Medicines Safety: Paediatric formulations in UK hospitals

#hello my name is...

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LEVEL 1 TRAUMA CENTRE FOR WEST AND NORTH YORKSHIRE

SEVEN HOSPITALS SIX SITES
1. WHARFEDALE HOSPITAL
2. LEEDS GENERAL INFIRMARY
3. ST JAMES’S UNIVERSITY HOSPITAL
4. SEACROFT HOSPITAL
5. LEEDS DENTAL INSTITUTE
6. CHAPEL ALLERTON HOSPITAL
7. LEEDS CHILDREN’S HOSPITAL

STAFF 15,000
NURSES & MIDWIVES 5,000
DOCTORS 2,000
CONSULTANTS 800

WE TREAT MORE THAN 1,500,000 PEOPLE EVERY YEAR
2,000 BEDS 120 WARDS AND DEPARTMENTS

£1 BILLION ANNUAL BUDGET

12,000+ PATIENTS INVOLVED IN LEADING EDGE CLINICAL TRIALS
A little about me....the Isle of Man
Issues to cover...

• Understand some of the challenges and risks associated with choosing the right medicine for a child

• Consider the assessment of quality and “fitness-for-purpose” (appropriateness)

• Use the treatment of Tuberculosis in children in England as an example of a Medicines Optimisation strategy
Important considerations for medicines for children (CHMP)

- Minimal dosage frequency
- One dosage form fits all or a full range
- Minimal impact on lifestyle
- Minimum, non-toxic excipients
- Convenient, easy, reliable administration
- Easily produced, elegant, stable
- Cost and commercial viability

CHMP. Formulations of choice for the paediatric population. EMA, 2006
How do you know the medicine you prescribe is of acceptable quality?
Licensing Prefixes

- MA = Marketing Authorisation (UK)
- PL = Product Licence (UK)
- Zul-Nr = Marketing Authorisation (Germany)
- EU = European Union Licence

UK Medicines Guidance Note 14 – need a “special clinical need” to justify the unlicensed use of a medicine
Medicines Regulation

• Committee on Safety of Drugs (UK) 1963
• First EU Regulation 1965 – Council Directive 65/65
• The Medicines Act (UK) 1968

So......why was licensing introduced?
Licensing

Why?

• (Diethylene glycol poisoning)
• Thalidomide tragedy
• “Gray Baby Syndrome”

• The licence assures us of: 
  Quality, Safety, Efficacy

Note: Up to approx. 500,000 euros to 1 billion euros in R&D per new product licence
Quality, Safety & Efficacy

- Validated formulation
- Validated shelf-life
- Approved starting materials
- cGMP
- Detailed specification
- QC testing
- Toxicology & animal studies

- Clinical trials
- Continuing pharmacovigilance
- Summary of Product Characteristics (SPC)
- Patient information
- ADME studies
- Approved indications
- Etc etc etc!!!
Using Licensed Medicines

- Licence application includes SmPC and PIL
- Summary of all data from clinical trials
- If used according to SmPC, liability is manufacturers
- Strict pharmacovigilance needed to keep licence, including use of “Black triangle” drugs in UK
- Licensed medicines should be used wherever possible (Medicines Guidance Note 14)
• Why aren’t all medicines used in a licensed manner?
Why aren’t all medicines used in a licensed manner?

• “Off-label” use
• Commercial Viability
• Niche markets
• Dosage form inappropriate for children
• Discontinued products
• Withdrawn products
• “Compassionate use” products

• Individualised therapy e.g. Extemporaneous preparation
• Use of herbal/homoeopathic remedies
• Ethical issues e.g. trials in children
• Trial design, consent
Paediatric Regulation, 2007 (EMA)

• Aims

  – Encourage & enable high quality research into the development of medicines for children
  – to ensure, over time, that most medicines used by children are specifically authorised for such use with age-appropriate forms & formulations
  – to increase the availability of high quality information about medicines used by children
Paediatric Regulation, 2007 (EMA)

- Includes incentives (& waivers) to encourage research in paediatric populations
- Specific rewards for Orphan Medicines (10+2 year market exclusivity)
- Paediatric Usage Medicines Authorisation (PUMA)
- Free scientific advice
Paediatric Regulation, 2007 (EMA)

- 10 year review in 2017 found:
  - >260 new medicines for use by children (indications & marketing authorisations)
  - >1000 Paediatric Investigation Plans but only 131 completed
  - Proportion of trials in paeds ↑ from 8.25% to 12.4%
  - Only 3 PUMA’s & few Orphan drugs in children
  - Vast majority of progress linked to an adult development (no paediatric strategy)
Progression of Risk
(Adapted from Beaney, 2006)

Ward-based preparation

Preparation in Pharmacy ("Extemps")

GMP Batch production ("Specials")

