European Federation of Pharmaceutical Industries and Associations

Industry Experience with Art. 46 of Regulation (EC) No 1901/2006

Michel Stoffel

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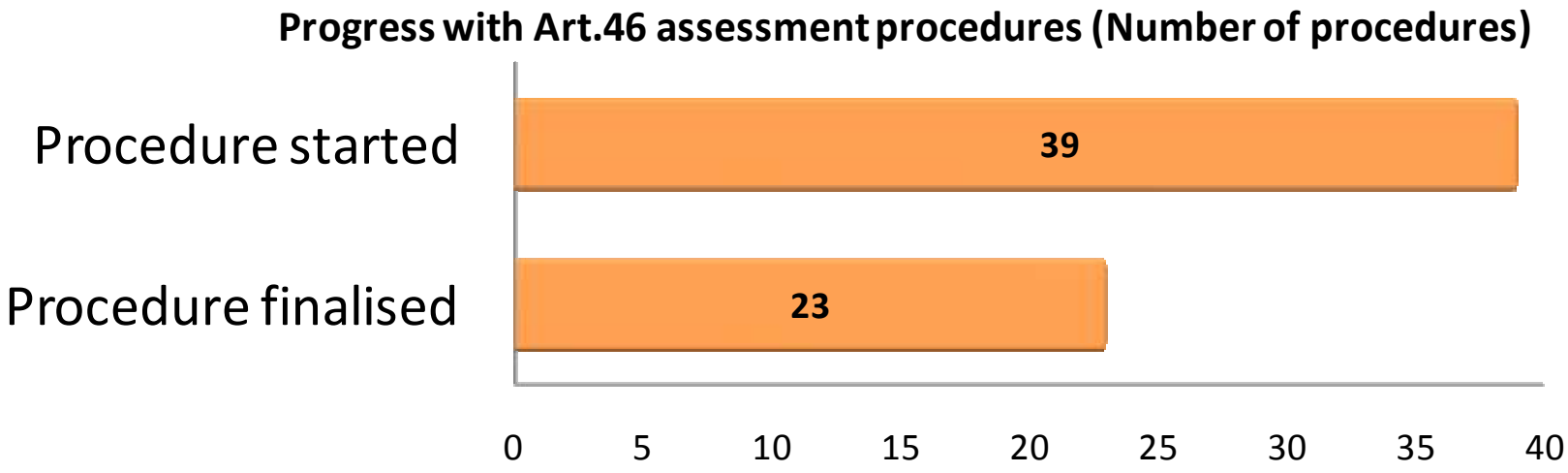
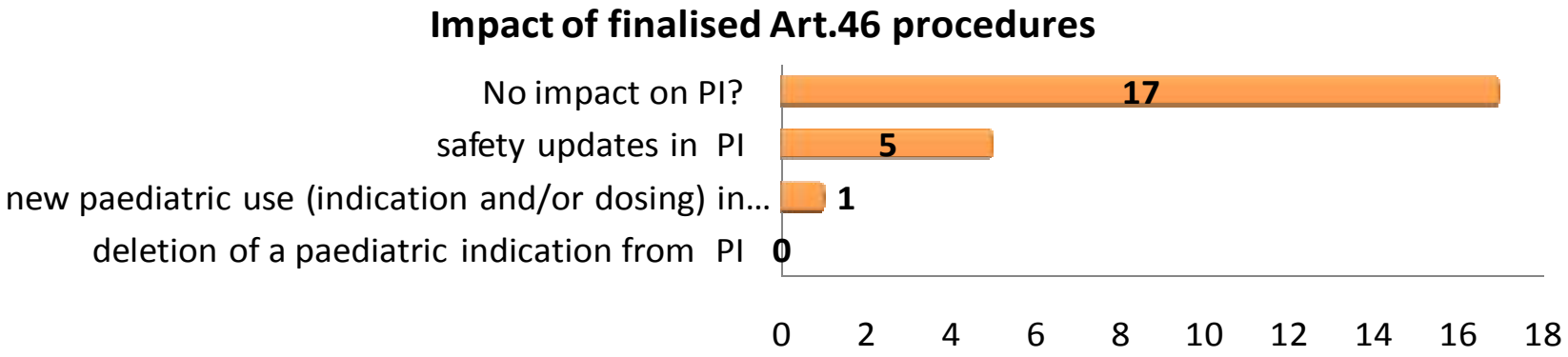
Article 46 procedures

