

Medicines Safety: Paediatric formulations in UK hospitals

#hello my name is...
😊

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Leeds Children's Hospital





STAFF

15,000



NURSES &
MIDWIVES

5,000



DOCTORS

2,000



CONSULTANTS

800



£1
BILLION
ANNUAL BUDGET

LEVEL 1
TRAUMA CENTRE
FOR WEST AND NORTH
YORKSHIRE

**SEVEN HOSPITALS
SIX SITES**

**WE TREAT
MORE THAN
1,500,000
PEOPLE
EVERY YEAR**

**2,000
BEDS
120**
WARDS AND
DEPARTMENTS



1 WHARFEDALE
HOSPITAL

5 LEEDS DENTAL
INSTITUTE

2 LEEDS GENERAL
INFIRMARY

6 CHAPEL ALLERTON
HOSPITAL

3 ST JAMES'S UNIVERSITY
HOSPITAL

7 LEEDS CHILDREN'S
HOSPITAL

4 SEACROFT HOSPITAL

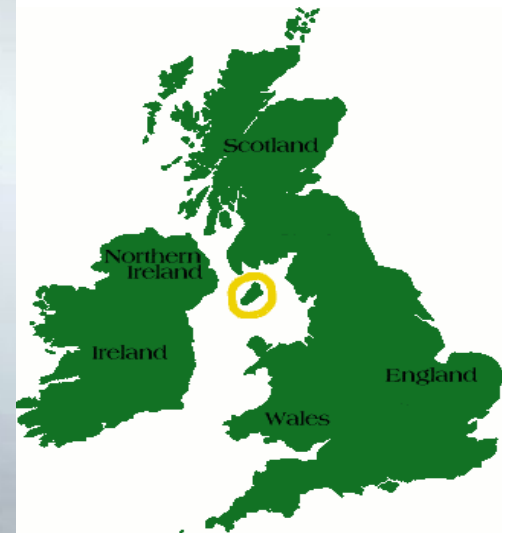


12,000+ PATIENTS

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 life style
- 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
- (US – The Federal Food Drug and Cosmetic Act 1937 & The Drug Amendments Act 1962)

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. 500,000euros to 1billion 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

