EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Comments and proposals on the results of the EFPIA survey

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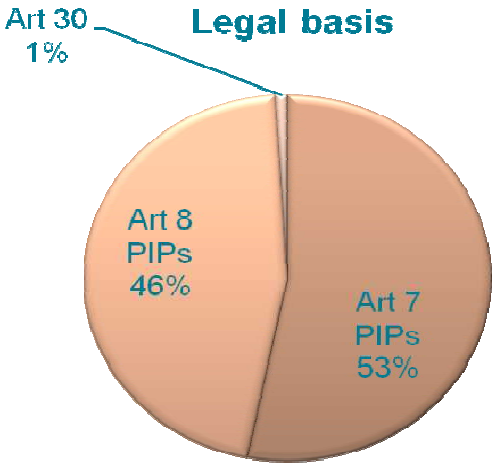
General comments

- First 360° analysis of impact of Paediatric Regulation
- Very detailed survey
- No big surprise in results
- Some common aspects and proposals with recent EVM "White Paper"
- EMA performance described as good
- Timelines respected
- Some companies are starting to obtain the benefits/rewards

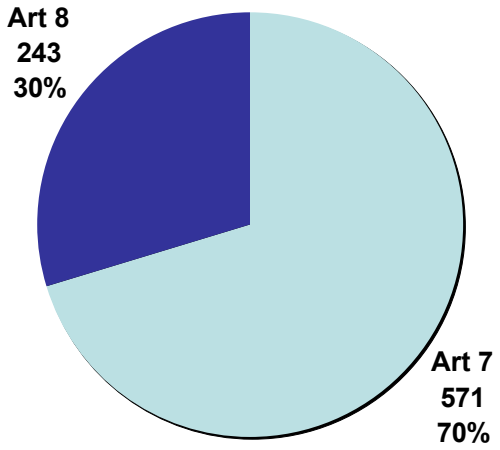
Data sources

- 34 companies, usually at least 28-30 answers per question
- Significant sample
- Slightly skewed distribution Art. 7 / Art. 8

EFPIA



EMA



All PIP/waiver applications
(including modifications)

Procedural aspects

- EFPIA data confirm EMA data that applicants submit PIP/waivers later than recommended by the regulation in the vast majority of cases
- Late applications:
  - ✓ EFPIA: 75%;
  - ✓ EMA: 69% (PIPs 74%, waivers 59%; 2010 data)

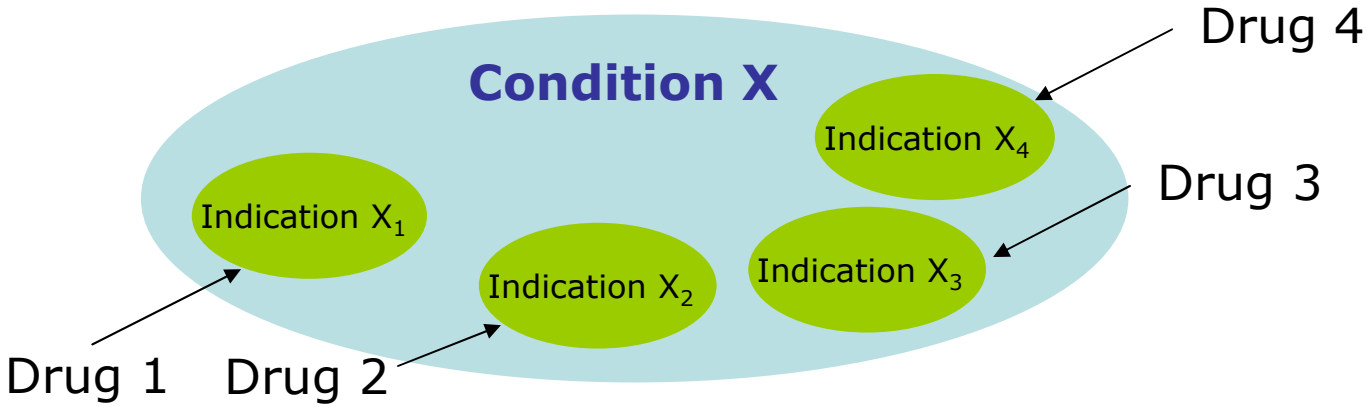
- Request of "major modifications" does not decrease in late or very late applications
- Percentage of withdrawals decreases in "late submissions" (expected)
- Long clockstop: companies slow or complex requests for modification?

