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Efpia survey on impact of the paediatric regulation on marketing authorization holders (Jan 2007 – Jun 2010)

Judith Creba (Novartis Pharma)
Craig Johnson (Eli Lilly)
Angelika Joos (Merck Sharp & Dome)

23 May 2011

Agenda

- Introduction and overview of survey data **(Judith Creba)**
- Presentation of survey data covering:
  - Procedural aspects **(Judith Creba)**
  - Content and Scope of PIPs **(Craig Johnson)**
  - Impact on Drug Development and Marketing Authorisations **(Angelika Joos)**
- Conclusions & Recommendations **(Angelika Joos)**

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Introduction and overview of survey data

Judith Creba (Novartis Pharma)

EFPIA survey on paediatric regulation (Jan 2007 – Jun 2010)

Objectives:

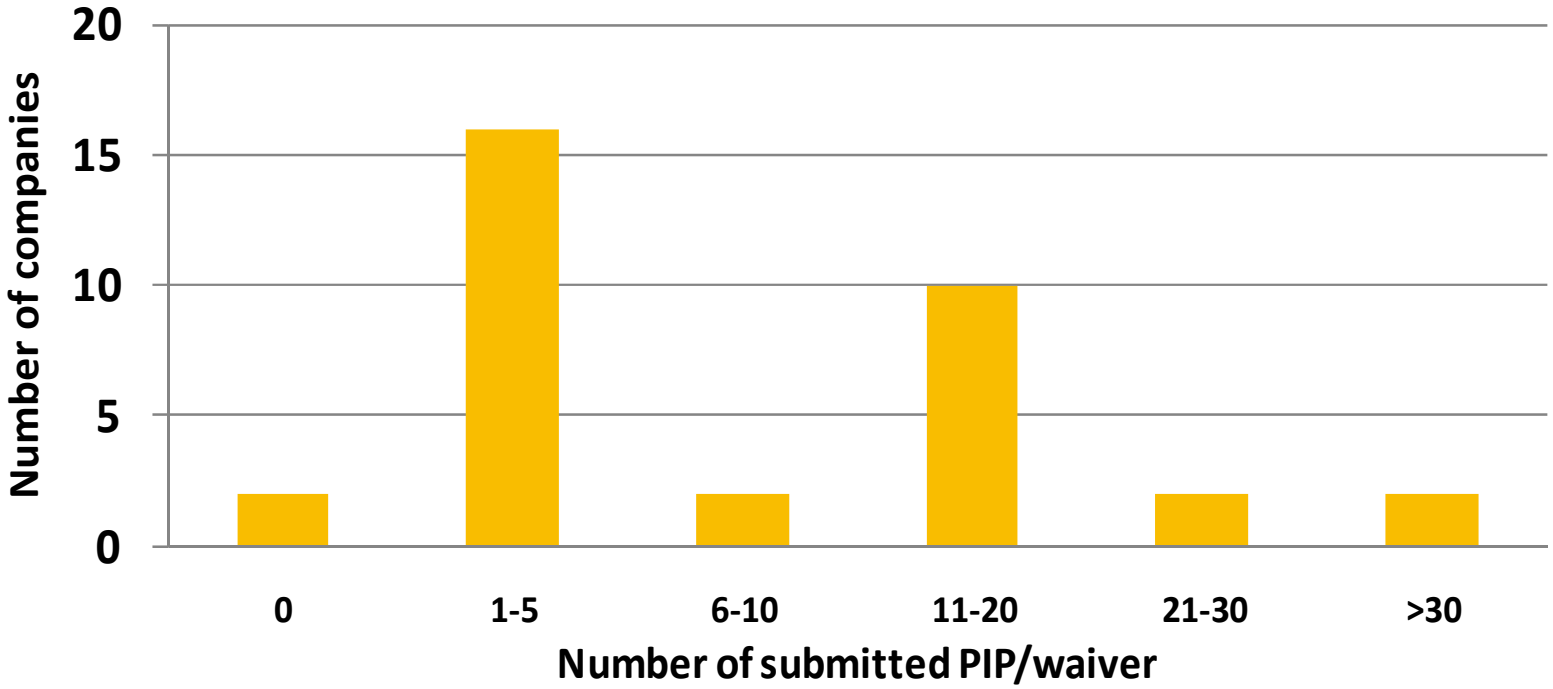
- To assess the impact of the first 3.5 years of implementation of the paediatric regulation on marketing authorization holders (Jan 2007 – Jun 2010)

