Safeguarding public health

Presentation and discussion of various case studies

Matthew Thatcher
Clinical Assessor
Special Populations Unit
VRMM
MHRA
United Kingdom

4th EMEA Workshop for SMEs - *Paediatrics*
23 October 2009

“Disclaimer”

Opinions expressed are MINE ALONE !!
and are not those of :-

- The MHRA (the “Management”)
- Paediatric Committee (PDCO)
- EMEA

-Medicines in the examples are anonymised

-Commercial future plans are confidential and sensitive.
-All PIP communication is by secure link-EUDRALINK.

→Difficult to discuss all issues surrounding the individual medicines in the examples.

-Hope what there is will be beneficial

Paediatric Regulation

Stated objective:

to improve the health of children in Europe by:

- **Facilitating the development and availability of medicines for children aged 0 to 17 years,**
- **Ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,**

- *This should result in a shift in the current status where medicines used in children are generally unlicensed and used "off label" to a state in the future where majority are licensed and have age appropriate formulations available.*

Initial thoughts when Rapp/Peer Reviewer for an individual PIP.

1. Is there a paediatric need for this drug?

   What existing therapies (if any) are used for the condition(s) under consideration in application.
   - What is the likely use in the indicative condition(s) in the application.
     - Which paediatric age groups?
     - Dosing regimen?
       - Probable route(s) of administration?
       - Probable Duration of dosing?
       - Probable Dose?

   *How will the product actually be likely to be used in the paediatric population?
   - What disease(s)
     (May be substantial use in variety of conditions including indicative ones)
   - Which paediatric age groups will it be used in?
   - Dosing regimen?
     - Route of administration?
     - Duration of dosing?
     - Dose?

[*Needs addressing to prevent / minimise future off label use]
→Informs on Formulation & strengths likely to be required

Initial thoughts when Rapp/Peer Reviewer for an individual PIP.

2. Are there any potential advantages of this drug over other medicines which currently exist?

3. What Guidance exists?
   -CHMP Guidelines
   -Is it on the "Paediatric Needs" List ?
   http://www.emea.europa.eu/htms/human/paediatrics/inventory.htm
   -Is it on the "Priority List"
   http://www.emea.europa.eu/pdfs/human/paediatrics/41493609en.pdf
   - Is there any other authoritative Guidance?
   e.g NICE, BNF-C, European / National Learned Societies etc.

4. Does the drug need studying in paediatric population? (PIP and /or Waiver)

   - Which age groups?
   - What diseases?
   - What data are needed – what extrapolation can be accepted?
     - PK ?
     - Safety?
     - Efficacy / Safety?

Initial thoughts when Rapp/Peer Reviewer for an individual PIP.

5. How can safety in paediatric studies be maximised? (Deferrals)

- Are preclinical studies in juvenile animals needed before paediatric trials
  - (effects on developing organs, growth, maturation) ?
- Should adult data be available before paediatric trials commence?
- Should there be a “Stratified approach” in the paediatric population?

→Informs Waivers/ Deferrals and studies likely required

Understanding the above might help applicants understand where PDCO might be coming from.

Examples of issues which have arisen in practice

Medicine 1.	**Compliance check**
Medicine 2.	**A PUMA problem**
Medicine 3.	**A communication issue**
Medicine 4.	**Interaction with FDA Written Request**

(3 are from SMEs – 1 from Big Pharma)

Medicine No. 1

Compliance Check

- Agreed PIP - Month 0
- Compliance Check requested - Month 2

(Submission extension for new formulation in adults – Month 5)

2 studies in compliance check

- Juvenile animal study
- Clinical Study : placebo controlled dose finding study in adolescents

Medicine No. 1

Juvenile Rat study : **Compliant**

Clinical Study 1

PIP Measure: : placebo controlled dose finding study in adolescents
"At least 200 evaluable patients".
"**50 patients per each treatment group"**.