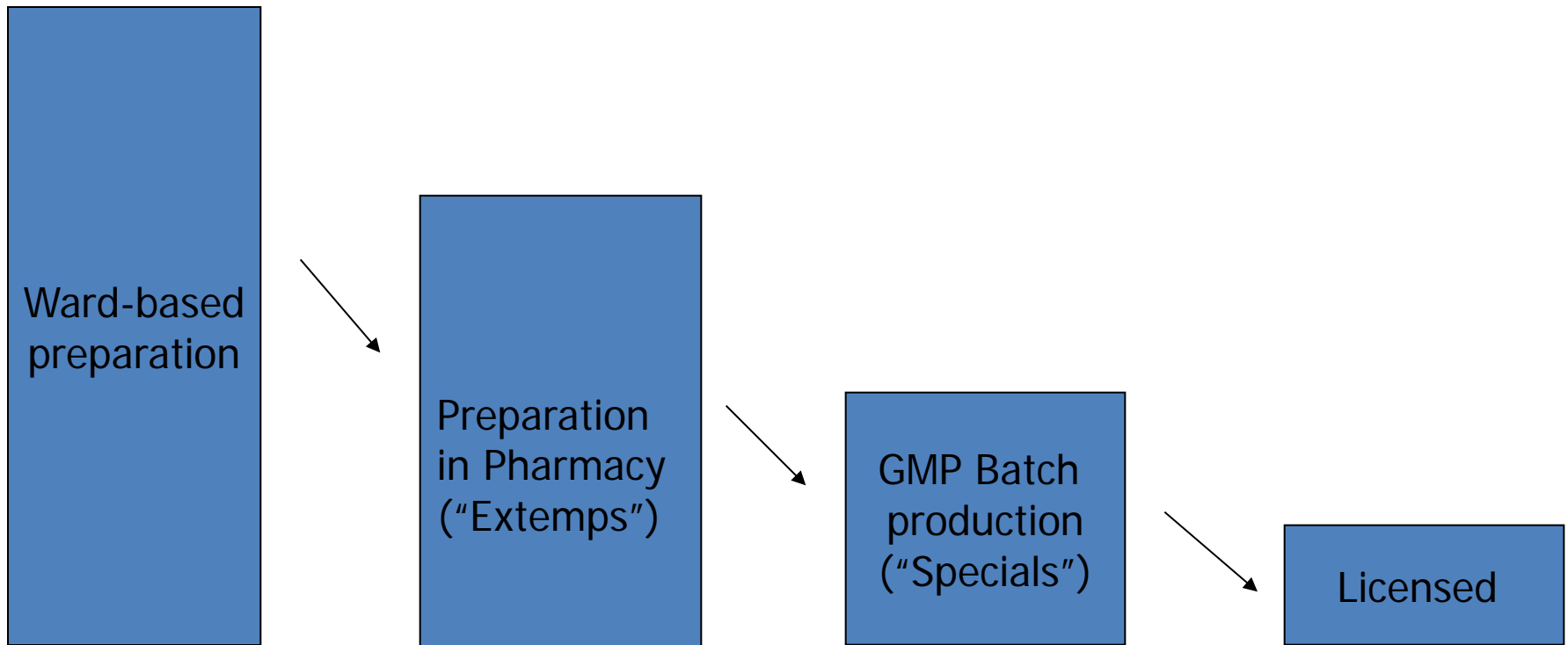
Paediatric Regulation, 2007

(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 paediatrics ↑ 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)