Content and scope of PIP

- EFPIA data: PDCO requests development of a paediatric indication outside the adult condition in 10% of PIPs (32/319) – expected
- Additions most often requested: paediatric subsets, efficacy studies, quality (formulations, dosage forms) – expected
- Requests impacting on feasibility: date of completion can be reasonably postponed if additional studies/patients are requested

Content and scope of PIP

- The problem of "rare" conditions with several drug candidates:
  - e.g. hypertension, type 2 diabetes, JIA
  - Competition for patients
  - Difficult to reach a balance between "diversification of the development" and need to be fair to applicants and examine each application independently



Cost of paediatric studies

- EFPIA company estimates:
  - ✓ ~ € 0.2 M juvenile animal studies
  - ✓ ~ € 0.3 M BE/NA studies related to specific paediatric formulations
  - ✓ up to € 2 M for Phase I
  - ✓ up to € 40+ M for Phase III
  - ✓ **€ 50 – 100 M** for entire development
- other estimates may be lower:
  - ✓ NICHD: $1 – 7.5 M USD for a safety and efficacy study, $0.25 – 0.75 M for a PK-study
  - ✓ PhRMA: $5 - 35 M (http://www.gao.gov/new.items/d01705t.pdf.)
  - ✓ **$3.87 M per FDA written request** (Milne CP. *The Pediatric Studies Incentive: Equal Medicines for All.* Boston, Mass: Tufts University; 2001.)

There is also a benefit, not only a cost

Li et al. JAMA 2007

Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program (USA)

- $12.3 M (median) per written request (5 – 44 M)
- $ 0.9 M (median) per single-dose PK study (0.6 - 7 M)
- $ 2.3 M (median) per multi-dose PK study (0.6 – 21 M)
- $ 6.5 M (median) for efficacy study (1.8 – 13 M)
- **net economic return from –$8.9 M to $507.9 M and net return-to-cost ratio ranged from –0.7 to 74 M**

Limitations

- Software for calculation designed for adult trials
- No access to juvenile animal data
- No access to formulation costs
- Economic costs to health care incurred by delay in generic versions not included

Outcome of applications

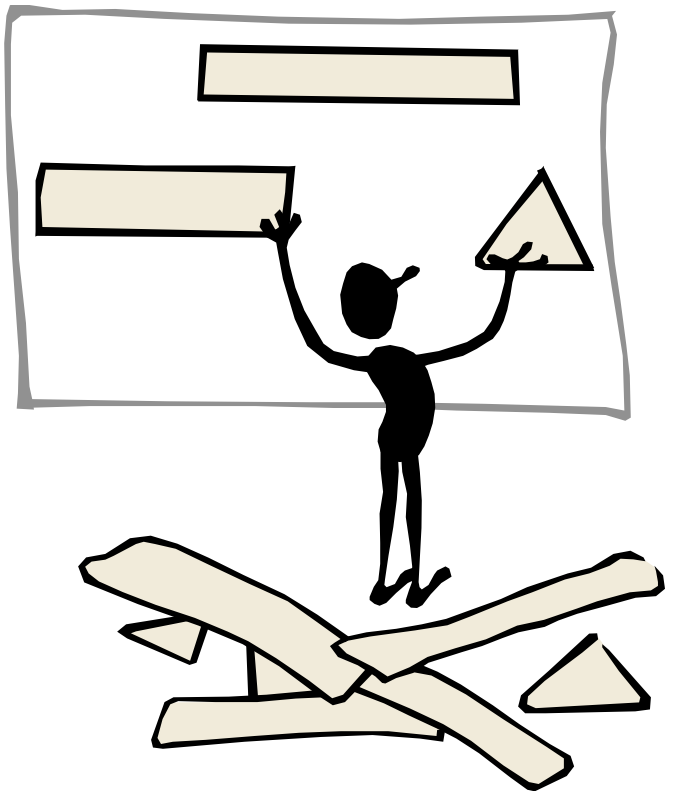
- Low number of negative outcomes:
  - ✓ EFPIA: 3.6% (PIP+waivers)
  - ✓ EMA: 4% (2009 data)

- Withdrawals: several causes (depending on stage)
  - ✓ EFPIA: 56% in D61-D120, 21% of withdrawals (N=19) "to avoid negative opinion"
  - ✓ EMA: 12% of all procedures in the last 30 days before expected opinion- 2009 data)

- 84% global positive rate of PIP/waiver opinions is higher than most procedures

Modification of agreed PIPs

- High number of modifications reported and expected
- PDCO accepted most or all the requests in a high percentage of cases
- No breakdown by timing of first PIP application (do PIPs agreed early require more modifications?)