Clinical Trial report: 201 patients recruited in total
54 in placebo arm
48 in active medium dose arm
47 active high dose arm

Therefore NOT compliant with agreed PIP

Medicine No 1

Moral:

- Either compliant or not compliant

-If trials do not quite go as expected, consider future strategy:-

- if appropriate make application to modify PIP to ensure compliance at compliance check

and

-consider PIP as a whole.

Medicine 2

An old remedy - patent ran out in mid 1990's

- Medicine not licensed for paediatric use in EU
  (but used for all ages adults → neonates)
  -Considerable paediatric off-label use.

- Diminishing quantity and quality of clinical data in literature for younger age groups.
- No age appropriate formulation available in EU
  → young age appropriate formulation imported from non-EU states
  → Extemporaneous manufacture in EU with consequent variability

- "Paediatric Needs" includes-
  - "lower age limits to be defined. Investigate where deficient.
  - Age appropriate formulation.

Medicine 2

Article 30 application

- No waiver requested.
- However formulation not suitable for older children (strength)
- No deferral requested.
- PIP comprised entirely of *Quality* proposals
  - No preclinical studies
  - No clinical studies proposed
    (reliance upon published bibliographic data)

Day 60 PDCO

- Proposes Waiver ≥ 6 years
- No deferral

Medicine 2

Quality

Drop formulation

Day 60 PDCO

- Good formulation for younger ages.
- Waiver appropriate ≥ 6 years
- Is accuracy of dosing provided by drug delivery system adequate?
- Inadequate information on age-related safety of excipients
- Strategy for taste / taste masking necessary

Medicine 2

Non-clinical

No further studies proposed

Day 60 PDCO

-Substantial human use over nearly 25 years, both in adults and, to a lesser extent, in children.

-Further preclinical studies in juvenile animals unlikely to provide substantive new information

Medicine 2

Clinical
No studies proposed

Day 60 PDCO

- Experience in children substantial but an imperfect *literature* database. Poor literature evidence in youngest children/neonates of safety and efficacy and dose.
- PK & dose finding data in neonates & infants necessary
- Further full *efficacy* studies *throughout* paediatric population not necessary.
- Efficacy study needed in neonates/infants
- Safety data in children sparse and requires reinforcement. Short term AE data and long term effect on organ development/growth

(These data likely needed to support an MAA)

Medicine 2

Moral:

- PUMA's are not just about providing useful paediatric formulations
- Gaps in clinical knowledge in paediatric population need filling too if future MAA likely to succeed.

Medicine 3

Art 8

- Expiry date of SPC long way off
- Indicative Condition occurs in children 6 years -18 and in adults
- CHMP Guideline exists including advice for paediatric studies
- Licensed in adults but no drug in class licensed anywhere in under 12's
- Liquid formulation approved in adults
- Development **6-18yrs** identified as a Paediatric Need
- Difficult to demonstrate efficacy in younger children
  - Subjective efficacy endpoint difficult in younger patients.
  - Disease changes in character as age increases
  - Kinetics of drug varies as age increases – relative underdosing? in youngest patients

Medicine 3

- Studies in those aged 12-18 years already completed and in Co. view demonstrate positive R/B but no EU Variation application made to date

  Company request Waiver 0 to <12 years

Day 30 60 & 90 PDCO

Waiver not acceptable 6-12 years. Waiver acceptable for 0< 6 years

Company view :

- Other drugs in class have failed to show efficacy in paediatric population
- Ability to prove efficacy decreases as patients get younger
- Therefore trials in those 6-12 years of age will probably not be able to demonstrate benefit
- Trials 6-12 years will therefore subject children to an unnecessary study (Regulation seeks to avoid this).
- Company too small to undertake study in 6-12 year olds
  - financially
  - logistically

Conclusion : Cannot do it - Will not do it

- *If no PIP or waiver agreed – no variation application possible for those 12-18 who will be deprived of a medicine that has shown benefit in this age group*

Medicine 3

Pre Day 120 Teleconference (EMEA + Rapp+ Peer Reviewer)

- Cannot speak for entire PDCO as to whether waiver acceptable.
- Possible compromise explored.