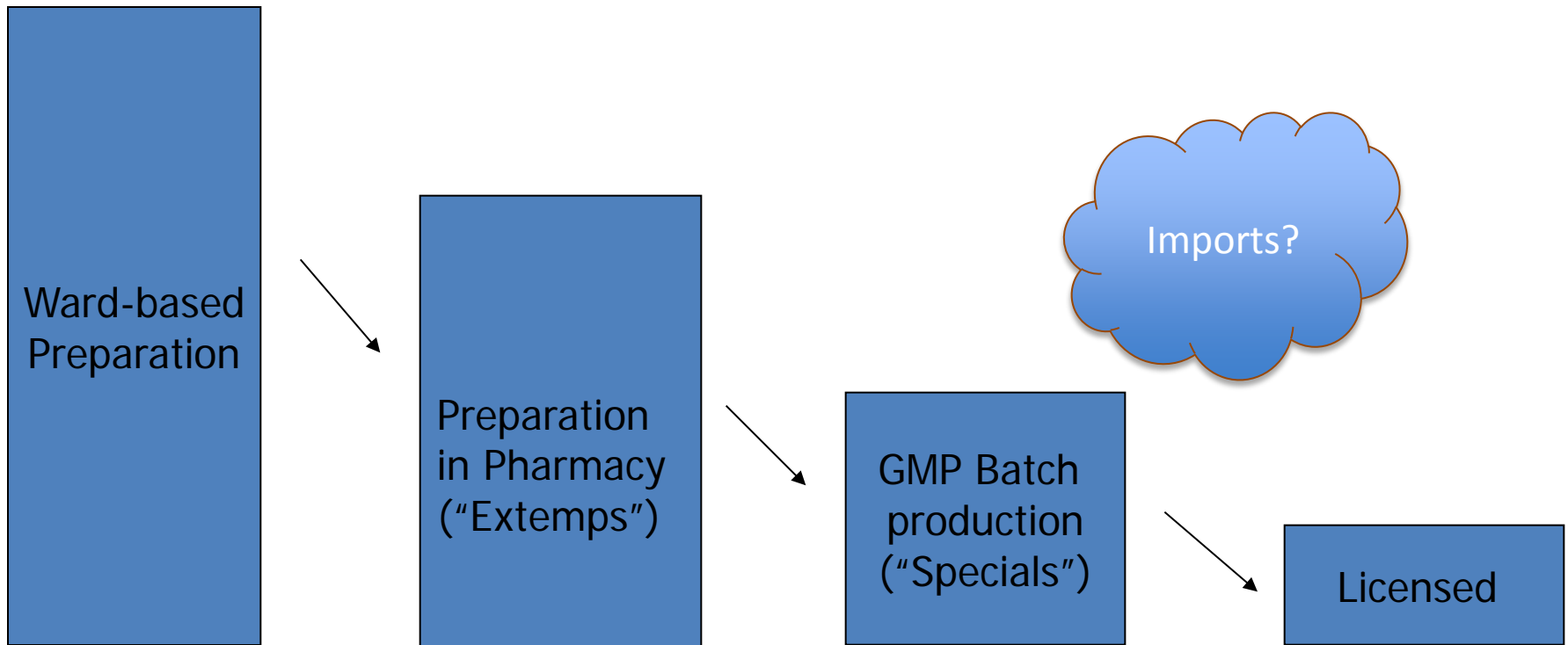
Progression of Risk

(Adapted from Beaney, 2006)



Progression of Risk

(Adapted from Beaney, 2006)





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?

What did UK Hospitals choose

to do? (Mulla *et al. Arch Dis Child* 2007; 92: 409-411)

- 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
- Use of adult liquids in children associated with dosing errors (Koren *et al*, 1986; Wong *et al*, 2004)
- 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)

Organisation	Purpose within NHS
Commercial Medicines Unit (CMU)	Focus on the strategic supply management and procurement of medicines for use in secondary care
Department of Health Medicines, Pharmacy and Industry Group	Overall responsibility for medicines-related policy
Medicines and Healthcare Products Regulatory Agency (MHRA)	Responsibility for regulating all medicines and medical devices in the UK
National Pharmaceutical Supply Group (NPSG)	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
Pharmaceutical Market Support Group (PMSG)	Provide strategic advice to the pharmaceutical industry and contracting groups, focusing on critical product areas e.g. where there are availability concerns
Public Health England (PHE)	Aims to protect and improve the nation's health and to address inequalities
Specialist Clinicians and Pharmacists	Provide direct clinical care to patients in the NHS

Progress in England – Project Work

- Agreement across professional groups:
 - Standardise the concentration
 - Standardise the specification
 - Batch manufacture
- Endorsed by NHS Production Committee & national guidance from NHS England <https://www.sps.nhs.uk/articles/standardising-strengths-of-high-risk-unlicensed-oral-liquids-formulations-for-anti-tb-medicines/>
- Standard concentrations now in British National Formulary for Children
- New monographs in the British Pharmacopoeia

NHS	National Advisory Board for NHS Manufacturing & Preparation Services	Date of issue:
	Product Specification	Version 1.0

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)
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2. Container system

Pack size	150ml or 200ml
Type of container	Amber glass medical bottle or inert plastic
Type of closure	Child-resistant and tamper-evident closure
Other requirements eg latex free	

3. Formulation

Key formulation requirements:

Ingredient (Approved name eg rINN, BAN)	Quality Specification eg BP, Ph Eur *	Quantity
Ethambutol hydrochloride	BP	80mg/ml

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)