PIPs and Clinical Trial Authorisation

- 21% of companies report problems (14 protocols). However problem eventually solved in 11 cases.
- No denominator, difficult to assess size of problem
- Many countries involved are outside EU
- EMA/PDCO would like to be informed of specific problems
- Some issues do not appear to be due to intrinsic problems with PIPs (e.g. delayed initiation of studies when recruitment was not possible)
- EMA/PDCO works with CTFG to prevent issues

Compliance checks

- EFPIA: low percentage (5.5% on 54 total) of negative compliance check =
  - ✓ 3/17 final/full CC
  - ✓ 0/34 interim CC
- EMA: 3.8% on 104 total =
  - ✓ 1/25 final/full CC
    (positive after modification)
  - ✓ 3/79 interim CC
    (1 positive after modification, 2 are recent - 2011)
- Good agreement of data, good compliance, good results!

Compliance checks

- EFPIA comment:
  "Industry expectation that recent changes in partial compliance checks will have a high impact on Regulatory submission strategies"

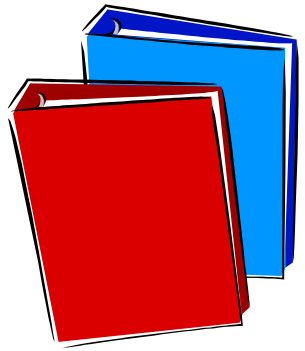
  - Initiation date?
  - Deferral by study/measure?
  - Difference between deferral and completion date?

Interaction with EMA/PDCO

- Positive evaluation of interaction with EMA staff (83% agree or strongly agree it is satisfactory) but is lower for interaction with PDCO
- How to improve?
  Possible strategies:
  - ✓Presubmission meeting
  - ✓Early TC for clarification of RfM
  - ✓Direct email contact (cc Paediatric coordinator)

Interaction with EMA/PDCO

- 24% of companies do not believe that the quality of the Day 60 / Day 120 Summary Reports is sufficient, and useful to understand the rationale of the PDCO RfM / opinion
  - ✓ OFI (opportunity for improvement): suggestions?
- Answers on Oral Explanation question its utility (44% neither agree nor disagree)
  - ✓ Possibility: OE at D90 or other solutions



Interactions between EMA Committees

- EMA's coordination efforts acknowledged
- Report on 3 instances of CHMP questioning the development plan as agreed by PDCO.
  - ✓ Coordination effort stepped up (routine interaction with PTLs and CHMP rapp./ co-rapp., participation at CHMP, involvement of paediatric PTM, etc.)

- Routine involvement of PDCO delegate + Paediatric coordinator for new/revised guidelines of paediatric interest/relevance

Impact of paediatric regulation

- Positive improvement in companies' awareness and involvement
- Approximately half of art. 45 procedures completed have changes in SmPC: more was hoped for
- Development of NCE/NBE delayed/abandoned because of perceived paediatric costs in 7 cases (7/171 = 4%):
  - Need to understand better
  - Small or large companies?

Impact of paediatric regulation - delays

- 13% of MAA / variations postponed because of paediatric regulation/requirements

- Possible causes:
  - Delay in submitting PIP/waiver application
  - Intrinsic length of procedure (PIP and CC)
  - (Inadvertent) non-compliance with PIP decision

Impact of paediatric regulation - delays

- Avoidance of delays requires preparation and collaboration between applicant and Agency – necessary timelines need to be factored in
- Deferral is the instrument of the Paediatric Regulation to avoid delays
- Flexible approach by Agency demonstrated on multiple occasions
  (modification of agreed PIP + second compliance check performed in a few days vs. 60-80 + 30 days)

Improving the system

A) Proposals conflicting with the paediatric regulation

- Clockstop at D90
  - ✓ procedure is 60+60 days by regulation.
  - ✓ however, postponement of the OE has been agreed in selected cases
  - ✓ evaluation time cannot be prolonged
  - ✓ third proposal / major changes not acceptable after D61
- Clockstop during modification process
  - ✓ Rapid modifications or clockstops…
  - ✓ Good quality of application helps (as no validation step)

