Safeguarding public health

# *"Practical examples of PDCO advice on development programme; presentation of various case studies"*

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**A somewhat difficult topic – but all about COMMUNICATION between Regulators and Companies and how in my experience this sometimes breaks down.**

# The Plan !!

- Why a Paediatric Regulation?
- Looking at it from the Regulatory side
- Some anonymised examples
- Questions (& Answers ???)

# What makes a good PIP?

-From whose perspective? Who judges?

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-PDCO / PDCO delegate?
-EMA?
-Company?
-The Regulatory Process?
-Paediatricians/ health care professionals?
***-Children !!***

***-Now or in the future??***

# Why a Paediatric Regulation

# Where we started - 2001

***Increasing pressure since late 1990's by paediatricians / paediatric pharmacists / health care workers for paediatric formulations strengths which are licensed.***

**UK Parliamentary Question reply** *: Reports in the literature of results of hospital - based surveys indicate that such prescribing is extensive in children.*
*-For example, in a neonatal intensive care unit around 90 % of neonates received off-label or unlicensed medicines.*
*-In intensive care units, around 70 per cent. of children receive a medicine outside a licensed indication and 31 per cent of prescriptions are for unlicensed or off-label use.*
*-In a study of children in medical and surgical wards, 25 per cent of the products prescribed during the admission were for unlicensed indications.*
*-In primary care the incidence of off-label or unlicensed prescribing to the paediatric population is thought to be around 10 per cent.*

In the case of paediatric medicines there is a *mismatch* between public health needs and the medicines which the commercial environment has made available.

The ***sicker the child the more likely*** they are to receive an unlicensed medicine.

## What happens when a child is ill and needs a medicine not licensed for paediatric use?

- The dose and dosage interval is "*guessed*" We *hope* it will work and that it will be safe

- Formulation may be made up on an ad hoc basis:-
  "extemporaneous formulations" made in pharmacies
  *e.g. Tablets are divided, crushed and mixed with sweetener to make a liquid*
  *(these may differ in strength and stability with each manufacture)*

- Liquid dosage forms which are unlicensed in UK may be imported and used (may be from EU countries, non – EU countries, may be human or veterinary). This importation may be extensive and is not easily controlled, as restricting importation may cause problems.

- Injectables may be diluted and the dose to be drawn up is calculated.

**- Children cannot necessarily be dosed easily and appropriately**
**- Dosing Errors are common – 13-20%**
**- Paediatric Medicine /paediatric dosage form withdrawal is common and can be problematic**
**- How ethical is it in fact to give unproven medicines to sick children.**

**To change this unsatisfactory state of affairs the Paediatric Regulation was brought into force.**

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## This should *eventually !!* result in a fundamental change

-From the current status where medicines used in children are ***generally unlicensed or used off-label*** to a state in the future where they are generally ***licensed for use***

-***This is what drives the Regulators***

# Looking at it from the Regulatory side

**- Put yourself in the mind of the "other side".**
**- Not – what do *I* think of my proposals but what will *they* i.e. the Regulators - think of them bearing in mind where they are coming from.**

***PDCO Members and assessors are (like those who work in the pharmaceutical industry) human ! – BUT have a heavy workload, few friends and unlike drug company executives are poorly paid. (PDCO work attracts no fee). They have limited resources and can only spend a limited time on your application.***
***Many of them are senior paediatric health care professionals who have spent a lifetime struggling with the unsatisfactory paediatric medicine portfolio.***

***PDCO meetings are gruelling in terms of travel and of duration.***

# Some potential problems on assessing a PIP

- **May be no specific CHMP Guidelines / National or Learned Society Guidelines or previous PDCO "*case law*" as yet.**
- **External independent expert advice may not be obtainable.**
- **Different companies / different experts may have different views on trial feasibility of similar PIPs.**
- **We are learning !! Things are improving as experience increases.**

# Thoughts when Rapp/Peer Reviewer for a PIP.

1. **What is the paediatric need for this medicine?**

   **-What existing therapies (if any) are used for the condition(s) under consideration in application. How satisfactory are they?**

