal patch manipulation, check with the pharmacy department what release characteristics the patch has (i.e. whether the patch is a matrix or a reservoir patch)
- Do not manipulate reservoir transdermal patches
- Where a proportion of a matrix transdermal patch is required cut with scissors along the full thickness of the patch to produce symmetrical segments
- Do not cut patches into more than 4 segments
- Follow local policy on storage or discarding the remainder of the patch.

2.10. SUPPOSITORIES

2.10.1. *Systematic review evidence*

There was one study [50] identified through the systematic review which considered the manipulation of suppositories. This study asked anaesthesiologists to split acetaminophen (paracetamol) suppositories using the technique they would use in practice. This resulted in wide variation from the intended dose: intended dose 40mg (range 30-78mg), 53mg (range 27-79mg), 60mg (range 47-82mg), 80mg (range 38-92mg), 162mg (range 112-250mg), 217mg (range 113-259mg).

Suppositories evidence summary statement:
• One study split suppositories and found wide ranges in the resultant doses

2.10.2 *Questionnaire evidence*

15/153 (9.8%) of questionnaire respondents reported the manipulation of suppositories. These respondents identified 15 manipulations of four drugs (paracetamol, diclofenac, glycerin, choral hydrate). Of these manipulations seven required half of the original suppository dose, one required three quarters and one required two-thirds of the original suppository dose, one required 48% of the original strength (three reported manipulations did not specify the dose required). Two reported manipulations of glycerin suppositories as a “slither” or a “chip”.

Within the questionnaire, respondents were asked about methods of manipulating suppositories. 69/153 (45.1%) reported that they do not cut suppositories. Of the 83 who did report cutting suppositories, 50/83 (60.2%) cut longitudinally and 32/83 (38.6%) cut transversely; one respondent

reported cutting both transversely and longitudinally.

Questionnaire summary:
• 53.3% of suppository manipulations reported in the questionnaire required a half or a quarter of the original suppository dose.

2.10.3 *Observational study*

There were six manipulations of suppositories involving three drugs (diclofenac, paracetamol, glycerin) which aimed to achieve the required dose. Of these manipulations, one required three-quarters and three required half of the original suppository dose (one of the reported manipulations did not specify the dose required). One manipulation required 87% of the original dose. Where suppository manipulations were observed the suppositories were cut with scissors.

Observational study summary
• 66.7% of suppository manipulations identified required a half or a quarter of the original suppository dose.

2.10.4 *Evidence to recommendations – suppositories*

The group noted the very limited evidence available for suppository manipulations. Furthermore the group acknowledged that the distribution of the drug throughout the suppository may not be homogenous. The observational study and questionnaire did provide evidence that suppository manipulations are being undertaken in neonatal and paediatric clinical practice. The group discussed that the responses from the questionnaires did not show consistency on the direction of cutting suppositories. The group agreed that the method which would be liable to produce the most accurate halves which could be visually assessed is to cut the suppository longitudinally. The group are also aware of the use of glycerine chips/slivers in practice. No evidence has been found to support this approach and the group do not recommend it. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.10.5 *Suppository recommendations*

- Consult pharmacist to identify whether drug distribution is homogenous within the suppository
- Cut suppositories from tip to base using a scalpel blade
- Visually assess the suppository segments to establish if they appear equal in size prior to administration
- Manage the remaining suppository segments in accordance with local policy

2.11 ENEMAS

2.10.1 *Systematic review evidence*

There were no studies identified through the systematic review which considered the manipulation of enemas.

2.11.2 *Questionnaire*

6/153 (3.9%) of questionnaire respondents reported the manipulation of enemas; in all, six cases phosphate enemas were involved. Of these manipulations, five required a half of the enema dose (one reported manipulation did not specify the dose required).

In the questionnaire, respondents were asked about methods of manipulating enemas. 73/153 (47.7%) reported that this was not applicable as they do not manipulate enemas. Of the 75 who did report manipulating enemas: 51/75 (68%) discard the unwanted proportion first and then administer the remainder, 15/75 (20%) administered the proportion required and discarded the remainder and 9/75 (12%) withdraw the proportion required and then administer it.

Questionnaire summary:
• One drug (phosphate enema) was reported as manipulated, where half of the original enema dose was required. • Enemas were reported as being manipulated either by discarding the unwanted proportion first and administering the remainder (68%), or by administering the proportion required and discarding the remainder (20%) or by withdrawing the required proportion and then administering it (12%).