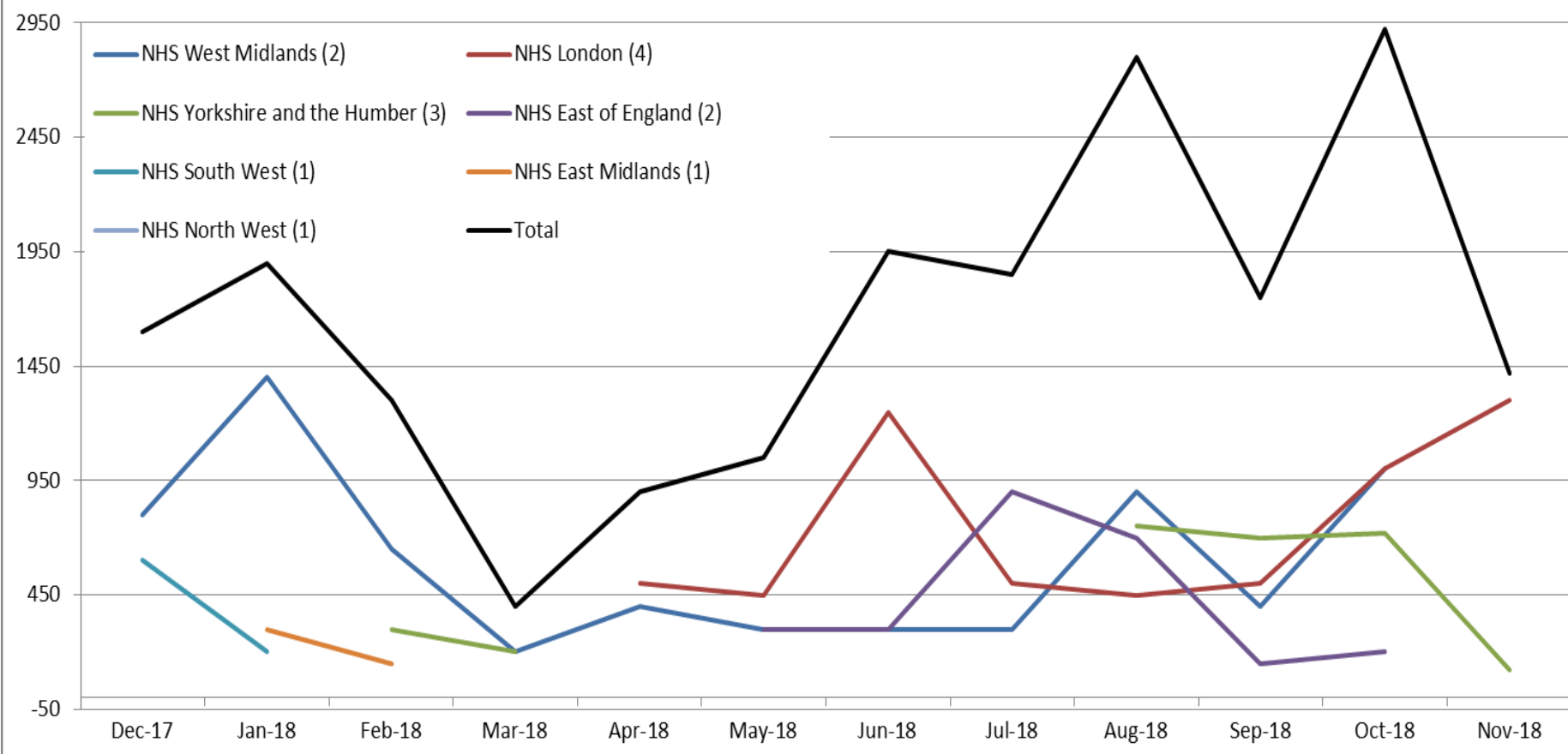
Outcomes (Hospital data)