- **122** submissions by **31** companies to comply with Art.46
- For **13** (11%) submissions, assessment deferred because of planned future regulatory procedures (variations, line extensions)
- High proportion of assessments finalised



Impact of Article 46 procedures

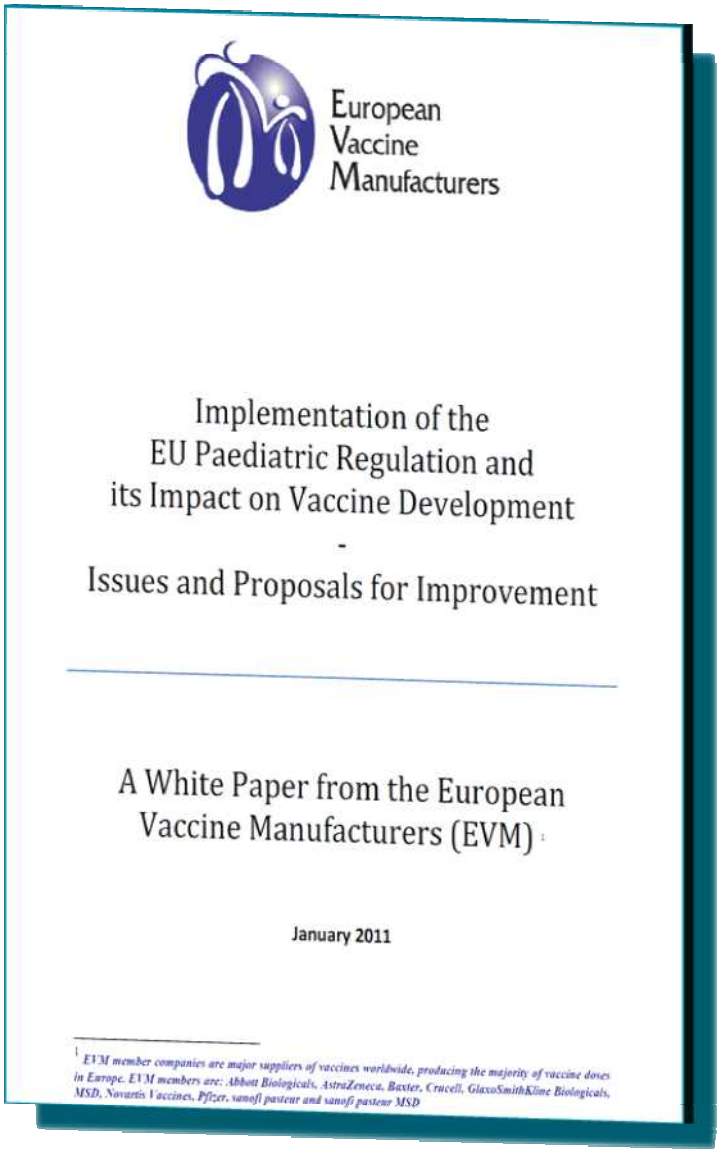
- Based on **23** reported finalised Art.46 procedures, a low number of procedures have resulted in revised product information
  - Suggests start of more procedures should be deferred until additional data available?
  - Or suggests need to rethink the need for submission of paediatric trial results within 6 months of completion?