A) Proposals conflicting with the paediatric regulation

- compliance check "in parallel" to MA application validation
  - ✓ CC is prerequisite for validation
- initial PIP submitted only after "Proof of concept" in adults
  - ✓ Timely applications avoid rush in the final stages before MAA
  - ✓ Benefit of early advice from PDCO on global paediatric development issues
  - ✓ EFPIA data suggest that the percentage of "major changes" requested by PDCO is not significantly higher for on-time applications

A) Proposals conflicting with the paediatric regulation

- Limit mandatory paediatric development to corresponding adult indication and defined critical unmet medical needs
  - ✓ Against recitals and spirit of paed regulation (art. 1, art. 17)
  - ✓ Who defines "critical unmet needs"? PDCO?
  - ✓ A number of paediatric indications do not exist in adults "by definition" (e.g. JIA), and would never be studied if strict interpretation is adopted

B) Proposals requiring a change in the EU guideline / EMA guidance

- "high-level" compliance check
  - ✓ All key binding elements are, well, binding
  - ✓ Possibility to insert "advice" in opinions: not done so far
  - ✓ Simplification of PIP opinions could be solution
- Limit interim CC to measures related to the scope of the specific application
  - ✓ Already the case (only measures for condition[s] being applied for are checked)
  - ✓ ?

B) Proposals requiring a change in the EU guideline / EMA guidance

- initial PIP: "high-level" information (agree paediatric needs, target indication, target population, formulation and projected timeline depending on development milestones)
  - ✓ Already tried in some cases/areas (e.g. oncology)
  - ✓ Difference with FDA: PIP cannot be changed by EMA once agreed + final clinical trial protocols not discussed with EMA but with CTA authorities
  - ✓ Simplification of PIP opinions could be solution

B) Proposals requiring a change in the EU guideline / EMA guidance

- "Commitment" to come back with detailed study design proposals before paediatric studies are started
  - ✓ Experience suggests that "commitments" were not followed
  - ✓ Done in some cases ("procedural obligations") for doses, pharma forms, even PIP indications (oncology)
  - ✓ Extension of practice of procedural obligations may be discussed as policy, but has consequences

B) Proposals requiring a change in the EU guideline / EMA guidance

- 12 months instead of 6 months limit to submit studies under art. 46

1) Requirement is there for a reason (SSRI AEs in adolescents)
2) See separate presentation on timely compliance with art. 46 requirement (very poor)

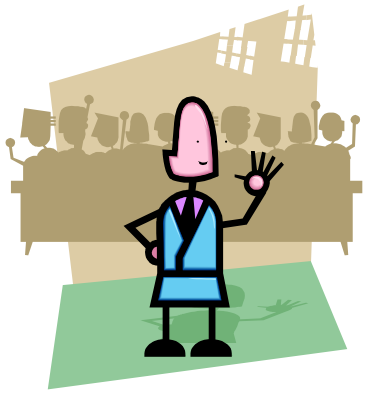
✓ Some products may have objective difficulties to comply

✓ Guidelines could recognise instances of justified delay (need to change 2 guidelines)

✓ Interim reports could be acceptable here

C) "Short-term" proposals

- optional interactive discussion meeting with PDCO on Day 90
  - ✓ OE at D90 (may be useful in some cases)
  - ✓ Time for answer PDCO's RfM is during clockstop / only minor adjustments thereafter
- more direct discussions between PDCO Rapporteur(s) and sponsor, where required
  - ✓ We can certainly work on this
  - ✓ Suggestions?



C) "Short-term" proposals

- Ensure submission format and dossier requirements are consistent with general EMA standards
  - ✓ ? Please specify

- Definition of condition vs. indication for the scope of PIP
  - ✓ Work in progress! See separate presentation
  - ✓ Collaboration / comments from industry and EC is sought

C) "Short-term" proposals

- Facilitate early joint discussions between regulatory experts, academia, learned society and the pharmaceutical industry
  - ✓ ENPREMA: regular (annual) forum
  - ✓ Questions submitted to EMA expert meetings
  - ✓ Model PIPs discussed with stakeholders
  - ✓ Interest from Industry necessary (PRES case)
- Build paediatric requirements into the regulatory therapeutic guidances as soon as possible
  - ✓ Systematic involvement of PDCO/PDCO members and EMA secretariat in all new / updated guidelines of paediatric interest