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

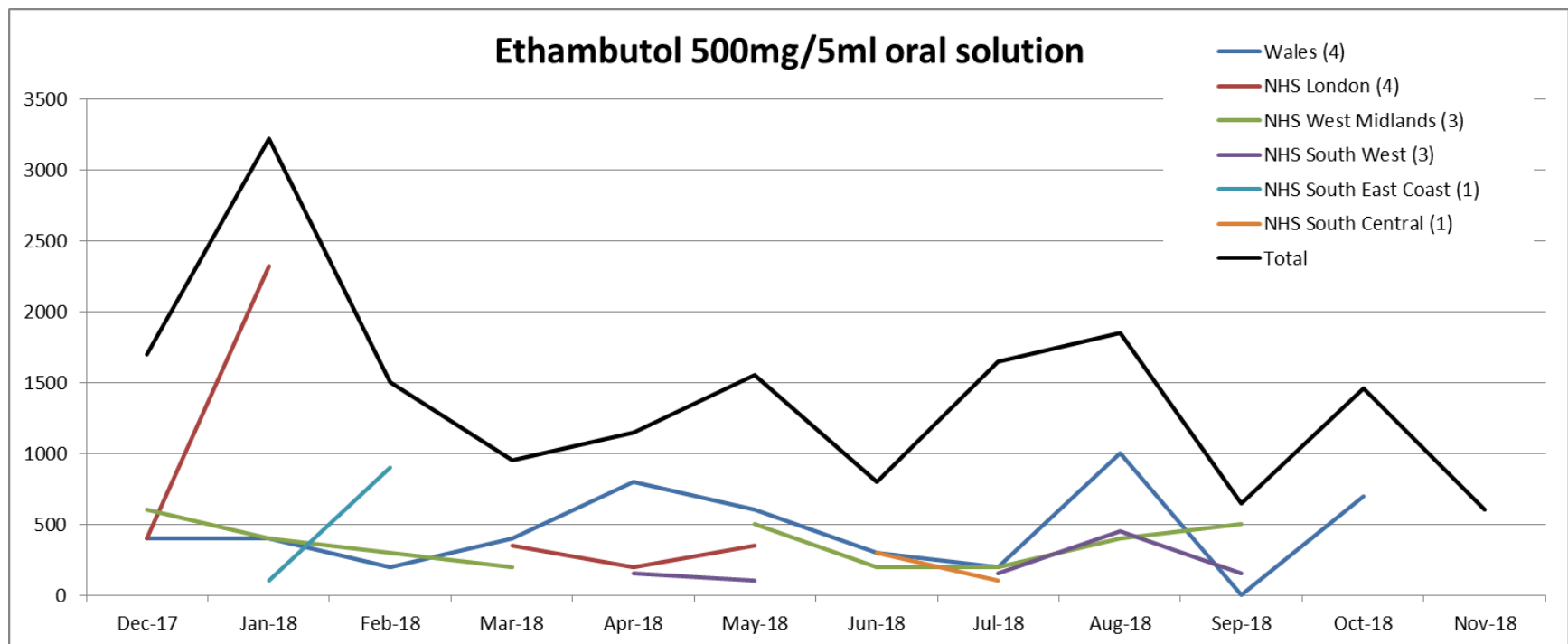
(All England Hospitals data Dec 17-Nov 18 2018)

Outcome

Ethambutol 400mg/5ml oral solution



Use of the “wrong” strengths....



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)

<https://solutions.hsj.co.uk/story.aspx?storyCode=7017152&preview=1&hash=6665B17DDA4563D54EA30195F3046E36>