2.11.3 *Observational study*

No manipulations which involved enemas were identified during the observational study.

2.11.4 *Evidence to recommendations – enemas*

The group noted the lack of evidence available for enema manipulations. The questionnaire did provide evidence that enema manipulations for phosphate enemas are being undertaken in paediatric clinical practice. The group agreed that the most appropriate method of obtaining a proportion is to withdraw and discard the proportion which is not required assuming the original sachet and nozzle is suitable for administration. Where this is not the case the required dose should be removed to a suitable container for administration. The group discussed the limited evidence available and used their expertise through this discussion to develop the recommendations.

2.11.5 *Enema recommendations*

- Withdraw from the container using a syringe and needle, the proportion of the enema which

is NOT required and discard: administer the remainder of the enema from the original container.

    - Note: if a needle is required to extract the enema contents an IV syringe will have to be used – ensure the syringe and unused contents are disposed of immediately.

- If the enema container nozzle is not suitable for administration, then the dose required should be withdrawn and administered via a suitable rectal tube.

3 RECOMMENDATIONS

3.1 RECOMMENDATIONS TO THE PHARMACEUTICAL INDUSTRY

- That the Pharmaceutical Industry should note the lack of evidence relating to the manipulation of medicines for the purposes of achieving a suitable dose for administration
- That the Pharmaceutical Industry take note of the research findings within the guidelines and be prepared to support practitioners in their requests for information around manipulations of medicines.
- That the Pharmaceutical industry should consider the need for the following:
    - A smaller dose unit for ipratropium nebuliser solution (125 microgram)
    - A smaller size of hyoscine transdermal patches (equivalent to ¼ and ½ of existing strengths), which ideally would be authorised to reduce drooling in children with cerebral palsy.
    - An alginate antacid preparation for addition to feeds which is available in a smaller dose sachet.
- That the Pharmaceutical industry recognise that children may require a range of doses that require manipulation of adult dosage forms

3.2. RECOMMENDATIONS TO THE REGULATORS

- That regulatory authorities recognise that manipulation is being undertaken in the paediatric population.
- That the regulatory authorities recognize the lack of evidence and encourage the Pharmaceutical industry to provide evidence where reasonable and available.

3.3. RECOMMENDATIONS TO NHS HOSPITALS AND SIMILAR ORGANISATIONS

- That the Trust/organisation should bring the guidelines to the attention of the Medical Director and Heads of Pharmacy and Nursing
- That the Trust should discuss the recommendations within the MODRIC Guidelines and produce their own local guidance to support staff.

3.4. RECOMMENDATIONS FOR FUTURE RESEARCH

- To generate evidence for the manipulations which are being undertaken. There is little evidence for manipulations of specific products which are occurring in practice within the

UK or more generalisable evidence for products in other countries.

- To consider focusing research on manipulations of tablets which are the most common manipulations undertaken and on measurement of small volumes, which is a cause for concern to many practitioners
- Where the therapeutic index is known to be small (e.g. digoxin/warfarin), evidence about the validity of the manipulation should be sought.

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5. APPENDICES

APPENDIX 1: **GUIDELINE SCOPE** (DRAFTED 2010)

Guideline title

Manipulating medicines to deliver accurate, reproducible doses to paediatric patients where no suitable age appropriate product is available at the point of care: a guideline for Healthcare Professionals.

Short title

Manipulating medicines for children: a guideline for Healthcare Professionals.

Background

The Pharmaceutical industry invests considerable time & financial resource in the development of products designed for accurate and appropriate drug delivery.

Generally, currently available products reflect the licensed status of the medicine; in particular the intended consumer age group and intended route of administration of the product. Some products authorised for babies and children are not available as age-appropriate dosage forms (e.g. omeprazole, captopril) or the available preparation is not acceptable to the child.

Manipulation of dosage forms, to achieve a suitable paediatric dose, may occur because of the lack of available products in an appropriate paediatric dose, or because patients express a preference for a formulation type, which is not accommodated by the available commercial products e.g. young children preferring tablets even though a suitable liquid formulation exists. Temporary supply difficulties may also require professionals to improvise.

The evidence base supporting the manipulation of medicines for the purposes of achieving an accurate dose is often lacking.