- Survey comprised 61 questions with following scope:
- PIP applications (incl. partial waivers), “full” product-specific waivers & class waivers
- PIP/Waiver scope and content
- Timing of PIP applications for new medicinal products (Art. 7)
- Resubmission and/or application for changes of agreed PIPs/waivers
- Interaction with EMA/PDCO
- CTAs for clinical trial protocols included in PIPs
- Compliance checks
- Impact of the paediatric regulation on drug development and marketing authorisation
- Impact of the paediatric regulation on company resources
- Outcome for paediatric rewards
- Feedback on Art 45 & Art 46 procedures

34 companies provided input

Overview of number of PIPs by company

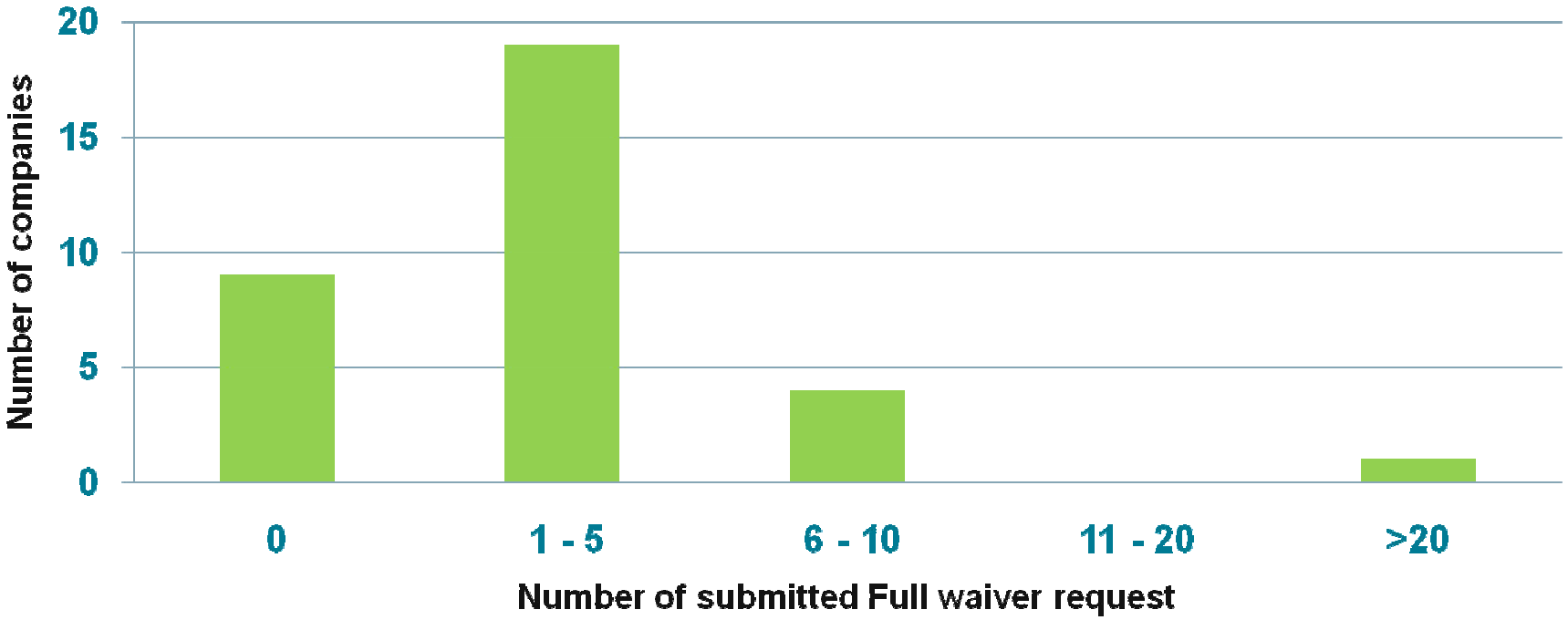
- Survey covers 316 submitted PIPs/partial waiver requests
  - This corresponds to 46% of EMA validated PIPs/partial waivers requests during same period



