# Experience of PIP/waiver/deferral process from an SME perspective

4th EMEA Workshop for SMEs -*Paediatric Medicines*
23rd October 2009

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# AGENDA

- Background
  - Company
  - Product
  - PIP/PUMA Approach
- Company's experiences with the PIP process
  - Getting the required information in PIP
  - Experience with the PIP procedure and interactions with EMEA/PDCO
- Summary and recommendations

# The SME partnership

- Founded in 2005
- Speciality pharma, niche technically complex products
- 5 marketed critical care products
- Strong development pipeline
  - Paediatrics, Critical Care & Addiction

- Founded in 2006 - Paediatric Healthcare company
- identifies niche areas of unmet medical needs and works on a collaborative basis
- Expertise in:
  - paediatric drug evaluation, formulation, and drug delivery,
  - clinical and regulatory strategy, clinical study design, management, analysis, and reporting,
  - interacting with Health Authorities and securing regulatory approvals

# Background

## Midazolam

- Off patent drug Midazolam Hydrochloride
- Licensed for children as Hypnovel® (1982) IV, IM and rectal, and Versed® Oral (1998 - USA) for premedication and sedation
- Published clinical studies support safety and efficacy of oromucosal (buccal) midazolam for treatment of acute seizures in children with epilepsy
- Common practice in hospital and community to administer via buccal route off-label using either:
  - Approved injectable formulation
  - Unlicenced “special” product

# Background
## CSE and Treatment

- CSE most common childhood neurological emergency in developed countries (17-23 per 100,000 per year - UK)
- Rapid treatment crucial to prevent neurological and systemic pathology
- Hospital settings provide treatment options via I.V, not routinely available in the community
- Rectal diazepam (licensed) is most commonly used for emergency treatment of seizures in the community, but not convenient or socially acceptable
- A need exists for an effective, easily administered treatment

# Background
## Development Programme

Development Programme to support:

- New indication: Treatment of acute seizures in children (from 3 months to <18 years) known to have epileptic seizures. (agreed PIP indication)
- New dosage form, specifically for oromucosal use in paediatrics (10mg/2ml Midazolam Hydrochloride plus limited excipients)
- New route of administration: Oromucosal (Buccal)
- Licensure via Paediatric Use Marketing Authorisation (PUMA) subsequent to securing agreed PIP

# Available guidance - PIP

- EMEA Medicines for Children Website (http://www.emea.europa.eu/htms/human/paediatrics/pips.htm) providing:

  - European Commission PIP Guideline (2008/C 243/01)
  - Procedural Advice
  - Submission deadlines
  - Links to relevant scientific guidelines