Clinical need for the guideline

Recent legislation (2007), in the form of the European Union Paediatric Regulation, was established to drive the development of appropriately licensed and formulated medicines for children, through a system of requirements and incentives.

Simultaneously the World Health Organisation (WHO) are spearheading a global campaign to raise awareness and accelerate action to address the need for improved availability and access to safe, child-specific medicines for all children under 12 years of age.

However, it will be some time before the influence of this legislation and campaign strategy is realised and suitably formulated medicines are made available to children. Even when age-appropriate formulations are

marketed, the need for manipulations will remain because of intermittent supply problems and the fact that drug development is not able to take account of all the possible circumstances in which product manipulation is required.

Currently in paediatric practice, where products may be used outside the terms of their licence and suitable formulations are lacking, healthcare professionals may be required to manipulate medicines in order to deliver the intended dose. Although this is perceived to be an established practice, the extent of this practice, and the precise mechanisms used to manipulate medicines have not been defined. Research work to gather these data and to inform the guidelines is in progress. The research work is not intended to examine extemporaneous formulations prepared in a hospital pharmacy or pharmaceutical manufacturing facilities. Initial data suggest that there is no evidence of acceptable product quality following manipulation for most products except for some tablets and that there is evidence of detriment following manipulation.

Manipulation of any medicinal product carries a number of potential risks which include:

a) Risks to the patient

Manipulation may result in the delivery of an inaccurate and non-reproducible dose to the patient and may be associated with altered efficacy of the product (e.g. sub-therapeutic doses) and increased adverse events (including adverse drug reactions and medication errors).

b) Risks to the product

Any alteration to the integrity of the final pharmaceutical form of a product is untested and may result in altered pharmaceutical, pharmacokinetic and pharmacological properties and performance, such as instability of the active ingredient (e.g., due to exposure to moisture or heat generated onmanipulation), contamination, altered dissolution characteristics, altered bioavailability and reduced efficacy.

c) Risks to the person performing the manipulation

Release of the active pharmaceutical ingredient or excipients may be associated with adverse events such as skin/mucosa sensitisation or unintentional inhalation of powder, in both the operator performing the manipulation and the patient.

d) Risks to the environment

Release of active pharmaceuticals, such as antimicrobials, and/or their use in sub-therapeutic doses may pose problems of drug resistance.

The identified risks may arise as a result of a lack of knowledge on the part of the operator or due to the lack of a standardised process of manipulation. In many cases the specific risks remain unknown.

Guidelines are required that bring available evidence to the attention of those who manipulate medicines so that the manipulators may take appropriate steps to minimise any associated risks to themselves, the patient,

the product and the environment.

At the same time it should be recognised that when products are used outside the terms of their licence, a greater liability (civil, criminal, professional) rests with the individual prescriber and the person responsible for the provision and administration of the product.

Guideline development method (in brief)

The guideline development process will be based on the SIGN 50 methodology guidelines. The MODRIC Steering Group will identify and appoint a Chair of the guideline development group. Members from the following disciplines will be invited to join the group:

- 2 Clinical Pharmacists (Paediatrics) one working in district general hospital (DGH), and one working in a tertiary healthcare setting).
- 1 Clinical Pharmacist (Neonatology)
- Formulations scientist
- Industrial Pharmaceutical Scientist
- 3 nurses (DGH children's nurse; tertiary children's nurse and neonatal nurse)
- Paediatrician
- Neonatologist
- Academic Pharmaceutical Scientist
- Parent representative
- Toxicologist
- MODRIC Research Associate
- MODRIC Administration Officer

Membership of the group is given in Appendix 2

The expert panel will develop draft guideline recommendations informed by a systematic review of the literature(completed), the findings from direct observation of drug manipulation in paediatric and neonatal secondary care settings (completed), a survey of practice within paediatric secondary care (ongoing) and a risk assessment (tool under development).

A wider panel of stakeholders will be consulted to achieve consensus as to the wording and the content of the recommendations.

Proposed scope of Guideline

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider:

Target Audience

Healthcare professionals, working in neonatal and paediatric healthcare settings, who are required to manipulate a medicinal product to deliver an appropriate dose, when no suitable formulation exists. The Guidelines will be developed primarily for Healthcare Professionals working in the UK, but could be used as a reference document by international parties developing local guidance.