- PIPs/partial waivers submitted by company:
  Average n=9, median n=5, maximum n=36

Overview of number of product-specific waivers by company

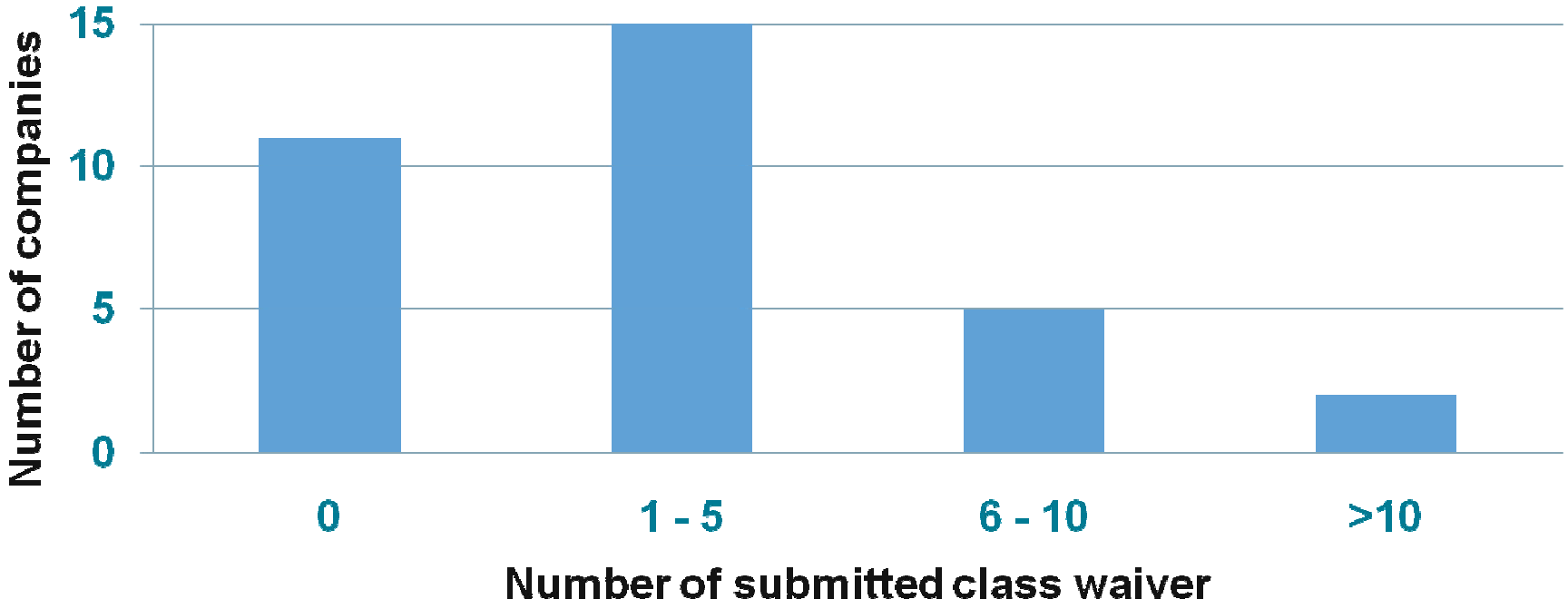
- Survey covers 98 applications for product-specific waivers
  - This corresponds to 50% of EMA validated product-specific waiver applications during same period