   **-What is the likely use in the indicative condition(s) in the application and in which paediatric age groups?**

   ***How will the product actually be likely to be used in the paediatric population?**
   **-In what disease(s) other than the indicative ones**
   **-In which paediatric age groups will it be used in?**

   **-What will be the likely dosing route(s) of administration and probable duration of dosing?**

**[*Needs addressing to prevent / minimise future off label use Regulation's objective is to ensure that the medicine for use in children will be authorised appropriately]**

**→Informs on Formulation & strengths likely to be required; whether waivers are appropriate and the likely need for long term safety data**

# Thoughts when Rapp/Peer Reviewer for a PIP.

2. **Are there any potential advantages of this drug over other medicines which currently exist?**
   - e.g. safety / efficacy / kinetics/ formulation

3. **What Guidance exists regarding use of this medicine in the indicative or likely use conditions?**
   -CHMP Guidelines
   -European / National Learned Societies / NICE etc.

4. **Considering prevalence of condition and available Guidance, does the drug need studying in paediatric population? (PIP and /or Waiver). If so:-**
   -Which age groups?
   -What diseases?

**→Informs on likely PIP clinical requirements and clinical trial design.**

# Thoughts when Rapp/Peer Reviewer for a PIP.

**5. Are there any preclinical safety issues that might require juvenile animal studies to better inform on likely safety BEFORE paediatric clinical trials commence?**

-What juvenile animal studies are needed.

**6. If paediatric development is needed:- What clinical data are needed – and what, if any, extrapolation from other populations (adults) can be accepted?**

- PK ?
- Efficacy / Safety?
- Long term safety

**→Informs on likely deferrals, PIP preclinical and clinical requirements.**

# Thoughts when Rapp/Peer Reviewer for a PIP.

**7. Are there any preclinical safety issues? Has the medicine been shown to be safe in adults or other populations (e.g. older paediatric age subsets).**

**→Informs on likely deferrals, "step-wise" paediatric development.**

**SAFETY FIRST !!!**

# The application - General points

-Should be timely – not immediately before an adult MAA

-Do not delegate writing the PIP application below level of competence of author.

-Pay attention to:-

*brevity*
*accuracy*
*comprehensiveness*
*understandability*
*coherence*

**Read the Commission Guidance and comply !!**

**Read the relevant CHMP Guidelines and either comply or provide robust justification for not doing so.**

**Look at PDCO Opinions for similar medicines (published on EMA website)**

**Safety First for the clinical studies**

**Paediatric Regulation is European Not American**
FDA WR requests do not *necessarily* fit well into European legislation.

**Quality issues are VERY important**
Age appropriate formulations and appropriate strengths to allow proper dosing of all age groups are expected.

**Article 8 applications and patent life**
Regulatory pragmatism cannot necessarily be assumed because patent life is short

# The PIP application /Summary Report / Guidance format

Part A: Administrative and product information
Part B: Overall development of the medicinal product including information on the conditions
Part C: Applications for product specific waivers
Part D: Paediatric investigation plan
Part E: Applications for deferrals
Part F: Annexes.

Commission guideline
*http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/com_2008_jo243/com_2008_243_en.pdf*

# The application – Section A
# Administrative information

-Details of the Medicinal Product (Formulation, strength, route )
*Development, waivers etc may be different for different formulations/routes of administration. Include all formulations.*

-Information on clinical trials related to the condition and to development in the paediatric population.
*Detailed information useful – will prevent a request for clarification*.