The guidelines will not be aimed directly at parents/carers. However it is recognised that in chronically sick patients, parents and carers may undertake a significant role in providing patient care and may adopt practices demonstrated by healthcare professionals. The guidelines will not be aimed at Regulatory Authorities or the Pharmaceutical Industry, but may be used to inform these groups of the specific needs of the paediatric population.

Target Healthcare setting

It is anticipated that the majority of manipulations to deliver a required dose will take place in secondary/tertiary paediatric and neonatal healthcare settings. Once an accepted or “common” method of manipulation for an individual product has been established in secondary care, then this may be continued in a primary care setting.

Paediatric and neonatal settings - that is, in people aged less than 18 years old

Topics be covered

a) The guidance will include an introductory statement on options to avoid manipulation of medicines (e.g. appropriate dose-rounding, consideration of a similar but alternative pharmacological product,)

b) The manipulation of medicinal products to deliver an appropriate dose in the absence of a suitable formulation at the point of care. This will include the methods of manipulation considered appropriate for solid oral dose forms and preparations intended for injection, inhalation, rectal and topical administration.

c) Assessment of risk potential for the patient, product and operator when performing a manipulation.

The guidelines will not address the manipulation of medicinal products, solely for the purposes of convenient administration, when a suitable formulation is not available, e.g. crushing tablets and mixing with food.

Overall aims of guidance

a) To provide readily accessible easy to read guidance for delivering effective and reproducible medicine doses to paediatric patients where no suitable medicinal product exists.

b) To provide a risk assessment tool for use at Ward Level, highlighting risks to the product, the patient and the operator.

c) To minimise risk to the product, patient, operator and environment.

d) To inform professions, regulators and the public of best practice and potential risk associated with manipulation of medicines.

Status

Scope

This is the consultation draft of the scope.

Timing

The development of the Guidelines will begin in December 2010.

Related guidance

Published guidance

Woods, D. Formulation in Pharmacy Practice (eMixt) available at http://www.pharminfotech.co.nz/

Further information

Information on the guideline development process is provided in:

SIGN 50: A guideline developer's handbook. January 2008

This is available from the Sign website: http://www.sign.ac.uk/guidelines/fulltext/50/index.html

APPENDIX 2: GUIDELINE DEVELOPMENT GROUP

Catrin Barker (Chair), Chief Pharmacist, Alder Hey Children's NHS Foundation Trust

Tony Nunn, Consultant in Paediatric Pharmacy

Mark Turner, Senior Lecturer and Honorary Consultant in Neonatology, Liverpool Women's NHS Foundation Trust, University of Liverpool

Matthew Peak, Director of Research, Alder Hey Children's NHS Foundation Trust, Cheshire, Merseyside & North Wales Medicines for Children Local Research Network

Utpal Shah, Formulation Research Fellow, Cheshire, Merseyside & North Wales Medicines for Children Local Research Network

James Ford, Director of School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University

Jean Craig, Research Advisor, University of East Anglia

Roberta Richey, Research Associate, Alder Hey Children's NHS Foundation Trust

Helen Sammons, Associate Professor in Child Health, Derbyshire Children's Hospital

James Birchall, Parent representative

Peter Timmins, Bristol Meyers Squibb

Neil Caldwell, Pharmacist, Wirral University Teaching Hospital NHS Foundation Trust

Liz McArthur, Clinical Nurse Specialist (Pain Service), Alder Hey Children's NHS Foundation Trust

Gemma Webster, Lead Pharmacist for Women and Children, Countess of Chester NHS Foundation Trust

Helen Hill, Research Fellow, Liverpool Women's NHS Foundation Trust

Linda Matthew, National Patient Safety Agency

Mark Jackson, Deputy Director, QC North West

Dan Hawcutt, Lecturer Paediatric Pharmacology, University of Liverpool

John Gibb, Consultant Paediatrician, Countess of Chester NHS Foundation Trust

The group is also thankful for comments from Andy Gray (Academic - SAfrica), Andy Fox (Chair Medicines Committee RCPCH), Colin Cable (RPS), Julie Williams (Pfizer), Andy Lowey (Leeds), Toni Tan (NICE), Carol Sykes (Martin House Children's Hospice), Piotr Kozarewicz (EMA), Nigel Fox MHRA, Steve Tomlin NPPG