Licensed
Progression of Risk
(Adapted from Beaney, 2006)

- Ward-based Preparation
- Preparation in Pharmacy ("Extemps")
- GMP Batch production ("Specials")
- Licensed

Imports?
How “risky” is extemporaneous dispensing?
Risks associated with Extemp dispensing

• Unstandardised formulations
e.g. captopril
(Mulla et al. Arch Dis Child 2007; 92: 409-411)
• Calculation errors
• Formulation failure
• Uniformity of dose
• Excipient issues – binding & toxicity
• Micro contamination
• Staff issues
• Organoleptic issues

• Measurement & labelling errors
• Use of concentrated raw materials e.g. conc’d chloroform water
• Toxicity & contamination of raw materials
• Bioavailability issues
• Safety & efficacy untested
• QA/GMP issues
The Peppermint Water Case, UK 1998
The “Peppermint Water Case”

• April 29th 1998
• Community Pharmacy, Runcorn, Cheshire
• Prescription presented for “Alder Hey Peppermint Water” for 5 day old baby
• Pharmacist experience = 21 months
• Passed to student pharmacist, as “good experience for him”
Peppermint Water continued...

- Amount Rx = 150ml
- Requires 3.75ml peppermint emulsion and 75ml of double strength chloroform water
- Instead, used 75ml concentrated chloroform water
- Instructions written on paper; pre-reg was not supervised
- 10ml measuring cylinder broken
- Peppermint emulsion volume checked only

- Outcome – cardiac arrest on first dose, baby died 17th May 1998, two and a half weeks later after suffering severe brain damage.
Peppermint Water - Findings

- “Book of formulae” was confusing and out of date
- Pharmacist was not qualified to be pre-reg tutor
- Rareness of extemporaneous practice noted
- Prosecution referred to “Undesirable difference” between practice in hosp/community pharmacy re: formulae and worksheets
- Health Authority called for proprietary products to be used in place of Peppermint Water
- Pharmacist & pre-reg cleared of manslaughter
- Guilty of not supplying “a medicine of the nature or quality demanded”
Case study - 2007

• A 4yr old child on your ward requires a low but flexible dose of ACEi for congestive heart failure
• They cannot swallow tablets
• They have no known allergies or sensitivities
Captopril (continued)

• Captopril is in solution at normal concentrations (1mg/ml)
• It is unstable in solution
• There is conflicting data for a plethora of different formulations

• What should we do for your patient?

- 13 tertiary paed centres & 13 referring hospitals
- 4 crushed tablets, 22 used 9 different formulations (3 from commercial “Specials”, 1 from NHS Manufacturing Unit, 4 extemps, 1 import)
- Differences between referring centres, paed centres and community
- Totally unstandardised, significant differences may well affect clinical outcome
Excipients in Children

• What are the “problem excipients” in children?
• Preservatives e.g. benzoates
• Sweeteners e.g. sorbitol, fructose
• Solvents e.g. ethanol, propylene glycol
• Colouring agents e.g. tartrazine
• Coating materials

• Be careful – risk assess before you avoid. Excipients are there for a reason!
Ward-based alternatives

- Tablet segments difficult to cut
- Health & safety concerns for crushing tablets
- Tablet dispersion safer but problems with insoluble drugs and/or excipients
- Injections show rapid absorption & peak levels and may degrade and contain toxic excipients
- Adding drugs to drinks/foods is not usually evidence-based
- Lack of QA infrastructure
Case study: Tuberculosis
Anti-TB Oral Liquid Medicines

- WHO priority to treat TB (1.5m deaths/year)
- Interruptions to supply problematic
- MDR-TB (and XDR-TB) a growing issue
- 4 main 1st line agents – rifampicin, pyrazinamide, isoniazid, ethambutol
- Only one licensed oral liquid in the UK (rifampicin)
- Many variations of formulation & concentration
- Risks – quality/efficacy/safety, especially at transfer of care (NB. vulnerable patients)
Example: Ethambutol Oral Liquid

- Made in at least 8 different concentrations in UK (Capstick et al, 2011) (100mg/5ml to 600mg/5ml)
- No agreed formula
- No agreed method of preparation
- Known toxicities (ADR’s) e.g. visual acuity, colour blindness, neuritis & thrombocytopenia
- Exhibits optical chemistry
- D-isomer used therapeutically; L-isomer is more toxic
- No published information on the effect of formulation or concentration on optical chemistry
# Project Group

(plus 32 stakeholders consulted)