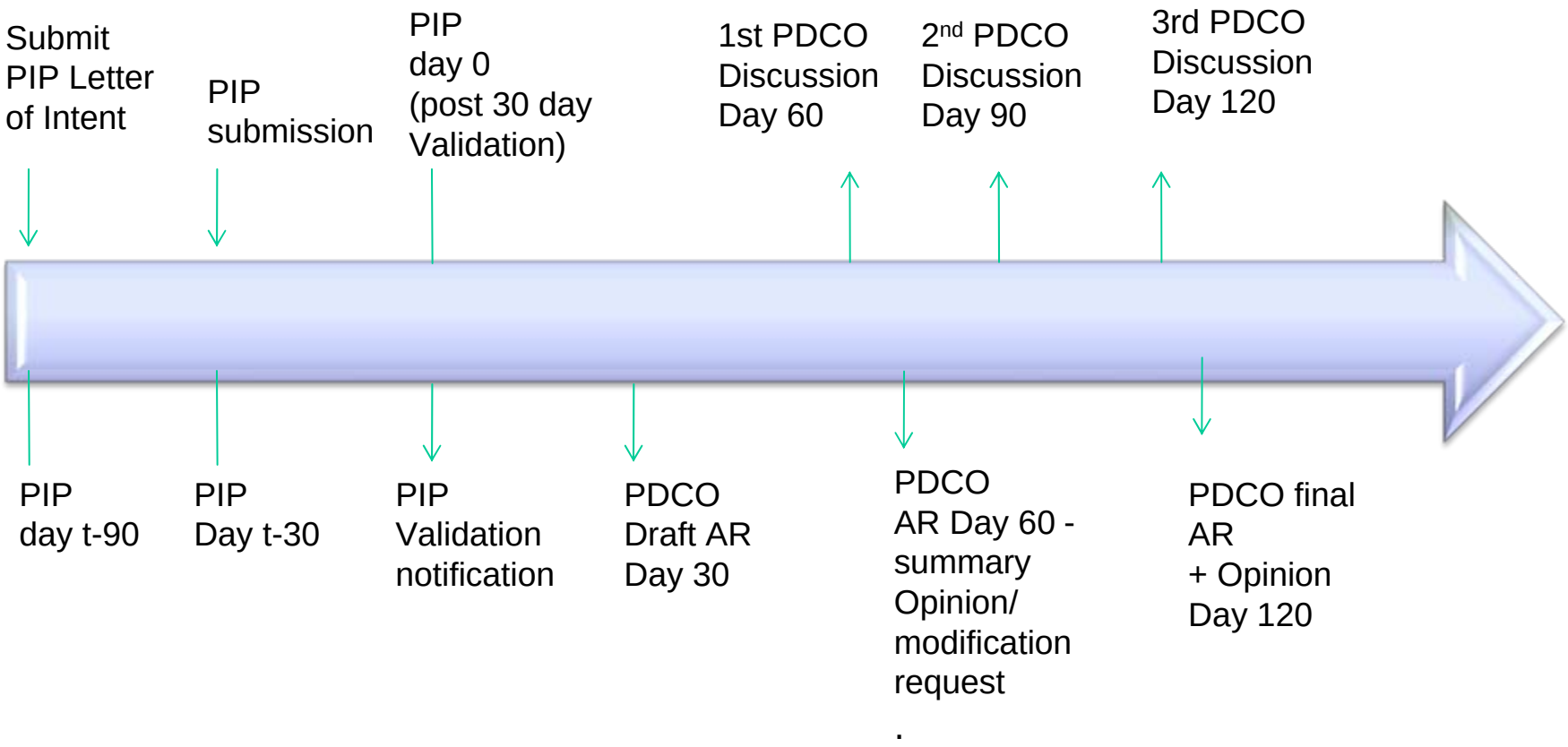
# PIP to PUMA

## One process

- PUMAs apply to ‘off-patent’ drugs
- Product must be for exclusive use in the paediatric population
- Applications for PUMAs must include documents to support quality, safety and efficacy in accordance with an agreed paediatric investigation plan (PIP)
- Applications can cross-refer to data in the dossier of an existing product owned by a different MA holder, providing appropriate data protection period expired.
- Data may be bibliographic or new pre-clinical or/and clinical data or a mixture
- A direct application for a PUMA can be eligible for the centralised procedure
- The PUMA, allows ten-years of data protection for innovation (new studies) on off-patent products

# Theoretical Process and timelines

## Our expectations



# In practice
## Our experience

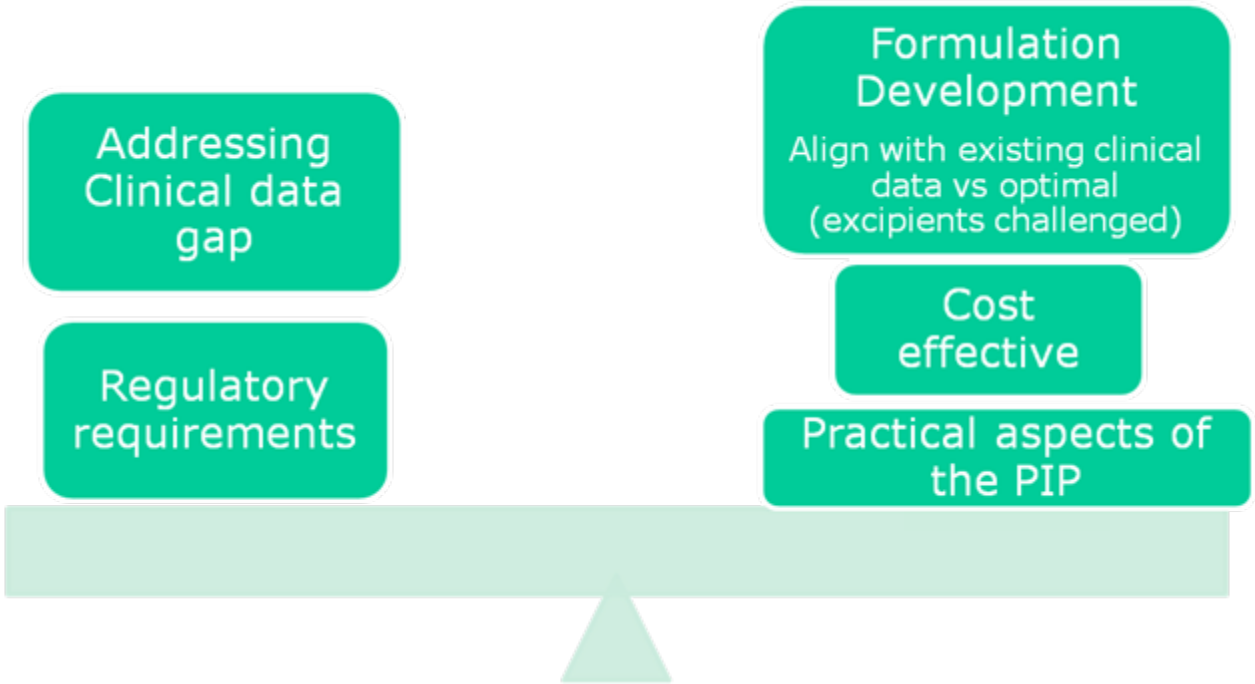
- Taking each phase in turn
  - Timelines
  - Queries
  - Challenges
  - Lessons learned