-Advice from any regulatory authority relevant to the development in the paediatric population
*CHMP Scientific advice, US Written requests. EU National advice. Often incomplete. Comprehensive data will prevent a request for clarification*

# The application – Section B
# Scientific Information

**More important than might be supposed**.

Discussion on similarities and differences of the disease/condition between populations

*-Don't forget :-*
*--Description of the pharmacological properties and mechanism of action*
*--Anticipated differences / similarities*
- *between the adult and the paediatric populations,*
- *between the different paediatric subsets.*

Current methods of diagnosis, prevention or treatment in paediatric populations

*- What medicines are currently used.*
*-Which paediatric subpopulations are relevant*

Significant therapeutic benefit and/or fulfilment of therapeutic need

*-What are the advantages and disadvantages of the applicant medicine compared to what exists*
*-What relevant clinical data exists for this and other medicines with same use*

# The application – Section C Waivers

**Class waiver.**

Only if on the class waiver list !
*If class waiver says "The treatment of Thatcher's disease", then an application to diagnose it, image it or to influence a sequela of the disease (e.g. dementia associated with Thatcher's disease) will be refused.*
http://www.ema.europa.eu/htms/human/paediatrics/classwaivers.htm

**Product specific waiver**
Often poorly argued

**Only 3 grounds :-**

**-product is likely to be ineffective or unsafe in part or all of the paediatric population**

**-disease or condition for which the specific medicinal product or class is intended occurs only in adult populations**
*Are you sure that the disease is in fact limited to adults? Low prevalence is not a ground for not undertaking a PIP*

**-product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.**
*Detailed justification needed. If trials unfeasible so that the benefit cannot be established – this is the ground to apply for.*

# The application – Section D: Paediatric investigation plan

**Selected age group(s)**

-Age classification of ICH/CHMP guideline E11, not essential. Make sure all age groups included in waiver / PIP proposals. [Don't forget pre-term neonates].

**Strategy in relation to quality aspects**

-Excipient safety can be an issue particularly in very young children.
Palatability / masking is often omitted and is considered important by PDCO.

**Strategy in relation to non-clinical aspects**

-Difficult to assess need for further juvenile studies without a summary of existing studies and the findings – often poorly done.
-Age of animals should reflect proposed paediatric usage – better to go too young than leave a safety "gap"

**Strategy in relation to clinical aspects**

-Identify the gaps in the available paediatric information and propose clinical studies which will lead to generation of robust evidence

# The application – Section D: Paediatric investigation plan

Measures for the development in the paediatric population
Overall Summary Table of all planned and/or ongoing non-clinical and clinical studies
Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development
Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies
Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies or trials

*More detail necessary than may be thought * – key issues are:-*
*-study design objectives, control therapy, patient numbers, treatment duration, inclusion/exclusion criteria, efficacy endpoints, power calculation stopping rules, safety assessments need to be detailed.*

** PDCO cannot force a PIP modification so having these parameters defined provides a safety that any change in feasibility etc. will generate a modification*

# The application – Section E: Deferrals

Safety First !

-Preclinical studies in general BEFORE clinical studies
-Adult studies in general BEFORE paediatric studies
-Older paediatric patients first.

Provide TIMELINES i.e. Dates!

# After the initial application and consideration

- **Make sure you understand the "Request for Modification" points**
  - Speak to the EMEA – Would a teleconference be helpful. If so remember that Rapp/Peer in teleconference cannot speak for the PDCO.

- **Don't rush the response**
  - The clock stop is the only one you have - Better to take a bit longer and get it right
  - It is impossible for the system to agree major changes between Day 90 and 120. The time to sort things out is at the clock stop
  - Answer the Questions!

- **Think very carefully before giving up option for a Day 120 Hearing**
  - It is the only time you will meet the entire Committee.
  - Excellent forum for exchange of views
  - Don't be discouraged by apparent negativity - You may win !! If not you will probably come away with the knowledge about what needs doing to fix the problem. You can then withdraw application and resubmit with the issues fixed.

# Some anonymised examples of when things go a bit wrong.

# Examples of issues which have arisen in practice

| | |
|---|---|
| **Medicine 1.** | **Compliance check** |
| **Medicine 2.** | **A PUMA problem** |
| **Medicine 3.** | **A communication issue** |
| **Medicine 4.** | **EU vs. USA** |

# Medicine No. 1

-Agreed PIP
-Compliance Check requested for a new formulation in adults

**In compliance check**

-Clinical Study : placebo controlled dose finding study in adolescents

**Clinical Study**

PIP Measure: placebo controlled dose finding study in adolescents
"At least 200 evaluable patients".
At least "**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 in active high dose arm**

**Therefore NOT compliant with agreed PIP**

# Medicine No 1

## Lesson:

-A PIP is either compliant or not compliant.
-Check yourself before you submit compliance check !!