Company perceptions of Art.45 and 46 procedures

Attribute	Companies feedback (Selection of the 3 highest percentages)
Overall, the procedure for appointment of the Rapporteurs was satisfactory	32% Agree
	32% Neither agree nor disagree
	6% Disagree or Strongly disagree
Overall, the interaction with the Rapporteurs was satisfactory	21% Agree
	29% Neither agree nor disagree
	15% Disagree
Overall, the total duration (from submission of data package to conclusion at European level) of Article 45 and 46 Worksharing Procedures was satisfactory	12% Agree
	32% Neither agree nor disagree
	21% Disagree

European Vaccine Manufacturers' difficulties with the implementation of Art. 46


European Vaccine Manufacturers

Implementation of the
EU Paediatric Regulation and
its Impact on Vaccine Development
-
Issues and Proposals for Improvement

A White Paper from the European Vaccine Manufacturers (EVM)[1]

January 2011

[1] EVM member companies are major suppliers of vaccines worldwide, producing the majority of vaccine doses in Europe. EVM members are: Abbott Biologicals, AstraZeneca, Baxter, Crucell, GlaxoSmithKline Biologicals, MSD, Novartis Vaccines, Pfizer, sanofi pasteur and sanofi pasteur MSD

Art. 46 timelines : realistic requirement?

- Art. 46 requires submission of paediatric studies involving the use of an authorised product, within 6 months of completion
- "Completion of study" is not defined in the Paediatric Regulation nor in the Clinical Trials Directive, however it is defined in:
  - Commission guideline [2008/C 243/01]: i.e. "Last Patient Last Visit" (LPLV)
  - Commission Guideline on Clinical Trial Applications [2010/C 82/10] : i.e. "The definition of the end of the trial should be provided in the protocol."
- Even for a "standard size" vaccine study in children it is **impossible in practice** to report in a **6-month time** frame following LPLV

Necessary steps between LPLV and finalisation of the clinical study report

- Transfer of biological samples from study sites to laboratories for analysis
- Sample testing (multiple tests needed, e.g. co-administration studies)
- Data monitoring and cleaning
- Statistical analysis
- Study report writing
- Obtaining the investigator's signature

A vaccine example

- Sample (e.g. serology) testing is one of the lengthiest steps
  → **this step alone often takes more than 6 months**
- A standard vaccine co-admin. study in paed. population :
  - *Prevenar 13*™ + *Infanrix hexa*™ with standard sample size of 500 subjects
  - blood samples are collected in two time-points (i.e. before vaccination and after the 3rd dose)
- *Prevenar 13*™ (13 antigens, 2 different assays needed)
  - ELISA for all subjects → 500 x 2 time-points x 13 Ag = 13000 tests
  - OPA for half of subjects → 250 x 2 time-points x 13 Ag = 6500 tests
- *Infanrix hexa*™ (10 antigens)
  - 500 subjects x 2 time-points x 10 antigens = 10000 tests
  - **In total 29500 tests are needed**

Other situations that could also delay the study report submission

- Outsourcing of study (e.g. to a CRO or a third party) adds complexity, and ultimately may delay the availability of the study report
- In the case of a trial conducted in the US under a Written Request, a slow enrolment may lead to an FDA Written Request amendment, which should be available before data is submitted to FDA
  - Preference is to submit first (or at least in parallel) to Agencies to whom commitment is made, before Article 46 submission in EU

Long-term solutions

- Harmonise reporting requirements for all clinical trials to 12 months
  - EC Communication 2009/C28/01[*] recognises that 6 months may be too short and allows derogation to extend deadline to 12 months for objective scientific reasons (except in case of Art.46 trials)

    [*] EC Communication 2009/C28/01 on entering result related information into EudraCT (cfr. Art. 41)
  - No public health justification to apply different rules for paediatric studies
  - One common set of rules for all trials facilitates implementation into company compliance systems
- Extensions beyond 12 months should be possible on a case-by-case basis if scientifically justified

Possible short term solutions

- Update definition of "study completion" in the following EC Guidelines in order to match timelines for Art.46 and EudraCT with practical reality:
  - EC Communication 2008/C 243/01 (Guideline on PIP format and content)
  - EC Communication 2009/C28/01 (Guideline on the paediatric trials information to be entered into EudraCT in accordance with Art. 41)
- Align definition with the one given in EC Communication 2010/C 82/01 (Detailed guidance on trial authorisation and end), which says:
  "The definition of the end of the trial should be provided in the protocol."
- Delete exception for Art 46 trials to allow derogation for all trials, and make the 12 months deadline a standard rule
- Allow possibility for company to send a letter to Authorities within 6 months to justify anticipated delays in study report submission
- Practical solutions need to be found a.s.a.p.