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Purpose within NHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commercial Medicines Unit (CMU)</strong></td>
<td>Focus on the strategic supply management and procurement of medicines for use in secondary care</td>
</tr>
<tr>
<td><strong>Department of Health Medicines, Pharmacy and Industry Group</strong></td>
<td>Overall responsibility for medicines-related policy</td>
</tr>
<tr>
<td><strong>Medicines and Healthcare Products Regulatory Agency (MHRA)</strong></td>
<td>Responsibility for regulating all medicines and medical devices in the UK</td>
</tr>
<tr>
<td><strong>National Pharmaceutical Supply Group (NPSG)</strong></td>
<td>Advises the CMU on cost-effective purchasing and distribution of pharmaceutical products to the NHS in England, and links to pharmacists at a national level</td>
</tr>
<tr>
<td><strong>Pharmaceutical Market Support Group (PMSG)</strong></td>
<td>Provide strategic advice to the pharmaceutical industry and contracting groups, focusing on critical product areas e.g. where there are availability concerns</td>
</tr>
<tr>
<td><strong>Public Health England (PHE)</strong></td>
<td>Aims to protect and improve the nation’s health and to address inequalities</td>
</tr>
<tr>
<td><strong>Specialist Clinicians and Pharmacists</strong></td>
<td>Provide direct clinical care to patients in the NHS</td>
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Progress in England – Project Work

• Agreement across professional groups:
  – Standardise the concentration
  – Standardise the specification
  – Batch manufacture


• Standard concentrations now in British National Formulary for Children

• New monographs in the British Pharmacopoeia
PRODUCT NAME / STRENGTH / FORM:
Ethambutol Hydrochloride Oral Liquid 400mg in 5ml

1. Product information

Purpose for which the product is to be used and method of administration where appropriate
Please refer to Appendix 1 – Clinical risk assessment form
Used for the treatment of tuberculosis in adults and children (oral route)

2. Container system

<table>
<thead>
<tr>
<th>Pack size</th>
<th>150ml or 200ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of container</td>
<td>Amber glass medical bottle or inert plastic</td>
</tr>
<tr>
<td>Type of closure</td>
<td>Child-resistant and tamper-evident closure</td>
</tr>
<tr>
<td>Other requirements eg latex free</td>
<td></td>
</tr>
</tbody>
</table>

3. Formulation

Key formulation requirements:

<table>
<thead>
<tr>
<th>Ingredient (Approved name eg rINN, BAN)</th>
<th>Quality Specification eg BP, Ph Eur *</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol hydrochloride</td>
<td>BP</td>
<td>80mg/ml</td>
</tr>
</tbody>
</table>
Progress in England – Project Work

• All available as batch products from NHS (& commercial) manufacturers in standard concentrations:
  – Ethambutol Oral Liquid 400mg in 5ml
  – Isoniazid Oral Liquid 50mg in 5ml
  – Pyrazinamide Oral Liquid 500mg in 5ml
• Moving towards product licence applications(s)
Outcomes (Hospital data)

- Pyrazinamide 95.7% standardised (total - 24,850ml)
- Isoniazid 99.9% standardised (total 2,085,174ml)
- Ethambutol 64.7% standardised (total 56,140ml)….but improving….

(All England Hospitals data Dec 17-Nov 18 2018)
Use of the “wrong” strengths....

Ethambutol 500mg/5ml oral solution

- Wales (4)
- NHS London (4)
- NHS West Midlands (3)
- NHS South West (3)
- NHS South East Coast (1)
- NHS South Central (1)
- Total

Graph showing usage trends from December 2017 to November 2018.
What more can we do?
(passive vs. active)

- Integrate with community Dr prescribing systems
- Target areas of England with poor “compliance”
- Patient Information Leaflets (completed)
- ??Consider incentivised commissioning (see dose-banded chemotherapy)
- Challenge the UK system for dispensing of ULMs in community
- Challenge MHRA restrictions on “advertising” of ULMs

14 more products now standardising....

- Azathioprine 50mg/5ml
- Chloral hydrate 1g/5ml
- Clonazepam 2mg/5ml
- Clopidogrel 25mg/5ml
- Hydrocortisone 5mg/5ml
- Lisinopril 20mg/5ml
- Melatonin 1mg/1ml
- Midazolam 10mg/5ml
- Omeprazole 20mg/5ml
- Phenobarbitone 50mg/5ml
- Sertraline 50mg/5ml
- Sodium Chloride 5mmol/ml
- Spironolactone 50mg/5ml
- Tacrolimus 5mg/5ml
What we’re working on…..