-If appropriate, make timely application to modify PIP to ensure compliance.

# Medicine 2

-An old remedy - patent expired

-Not licensed for paediatric use in EU (but in fact used for all ages adults → neonates)

-Considerable paediatric off-label use but no young child appropriate formulation available in EU → Extemporaneous manufacture in EU with consequent variability.

- *A formulation and strengths specifically for young children would be useful
- *Diminishing quantity and quality of clinical data in literature as patient age decreases. ? +ve R/B in very young. Needs researching.

* Reflected in “Paediatric Needs” List.

# Medicine 2

## PIP application

-PIP *Quality* proposals only (an age appropriate formulation suitable only for younger children – one strength.

- No preclinical studies
- No clinical studies proposed – no age limit waiver cut-off proposed

## PDCO

-Proposed Waiver ≥ 6 years

-Accuracy of dosing throughout 0-6 years age range in doubt

-No strategy for taste masking or palatability testing

- *PK & dose finding data in neonates & infants necessary
- * Efficacy study needed only in neonates/infants
- * Short term AE data and long term effects on organ development needed

** These data likely needed to support MAA – and reflect published paediatric needs*

# Medicine 2

**Lesson:**

-PUMA's are not just about providing useful paediatric formulations. Gaps in clinical knowledge in paediatric population need filling too.

-Appropriate strengths needed – not just a formulation.

-Palatability is important.

- Check what is published (if anything) about what is considered to be needed in the paediatric population for your medicine.

# Medicine 3

-Indicative Condition occurs in children (? 6 years and above) and in adults

-CHMP Guideline exists including advice for paediatric studies in those aged 6 years and above

-Licensed in adults but no drug in class licensed anywhere in under 12's

-Liquid formulation approved in adults

-Development in those aged **6-18yrs** identified as a Paediatric Need
-Studies in those aged 12-18 years already completed

-Company request Waiver 0 to <12 years

# Medicine 3

## Day 60 PDCO

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

**Company view :**

-Ability to demonstrate efficacy decreases as patients get younger because endpoint is subjective (debateable but probably true)

-Therefore trials in those 6-12 years of age will probably not be able to demonstrate benefit (debateable but probably not true – appropriate design and endpoints may resolve this)

- 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

At Day 90 at ateleconference Company declined Oral Explanation at Day120
-Insufficient resource
-Unlikely to get view to prevail

## Day 120 PDCO

**No option : Negative opinion**

# Medicine 3

**Lesson:**

-An existing CHMP Guideline defines the PIP

-PDCO cannot treat small companies differently to large companies.

-Rapporteurs cannot speak for whole PDCO at teleconferences

-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 despite view of Rapporteur !

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

# Medicine 4

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

-New product likely improved safety compared to off label products
-Less injections required than off label products
*Therefore a useful paediatric product.*

-Efficacy measured by hard laboratory parameter

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

**FDA Written request (preceded PIP)**
One indication for study (the index indication)
- Waiver 0-2 years
- 2 studies in 2 subgroups of index indication
- A comparator to be used
- 2 dose levels to be compared

# Medicine 4

## PIP

**Quality**
Adult vial sizes/ strengths.

**Clinical**
-As per FDA WR

## 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 indications 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.

**Clinical**
-Efficacy established in adults in index indication and extrapolation possible. Establishing the safety in paediatric population is PIP goal.
-No comparator necessary in index indication study.
-Long term safety follow up necessary in repeat use.

-Efficacy / safety data necessary in wider indication.
-Staggered approach recommended – older age groups first.

# Medicine 4

-Eventually agreement reached between PDCO and Company based largely on PDCO requirements.

**Lesson:**

-It can be difficult to get a completely identical agreed FDA WR and EU PIP - the 2 legislations differ in scope, regulatory view on requirements can vary and medical practice can differ.

-PDCO is concerned about potential future *significant* off-label use