- 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

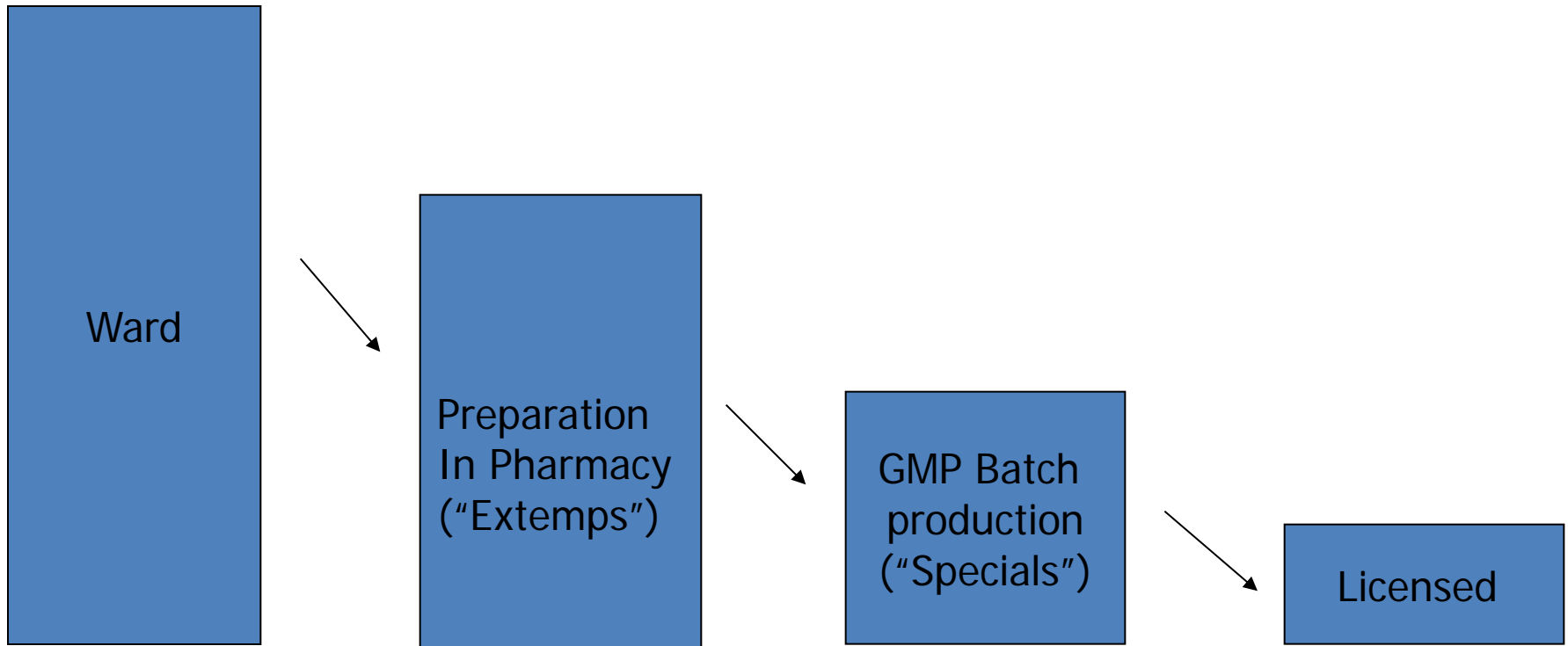
Medicines Optimisation...

“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)



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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³NHS 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 treatments¹. 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 use¹. Ethambutol is an optical isomer with known toxicity issues and is associated with significant ADR's e.g. reduced visual acuity and colour blindness.

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

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 liquids 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

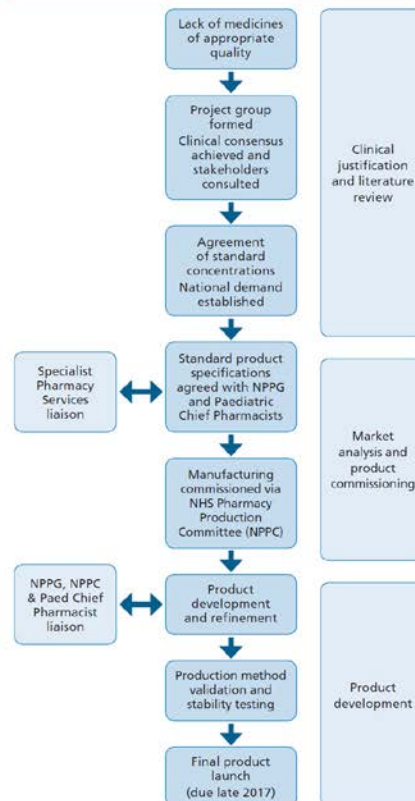
NHS Pharmacy Manufacturing Units are now in the process of developing new formulations to meet these specifications.

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.

Method



References

Capstick, T.G.D., Laycock, D. and Lipman, M.C.I. Treatment interruptions and inconsistent supply of anti-tuberculosis drugs in the United Kingdom. *Int J Tuberc Lung Dis*, 2011, 15(6):754-76

Acknowledgements

Project Group: Chaired by Mr Phil Deady, Chief Pharmacist of Mid-Yorkshire Hospitals NHS Trust (formerly Lead Procurement Pharmacist, LTH).
NHS Pharmaceutical Quality Assurance Committee – Working Group for Unlicensed Medicines.

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