APPENDIX 3: USEFUL RESOURCES TO CONSULT

- ***British National Formulary & British National Formulary for Children***

  Pub: BMJ group, Pharmaceutical press, RCPCH Publications Ltd

  Available at www.bnf.org and www.bnfc.org
- ***SPC (Summary of Product Characteristics)***

  Available direct from the manufacturer or at http://www.medicines.org.uk/emc/
- ***Martindale: the complete drug reference***

  The Pharmaceutical Press
- ***AHFS (American Hospital Formulary Service) Drug Information***

  American Society of Hospital Pharmacists
- ***Product Manufacturer***
- ***National Patient Safety (NPSA) Alerts***

  Available at http://www.npsa.nhs.uk/
- ***Databases***

  PubMed, Embase, International Pharmaceutical Abstracts (IPA) [as examples]
- ***Handbook of Pharmaceutical Excipients***

  The Pharmaceutical Press
- ***Merck Index***

  The Merck Publishing group

  Available at http://www.rsc.org/merck-index
- ***British Pharmacopoeia***

  Brtitish Pharmacopoeia Commission Secretariat of the Medicines and Healthcare products Regulatory Authority

  Available at http://www.pharmacopoeia.co.uk/
- ***European Pharmacopoeia***

  European Directorate for the Quality of Medicines and Healthcare

  Available at https://www.edqm.eu/en/european-pharmacopoeia-8th-edition-1563.html
- ***United States Pharmacopoeia***

  US Pharmacopeial convention

  Available at http://www.usp.org/reference-standards

APPENDIX 4: TECHNICAL AND CLINICAL RISK POINTS TO CONSIDER

Is a manipulation absolutely required? Can the dose be rounded or is a more appropriate formulation available?

What is the acceptable dose range for using the drug concerned in the particular patient and condition; consider the patient's current status and drug handling capability (e.g. liver and kidney function, drug interactions)?

Is the product to be manipulated designed to undergo such a manipulation?

Is there evidence that the manipulation can be performed adequately to achieve dose accuracy and reproducibility and maintain drug stability?

If there is a lack of evidence to support the manipulation, are there visible indicators about the quality of the manipulation that suggest dose inaccuracy (e.g. tablet crumbling, non-uniform dispersions)?

Can a successful/good quality manipulation be achieved repeatedly (i.e. for each dosing episode)?

Based on the ability to repeatedly achieve good quality manipulation and the drug's toxicity profile, consider the risk of the patient suffering an adverse effect as a result of receiving a >20% overdose or under-dose.

Is the pharmacy department aware of the need for manipulation? Has it been performed before or is usual practice and approved by pharmacy?

Where no alternatives are available and an unapproved/unrecognised/novel manipulation has to be performed in an acute situation (single dose), this should be reported to pharmacy at the earliest opportunity and a risk management process implemented.

APPENDIX 5: OBSERVATIONAL STUDY

A large regional children's hospital (18 in-patient wards, with care for >200,000 children annually), a regional specialist neonatal unit (54 cots, with care for >1000 babies annually and a district general hospital with one paediatric and one neonatal ward were used to identify and (where possible) observe drug manipulations. Clinical areas were included for two-week periods and manipulations identified through daily prescription reviews and alert cards which nurses could complete when they identified a manipulation while administering drugs. Where possible manipulations occurring in practice were also observed. 310 manipulations were identified during the observational study with 54 being observed.

APPENDIX 6: SURVEY

The results of the observational study were used with additional advice from clinical, formulation and research experts to design a questionnaire which was administered to a sample of paediatric nurses throughout the UK. The questionnaire enabled the collection of additional data on drug manipulations including areas which had arisen from the observational study like the measurement of small volumes and whether suppositories were being manipulated and if so what methods were being used. This questionnaire also explored the context in which manipulations occur by considering hospital policies, reference sources used and any concerns or additional comments that respondents may have. 560 questionnaires were administered with 153 returned, 27.3% response rate. Questionnaire respondents distributed included those who work throughout neonatal and paediatric practice, with the highest proportion of respondents from general paediatrics and neonatal clinical areas.