- Full waivers submitted by company:
  Average n=3, median n=1, maximum n=23

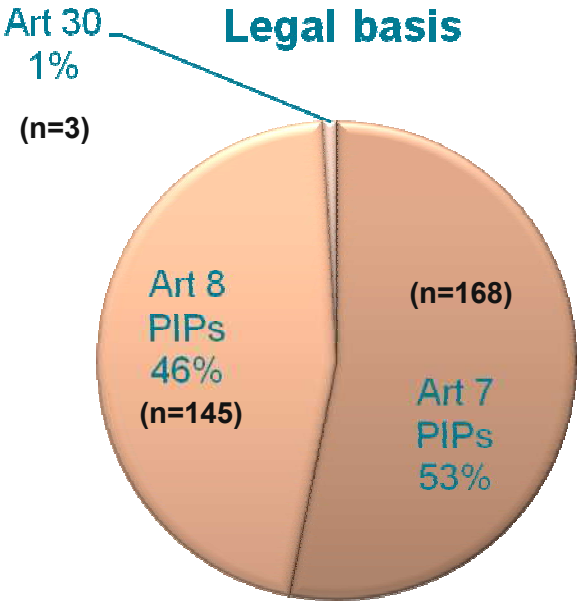
Overview of number of class waivers by company

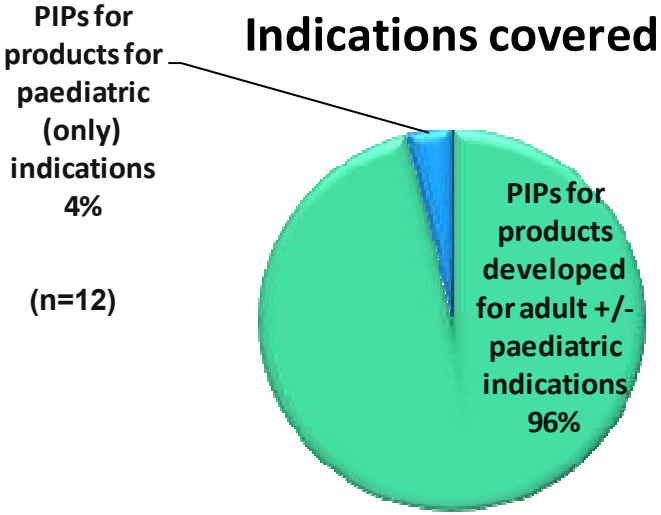
- Survey covers 87 requests for confirmation of class waivers

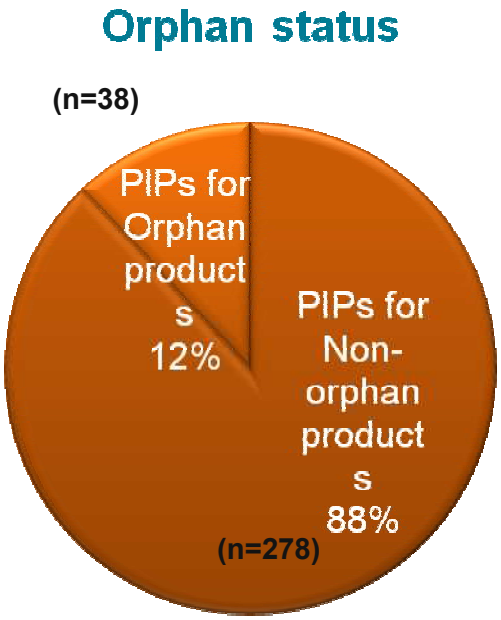


- Request for confirmation of class waiver submitted by company: Average n=3, median n=1, maximum n=15

Overview over 316 submitted PIPs/partial waiver requests:
Legal basis/orphan status/indication







