The Leeds Teaching Hospitals NHS
NHS Trust

Quality & Risk Assessment of Medicines for Children

Dr Andy Lowey
Lead Clinician – Clinical Pharmacy & Technical Services
Leeds Teaching Hospitals NHS Trust, UK

Leeds Children's Hospital

Disclosure

- Conflict of interest : I have nothing to disclose

Self-assessment questions

1. Extemporaneous or bespoke preparation of medicines for children is:

a) Low risk b) High risk

2. Children should be protected from clinical research for ethical reasons

a) True b) False

3. The EU Paediatric Regulation came into force in:

a) 2007 c) 2012

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

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

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

2,000 BEDS 120 WARDS AND DEPARTMENTS

12,000+ PATIENTS INVOLVED IN LEADING EDGE CLINICAL TRIALS

Leeds Children's Hospital

A little about me....the Isle of Man

Learning objectives

- Describe the difference between quality assessment and risk assessment
- Consider the relevant legislation and its background
- Understand some of the challenges associated with choosing the right medicine for a child

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 supply is of acceptable quality?

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 1938 & 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 SPC and PIL
- Summary of all data from clinical trials
- If used according to SPC, liability is manufacturers
- Strict pharmacovigilance needed to keep licence, including use of “Black triangle” drugs
- Only use medicines outside license where there is a “special clinical need”

- 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

Correlation between Surface area/body weight ratio vs Age

(adapted from Werfel S, Boeck K, Abeck D, Ring J (1998) Besonderheiten der topischen Behandlung im Kindesalter, Hautarzt 49: 170-175)

Age	Weight (kg)	Surface area (cm^2)	Surface/weight ratio (cm^2/kg)	Comparison (Adult = 1)
Newborn	3.4	2100	617.6	2.4
6 months	7.5	3500	466.7	1.8
1 year	9.3	4100	440.9	1.7
4 years	15.5	6500	419.4	1.6
10 years	30.5	105000	344.3	1.3
Adult	70	18100	258.6	1

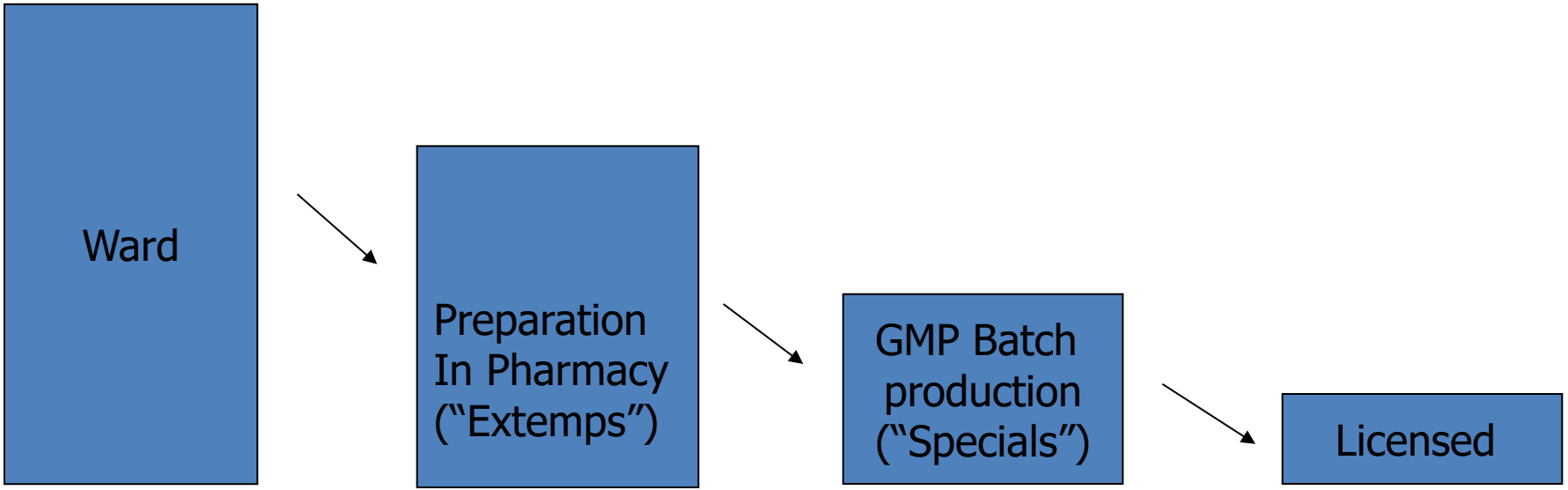
Introduction summary

- Licensed medicines should be used within their SPC wherever possible
- But there is a demonstrable clinical need for the unlicensed use of medicines
  - consider the risk of NOT treating
- Note: Unlicensed use of medicines (“off-label”) vs unlicensed medicines

- IRONY = Despite the origins of the licensing process, the group of patients that use most unlicensed medicines are infants & children (“Therapeutic Orphan” – Shirkey, 1968)

Progression of Risk

(Adapted from Beaney, 2006)



Quality Assessment of Unlicensed Medicines

Definitions

- “Ward-based manipulations” – dispersing, crushing, dissolving, cutting etc
- “Extemporaneous preparations” – made under the supervision of a pharmacist
- “Batch manufactured product” - supported by greater systems of QC/QA (“Special” in UK)
- “Import” – a product that bears a product licence in its country of origin

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

Extemporaneous Dispensing

- “Ex tempore” = “at the time”, “without preparation” (!)
- Also known as “Magistral formulations”
- Carried out under supervision of a pharmacist
- Often made for individual patients – does depend on the country
- If made for individual patients - no product testing?