APPENDIX 7: GLOSSARY OF TERMS

Active ingredient	see Drug
Active pharmaceutical ingredient (API)	see Drug
Active substance	see Drug
Additive	see Excipient
Adverse event	An untoward, undesirable, and usually unanticipated event, such as an unintended sign, symptom, reaction, disease or injury of a patient, an employee, or a visitor in a health care organisation that occurs during or after a manipulation of a dosage form
Area under the curve (AUC)	Area under the concentration-time curve in a selected body fluid or tissue for an administered drug
Bioavailability	The rate and extent to which a drug is absorbed from a dosage form and becomes available at the site of drug action
Bioequivalence	The absence of a significant difference in the rate and extent to which the drug in pharmaceutically equivalent dosage forms becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study in human subjects, **or** Two drug products are considered to be bioequivalent when their concentration vs. time profiles, from the same molar dose, are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects.
Capsule	A solid dosage form with a hard or soft soluble shell usually made from gelatin that is filled with a formulation to provide a unit drug dose and intended for oral administration. The contents of capsules may be solid (powder, granules or pellets), liquid or of a paste-like consistency. Capsule contents can be designed to exhibit modified-release properties. Hard capsules have prefabricated shells consisting of 2 pieces that fit one inside the other. The contents, usually in solid form (powder or granules), are filled into one of the sections that is then closed by slipping the other section over it Soft capsules are usually formed, filled and sealed in one operation and consist of a continuous gelatin shell surrounding liquid or semisolid contents.
Cmax	The maximum (peak) drug concentration observed in a selected body fluid or tissue.
Controlled-release	see Modified-release
Delayed-release	see Enteric coated
Different route	(Of administration) An instance where the drug is administered by a route of delivery (e.g. oral, rectal) that is not licensed for that particular drug product
Dilution	The addition of a suitable diluent to a drug product for the purpose of reducing the concentration of the drug(s) within it and not for the purpose of Reconstitution
Dosage form	The physical form created from a formulation containing a specified amount of drug that will be used to deliver the drug into the body. Examples include tablets, capsules, solutions, suspensions, suppositories, enemas, injections and transdermal patches.
Dose accuracy	The closeness of the actual dose obtained after manipulation to the dose intended for administration
Dose reproducibility	The ability to repeatedly obtain the same dose either when further aliquots are taken from a manipulated dosage form unit, or, when individual dosage units are manipulated on separate occasions

Drug	A substance that exerts a pharmacological effect on the body or affects its structure and is used for the prevention, diagnosis or treatment of disease and for the relief of symptoms. Synonyms: active substance, active ingredient, active pharmaceutical ingredient (API)
Drug product	The final packaged drug in a chosen dosage form including ancillary supplies (e.g. solvent for reconstitution) that complies with all the regulatory requirements for marketing
Enema	An oily or aqueous solution for rectal administration.
Enteric coated dosage form	A solid dosage form for oral administration with a polymeric coat applied onto it, which has a pH dependent solubility preventing drug release in acidic environments and thus protects the incorporated drug(s) against acid degradation in the stomach. It is a type of modified-release dosage form. Synonyms: gastro-resistant, delayed-release.
Excipient	A substance added to a drug to facilitate preparation, patient acceptability and functioning of the dosage form. Synonyms: additive, inactive ingredient
Extended-release	see Prolonged-release
Film coat	A polymeric coat applied to a dosage form which may have a pH dependent solubility preventing drug release in acidic environments and thus protecting the incorporated drug(s) against acid degradation in the stomach or be slowly soluble to allow a controlled release of the enclosed drug or to mask taste.
Formulation	A qualitative and quantitative recipe comprising drug(s) and excipients.
Fully dispersed solid	The absence of aggregated solid particles (clumps) or segregated solid in any part of the liquid into which a solid dosage form unit is added.
Gastro-resistant	see Enteric coated
Gestational age	(Of a newborn) Is the time from the first day of the mother's last menstrual cycle until birth, measured in weeks. (It is usually 2 weeks longer than the fetal age, which is measured from the estimated time of conception until birth)
Hazard	The potential of the manipulation activities and/or manipulated dosage form to be the source of causing harm to the patient or health care professional or having an altered effect on the patient
Immediate-release	Release of the drug(s) from the dosage form is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid dosage form, the dissolution profile of the drug(s) depends essentially on its intrinsic properties.
Inactive ingredient	see Excipient
Injection	A sterile dosage form intended for parenteral drug delivery by piercing through the skin using a needle and syringe or infusion, such as the intradermal, subcutaneous, intravenous, intramuscular, intra- articular, intrasynovial, intraspinal, intrathecal, intra-osseous, intra-arterial, intracardiac and ophthalmic routes of administration.
Intravenous	A term referring to the route of drug delivery directly into a vein using an injection
Manipulation	The physical alteration of a dosage form for the purpose of extracting a proportion of the drug dose (manipulation for intended accurate dose)
Modified-release	The rate and/or place of release of the drug(s) is different from that of an immediate-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified-release dosage forms include those that are enteric coated or exhibit prolonged-release or pulsatile-release. Synonym: controlled release
Nebule	An ampoule containing a single dose of a solution or suspension for inhalation using a nebuliser device
Polymorphs	Different crystalline forms of the same drug molecule (that consequently vary in their physical properties such as solubility, dissolution, solid state stability and processing behaviour)