• Standardised neonatal & paediatric PN
• Standardised IV syringes for ICU areas
• ↑use of solid doses (tablets/capsules) even in young children where possible (cost/UofD/stability)
• Dose-banded IV additives for adults & ?paediatrics e.g. antibiotics
Our new recruit…..”Gino”
Risk assessment – clinical pharmacy staff

• A “quality” product may not be suitable for all patients e.g. taste, excipients, dosage form, strength
• Therefore the ward pharmacist must take responsibility for the product’s “Fitness for Purpose”
• Consider your range of options carefully – and review as TIME changes
• Focus on unlicensed medicines as HIGH RISK in your care plans
• Feedback problems to manufacturers/QC departments to complete audit cycle
Summary

• Use licensed products for licensed indications where possible – but unlicensed medicines are needed
• Children remain exposed to greatest risks – “The Therapeutic Orphan” (Shirkey, 1968).
• Standardisation & rationalisation are key to progress
• Extemporaneously prepared medicines for individual patients are high risk – monitor your patients carefully

Note: Pharmacy staff are the only members of the multi-disciplinary team with formulation & quality knowledge
“The Medicines Optimisation approach will require multi-disciplinary team working to an extent that has not been seen previously”

(Medicines Optimisation – Helping patients to make the most of medicines, Royal Pharmaceutical Society)
Progression of Risk
(Adapted from Beaney, 2006)

Ward

Preparation In Pharmacy ("Extemps")

GMP Batch production ("Specials")

Licensed
Acknowledgements

• Project Group Chair – Mr Phil Deady, Previously Procurement Lead, Leeds Teaching Hospitals NHS Trust (LTH)
• Expert Clinical Pharmacist – Dr Toby Capstick, Consultant Respiratory Pharmacist, LTH
• NHS England Link – Mr Tim Root, Specialised Pharmacy Services
• NHS Production Committee Liaison – Mr Burrinder Grewal & Mr Roger Brookes, Huddersfield Pharmacy Specials, Yorkshire, England
• NPPG Representative – Mr Steve Tomlin, Previously Consultant Pharmacist, Evelina Children’s Hospital
• Mr Mark Jackson, Chair, NPQA Committee Working Group on ULMs
Developing a new national range of anti-tuberculosis oral liquid medicines: Medicines Optimisation in action

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1 Medicines Management & Pharmacy Department, Leeds Teaching Hospitals (LTH),
2 Medicines Assurance, NHS Specialist Pharmacy Service,
3 NHS Pharmaceutical Quality Assurance Committee (Working Group for Unlicensed Medicines)

**Background**

Almost two-thirds of hospital pharmacy departments in the UK have reported problems accessing anti-tuberculosis treatments. Only rifampicin is currently available as a licensed oral liquid, meaning that children face elevated potential risks with a lack of high quality, standardised products. Transfer of care can be a particular issue. As an example, at least six different concentrations of ethambutol are currently in use. Ethambutol is an optical isomer with known toxicity issues and is associated with significant ADRs e.g. reduced visual acuity and colour blindness.

A project group was formed to review the problem and make recommendations to improve patient safety. Thirty-two medical, nursing, pharmacy, government and commercial stakeholder groups were consulted (including NPSG, BTS, UKCPA & RCoP).

**Objectives**

To improve the quality of anti-tuberculosis medicines and the robustness of the supply chain. Recommendations included the use of standardised concentrations of batch manufactured medicines in preference to extemporaneous preparation.

**Results**

The strong clinical consensus has been converted to standardised concentrations and detailed product specifications for the three main unlicensed anti-tuberculosis oral liquid medicines. Following discussion with colleagues in Specialist Pharmacy Services and NHS Pharmacy Production Committee, the following final concentrations were agreed:
- Ethambutol 400mg/5ml
- Isoniazid 50mg/5ml
- Pyrazinamide 500mg/5ml

NHS Pharmacy Manufacturing Units are now in the process of developing new formulations to meet these specifications.

**Conclusion**

Product launch is expected in late 2017. Adoption of high quality batch-manufactured medicines with a standardised concentration will help to improve quality assurance and decrease the risk of error. Further work is needed to standardise formulations across the UK.

This model for product development can be adapted for use across the NHS to drive an improvement in medicines quality and decrease risk to vulnerable patient groups.

**References**


Acknowledgements

Project Group, Chaired by Mr Philip Bowney, Chief Pharmacist of Leeds Teaching Hospitals NHS Trust (formerly lead Procurement Pharmacist, ENHS), NPSG Pharmaceutical Quality Assurance Committee, Working Group for Unlicensed Medicines.
References

- Rawlence E, Lowey AR, Tomlin S, Auyeung V. Is the Provision of Paediatric Oral Liquid Unlicensed Medicines Safe? *Arch Dis Child Educ Pract Ed* 2018;0
- Lowey AR, Jackson MN. ‘Problem’ excipients: be cautious when making clinical decisions on formulation (letter)*The Pharmaceutical Journal, online, online | DOI: 10.1211/PJ.2018.20204508*
- Lowey AR, Capstick TGD. Standardising the use of oral liquid medicines to treat tuberculosis in the UK (letter) *Clinical Pharmacist, March 2018, Vol 10, No 3, online | DOI: 10.1211/CP.2018.20204497*