Quality

- Oral liquid formulation.
  Appropriate strengths.
  Palability test.

Clinical

- PK study 6-12 year subset.
- Efficacy /safety trial 6-12 year subset.
  - Trial designs discussed – second line? enrichment design?

☞**EMEA + Rapp+ Peer Reviewer proposed Oral Explanation before full PDCO for Company to put arguments re issue of Waiver 6-12 years**

Medicine 3

Company declined Oral Explanation

- Insufficient resource
- Unlikely to get view to prevail

Day 120 PDCO

Negative opinion Day 119
Company withdrew PIP application Day 120

No agreed PIP / Waiver so no MA Variation possible at present for patients aged 12-18

Medicine 3

Moral:

- Regulators have to deal with all companies in an equal manner.
- Rapporteurs cannot speak for whole PDCO
- Deviation from an agreed “Paediatric Need” is going to be tough.
- Take up opportunities offered for an Oral Explanation. (There is no negative opinion until end of procedure). This is the **ONLY** opportunity to meet the entire **PDCO** and explain your position - you may win !

Medicine 4

Article 7

-No similar product licensed in EU
-Considerable off label use of similar products
-Intravenous injection

-Likely improved safety compared to off label products
-Less injections required for efficacy than off label products
Therefore a useful paediatric product.

-Efficacy measured by hard pathological blood parameter

-Efficacy / safety established in adults in “index indication”

Medicine 4

FDA Written request (preceded PIP)

- One indication for study (the index indication)
- Waiver 0-2 years
- 2 studies in WR – 2 subgroups of index indication
- A comparator to be used (n=25 per study)
- 2 dose levels to be compared (n=25 per group per study)

Medicine 4

For PIP Company proposed:-

Quality
Adult vial sizes/ strengths.

Non-Clinical
-No studies

Clinical
-As per FDA WR

- One indication (index indication)
- Waiver 0-2 years
- 2 studies – 2 subgroups of index indication
- A comparator to be used (n=25 per study)
- 2 dose levels to be compared (n=25 per group per study)

Medicine 4

PDCO

- Usage will be wider than index indication in both adults and paediatric population.
- Will be used significantly in patients younger than 2 years of age.
- (Index indication will generally require repeat use, wider indication more often single use)

Waiver

Medicine will be used in non index indication down to 6 months of age. Therefore Waiver acceptable 0-6 months only

Quality

Appropriate strengths needed to minimise wastage and allow accurate dosing in younger children.

Non-Clinical

No studies necessary

Medicine 4

Clinical

- Efficacy established in adults in index indication and extrapolation possible.
- No comparator necessary in index indication.
- Establishing the dose regimen and safety in paediatric population is PIP goal.
- Better to establish dosage regimen and then do trials using identified regimen than study 2 doses and a comparator as this limits database available for safety.

-Efficacy / safety data necessary in wider indication.

-Staggered approach recommended – older age groups first.

-Long term safety follow up necessary in repeat use.

Medicine 4

New Company proposal

Waiver

Agree to waiver 0- 6 months

Indications

Agree to Index indication & wider use

Quality

Appropriate vial sizes / strengths for patients6 months and above.

Medicine 4

Clinical

-Index indication

-2 short term studies – 2 subgroups of index indication

A comparator to be used (n=25 per study)

2 dose levels to be compared (n=25 per group per study)

Stratified approach

-1 long term safety study

Including 2 subgroups of index indication

-Wider indication

1 study

No comparator

2 dose levels to be compared (n=50 per group per study)

Medicine 4

PDCO

Yet to decide
Main issue around safety cohort size in Index indication
Maybe OK Maybe not.

Medicine 4

Moral:

- It can be difficult to get a completely identical agreed FDA WR and EU PIP.
- Forcing one into the other can be problematic.
- The 2 legislations differ.

Thank You

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