How “risky” is extemporaneous dispensing?

Risks associated with Extemp dispensing

- Unstandardised formulations
- Calculation errors
- Formulation failure (OD or UD)
- Uniformity of dose
- Binding of drug to excipients
- 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

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!

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

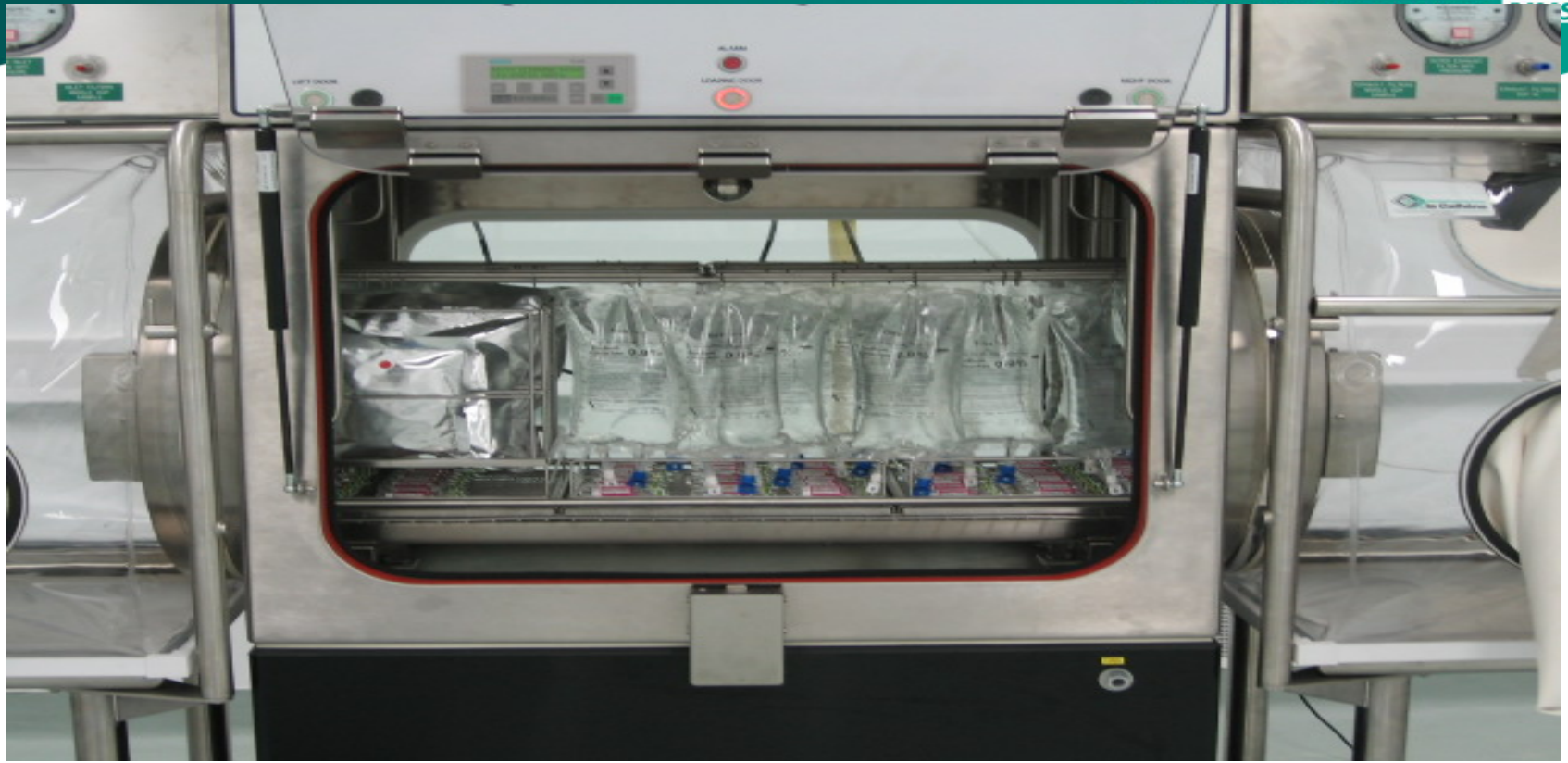
- Outcome – cardiac arrest on first dose, baby died 17th May 1998, two and a half weeks later after suffering severe brain damage.

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”

Batch manufactured products ("Specials" in UK)

- QA systems – training, documentation, clothing etc
- Products can often be tested – Certificate of analysis
- Finished Product Specification including sterility assurance methods (if applicable)
- TSE statements
- Review of appropriate licences (depending on country)



Imports - issues

- Quality, safety & efficacy established in country of origin
- Translation required for SPC and/or PIL?
- Who is liable for the translation?
- Is it appropriate to your use?
- Are you importing an adult formulation?
- Labelling?
- Which countries do you import from?