# Scientific advice phase (40-day process)
## Summary & Lessons learned

- Process and timings aligned with our expectations
- However, need to build in total time elapsed from letter of intent to receipt of final scientific advice
- In our case - 5 months
  - 23 Apr08 - LoI
  - 11 Jun 08 - Pre submission meeting
  - 17 June 08 – EMEA List of Comments from Pre-submission meeting
  - 19 June 08 - Final SA submission
  - 30 June 08 – Day 0
  - 25 Sep 08 - SA received (3 months post Day 0, 5 months post LoI)
    - Post SAWP 1-3 Sep 08
    - Post CHMP 22-25 Sep 08
- We found the advice helpful and a key element of the PIP process

# PIP application preparation
## Summary & Lessons learned (1)

- Consider need for Scientific Advice and build in time for this
- We obtained SA and found it  helpful and a key element of the PIP process
- Available guidance helpful in detailing what items must be covered
- The main challenge was delivering a balanced plan



# PIP application preparation
## Summary & Lessons learned (2)

- The paediatrics expertise and experience of the team was vital
  - Previous PIP experience
  - Practical experience of preparing a PIP
  - Key Opinion leader engagement
  - Understanding the needs of the target population

# PIP Validation

- Validation within the 30 days expected
- Communicated to the company on day 30 (13 Nov 2008)

# PDCO draft Assessment Report (AR) (day 30)

- Aligned with published timelines (30 days from day 0 start of procedure 13 Nov 08)
- Draft AR (88 pages) received, detailing discussion between EMEA Paediatric co-ordinator, Rapporteur and Peer reviewer
  - Level of detail and transparency of discussion was welcome
  - However, interpretation of probable final opinion was challenging
- Some elements contained in the summary at 30 day were different to 60 day output

# PDCO 1st meeting opinion - D60 AR
## Summary & Lessons learned

- Received shortly after Day 60 of the procedure – Request for modification (RFM) received
- All elements were evident in Day 30 summary, although some summary points were not part of the final request for modification
- Request included Indications/Waiver, Quality, Clinical, Timelines
- Clock stop 40 days (January to March 09)

# Clock stop
## Preparation of response to RFM

- Clock stop 40 days (January to March 09)
- Enabled clarification of key points
  - Pre-submission teleconference March 09
- Waiver/deferral discussion
  - Guidance (written and verbal) ‘initially’ indicated that age range may be selected for PIP to PUMA (off-patent) products without requirement for waiver/deferral, However:
  - Clarification received stating all subsets of the paediatric population must be included unless a waiver or deferral is granted

# RFM response
## Approach

- Following advice from 18 March telecon, submitted response 24 March 09
- Response included request for a waiver < 3 months age
- Only disappointment in the process was the change of deadline submission dates
  - Published on EMEA website, however we were unaware they were subject to change (over a 6 month timeframe)
    - Advice: check the dates on the website regularly

# Summary final Opinion
## day 90

- Transparent report detailing the thoughts of the Coordinator, Peer reviewer and Rapporteur
- Difficult to interpret
- Positive and open discussion with coordinator enabled clarification

# Final opinion
## Day 120

European Medicines Agency

Doc. Ref. EMEA/494800/2009
P/155/2009

**EUROPEAN MEDICINES AGENCY DECISION**

**of 11 August 2009**

**on the agreement of a Paediatric Investigation Plan and on the granting of a waiver for midazolam hydrochloride (EMEA-000395-PIP01-08 in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended**

# Summary
## Our experience

- Scientific advice meetings provided clear advice which facilitated PIP preparation
- Timelines of PIP assessment procedure were predictable and aligned with our expectations
- Transparent process
  - Detailed comments from EMEA coordinator, rapporteur and peer reviewer
- Good Communication
- Opportunity to gain advice and clarification throughout the process via teleconferences, face to face meetings and written requests

# Recommendations

- Do not underestimate the value of experience in PIP preparation
- Dedicated team experienced and focussed on PIP preparation/process
- Clear justification of therapeutic need and clinical benefit in children is a requirement, particularly for PIP to PUMA route
- The process is resource intensive. Allocate adequate resources beforehand – particular issue for SME
- Waivers and deferrals require thorough justification
- Paediatric expert input is very important from the start
  - Seek paediatric scientific advice, if appropriate
  - Identify external experts and key opinion leaders – particularly important for SME


THANK
YOU