C) "Short-term" proposals

- Publish available data and regulatory guidance related to epidemiology for known disease areas in order to avoid duplication of efforts
  - ✓ Applicant can examine previous PIPs and be creative in proposal to cover uncharted lands
  - ✓ Model PIPs
  - ✓ Publication of more details on PIP opinions might help to assess what has been covered

D) "Other" proposals

- Special consideration needed for the application of the regulation to Orphan medicinal products and vaccines
  - ✓ Collaboration between orphan drug and paediatric section
  - ✓ Coordination with EU Commission to improve availability of information on market exclusivity and rewards under both regulations
  - ✓ Meeting with EVM; response to EVM "White Paper" in preparation; some points in common with EFPIA comments

D) "Other" proposals

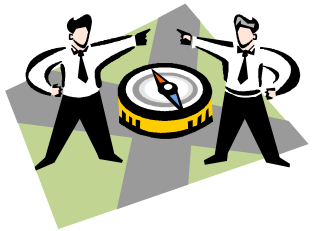
- Adequacy of rewards and incentives
  - ✓ EMA agrees that obtaining the reward should be easier
  - ✓ Work in progress on changes in PIP scopes to achieve that (specific presentation)
  - ✓ Meeting with patent offices planned

E) EMA suggestions / proposals

- Help us to have simpler opinions with relevant key binding elements!
  - ✓ An opinion is not a study protocol/synopsis
  - ✓ Although you are requested to submit the details of the protocols, that does not mean that all have to be key binding elements
  - ✓ When you receive the draft opinion after D90, there is often no need to ask us to reinsert in the opinion protocol details that have been deleted
  - ✓ You may also propose details to delete from key binding elements as considered minor
  - ✓ Example: no need for 22 secondary endpoints in a single-arm open-label study in 15 patients

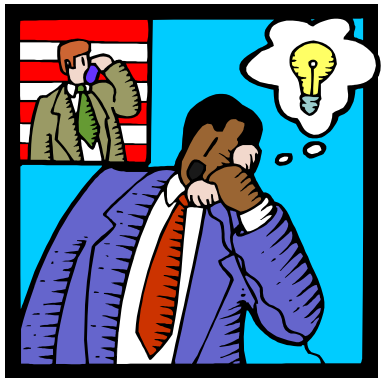
E) EMA suggestions / proposals

- Work in progress to have simpler opinions
  - ✓ Possibilities: applicant to provide
    1. both a) complete study synopses (e.g. in Scientific document B-E) AND b) proposed KBE (in the PDF studies form)
    2. PDF studies form: complete study synopses in the application, then only the suggested KBE in the response after the PDCO D60 RfM
  - ✓ Key aspects
    - ✓ 1: more detail, clearer; but risk of inconsistency, and more work required;
    - ✓ 2: simpler, less work; possible confusion due to use of one form for 2 scopes
  - ✓ Simplification of the opinion template: discussion in progress (however: instances of "oversimplification" already detected)



E) EMA suggestions / proposals

- Prevent problems with compliance check
  - ✓ Check carefully draft opinion as submitted by Paediatric Coordinator after D90
  - ✓ Particularly elements highlighted in yellow or otherwise
  - ✓ In case of doubt, contact Coordinator
  - ✓ Request compliance check in advance of the relevant regulatory procedure



E) EMA suggestions / proposals

- Additional recent improvements / proposals:
  - ✓ New compliance check guidance (Q&A published)
  - ✓ Guidance (one Q&A) on policy on "new pharmaceutical form" almost finalised, to be published soon
  - ✓ Flexibility and ultra-fast assessment of applications in justified cases (e.g. flu pandemic)
  - ✓ Possibility to discuss rapid and informal assessment of acceptability of changes by PDCO
  - ✓ Systematic publication of presentations from EMA staff in congresses / meetings
  - ✓ New "model PIPs" in collaboration with industry/academia

Conclusion

- We do work towards continuous improvement
- Collaboration and respect of rules and guidance is required from both sides
- Several initiatives implemented and in progress to answer EFPIA concerns
- Simplification is a worthy objective, provided it does not impact on the scientific quality of the opinions
- The PDCO and the EMA staff are keen to work to ensure the continuous success of the Paediatric Regulation, and the increase in knowledge on the paediatric use of good medicinal products