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
- Free scientific advice

Paediatric Regulation, 2007 (EMA)

- Outputs so far (2017 review):
  - >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)

Case study

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

ACEi of choice in children is Captopril

- There was no licensed oral liquid form of captopril in the UK in 2007
- Options:
  - Import from Australia/NZ
  - Purchase a batch manufactured “Special”
  - Prepare an extemporaneous preparation
  - Ward-based manipulation e.g. crush a tablet and disperse, taking an aliquot of the resulting liquid
  - Choose an alternative ACE inhibitor e.g. lisinopril

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

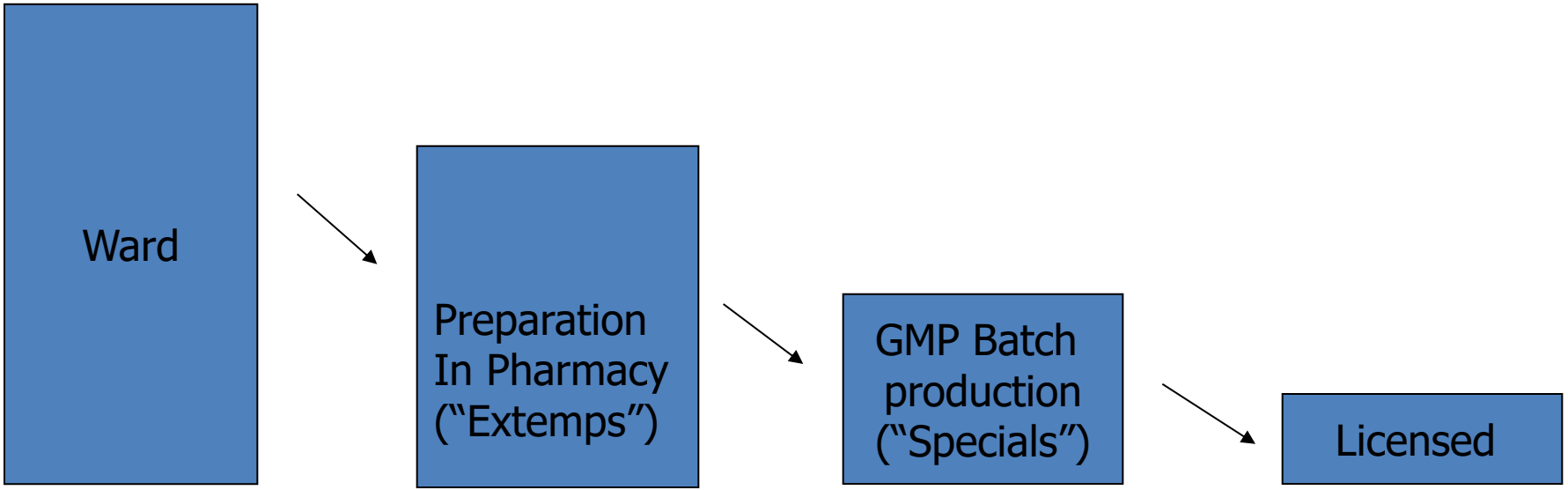
- 13 tertiary paed centres & 13 referring hospitals
- 4 crushed tablets, 22 used 9 different formulations (3 from commercial “Specials”, 1 from NHS Manufacturing Unit, 4 extemps, 1 import)
- Differences between referring centres, paed centres and community
- Totally unstandardised, significant differences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

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

Progression of Risk

(Adapted from Beaney, 2006)



"Take home messages"

- Use licensed products for licensed indications where possible – but ULM are needed
- Children remain exposed to greatest risks
- Standardisation & rationalisation are key to progress
- Unlicensed medicines are high risk – monitor your patients carefully

NB. Pharmacy staff are the only members of the multi-disciplinary team with formulation & quality knowledge

Self-assessment questions

1. Extemporaneous or bespoke preparation of medicines for children is:

a) Low risk **b) High risk**

2. Children should be protected from clinical research for ethical reasons

a) True **b) False**

3. The EU Paediatric Regulation came into force in:

a) 2007 b) 2012

Tuberculosis

Anti-TB Medicines

- WHO priority to treat TB
- Interruptions to supply problematic in many countries
- MDR-TB (and XDR-TB) a growing issue
- Only one licensed oral liquid TB medicine in the UK (rifampicin)
- Problems at transfer of care & in terms of prescribing responsibilities

Example: Ethambutol

- Known ADR's - visual acuity, colour blindness, neuritis & thrombocytopenia
- Made in at least 8 different concentrations
  (100mg/5ml to 600mg/5ml)[3]
- No agreed formula
- No agreed method of preparation or H&S protection
- 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

Progress in UK

- Agreement to standardise to one concentration for each agent
- Supported by Paediatric Chief Pharmacists, Neonatal & Paediatric Pharmacicts Group, NHS Pharmaceutical Production Committee
- Now available and included in the British National Formulary for Children (BNF-C)