Presentation	The way in which a particular drug product is made available for public use and when described, usually includes a statement of the dosage form, strength, volume, pack size and other packaging information
Prolonged-release	A type of modified-release where the drug is released from the dosage form in a controlled manner over a period of time showing a slower release of the drug than that of a immediate-release dosage form administered by the same route. Prolonged-release is achieved by a special formulation design and/or manufacturing method. Synonyms: extended-release, slow release, sustained release.
Pulsatile-release	A type of modified-release showing sequential release of the drug(s) from the dosage form. Sequential release is achieved by a special formulation design and/or manufacturing method.
Reconstitution	The preparation of a drug product for administration by mixing together separate components provided by the manufacturer or simply by the addition of a vehicle such as water
Risk	The chance or probability that a patient or health care professional will be harmed or experience an adverse health effect if exposed to a manipulation hazard, qualified by some statement of the severity of the harm.
Slow-release	see Prolonged-release
Solution	A homogenous liquid dosage form containing the drug dissolved in a suitable solvent(s) as a one phase system
Stability	A measure of the change in the physical, chemical or microbial properties of a drug, excipient or drug product as a function of time, environmental conditions or processing operations.
Subcutaneous	A term referring to the route of drug delivery into the subcutaneous tissue below the dermis using an injection
Suppository	A solid dosage form designed to be inserted into the rectum for drug absorption. It contains fatty or water- soluble bases that are solid at room temperature but melt or dissolve at body temperature.
Suspension	A liquid dosage form in which solid particles are dispersed in a liquid or semi-solid continuous phase, and in which the solid particles are practically insoluble.
Sustained-release	see Prolonged-release
Tablet	A solid dosage form obtained by compressing particles or granules containing drug(s) and excipients into a single dose unit intended for oral administration. Tablets can be coated, uncoated, modified release effervescent, chewable, soluble, dispersible, orodispersible or buccal
Tmax	The time at which the maximum concentration (Cmax) is observed.
Transdermal patch	Consists of a flexible sheet incorporating a drug which is either evenly distributed within an adhesive layer, in a matrix, or as a reservoir with a rate controlling membrane and full or peripheral adhesive layer. It is easily adhered and peeled off the skin and intended for drug delivery into the systemic circulation after passing through the skin barrier.

APPENDIX 8: RECENT STUDIES

The systematic review described in the guidelines has been recently published (Richey R.H., Hughes, C., et al, A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice, Int, J. Pharm., 518, 155 – 166). The following paragraph is quoted from that work.

“Subsequent to the completion of data searching in August 2015, two publications were noted that considered drug manipulation in children. Mistry and Batchelor (2016) highlighted the need for support knowledge around the acceptability of age-appropriate medicines and presented an algorithm to aid in formulation selection based on age range. Andersson et al (2016) concluded that tablets larger than 8 mm could be split only once to achieve an approximate half dose for paediatric use. The authors could not recommend that tablets be split more than once due to a lack of weight uniformity of the part tablets after splitting. Both Mistry and Batchelor (2016) and Andersson et al (2016) concluded that more age-appropriate dosage forms, including small tablets, should be available to children. Andersson et al (2016) considered that non-functional score lines should be avoided since both patients and health professionals falsely believed that a score line indicates the possibility of dividing the tablet in two equal parts.

Andersson, AC, Lindemalm S, Eksborg, S. Dividing the tablets for children–good or bad? Pharm Methods, 2016; 7: 23-27

Mistry P, Batchelor H (2016) Evidence of acceptability of oral paediatric medicines: a review. Journal of Pharmacy & Pharmacology, doi 10.1111/jphp.12610