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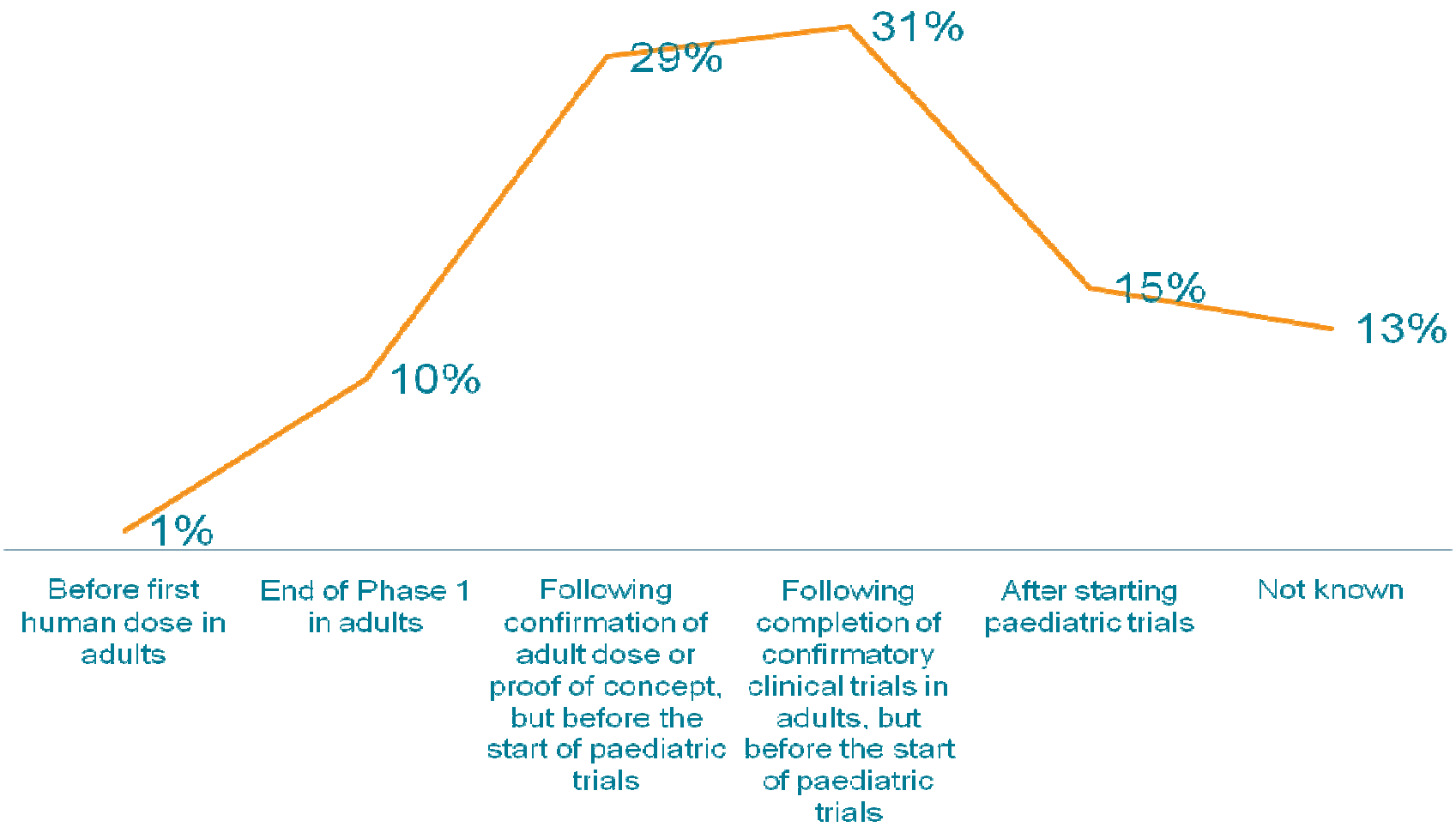
Procedural aspects

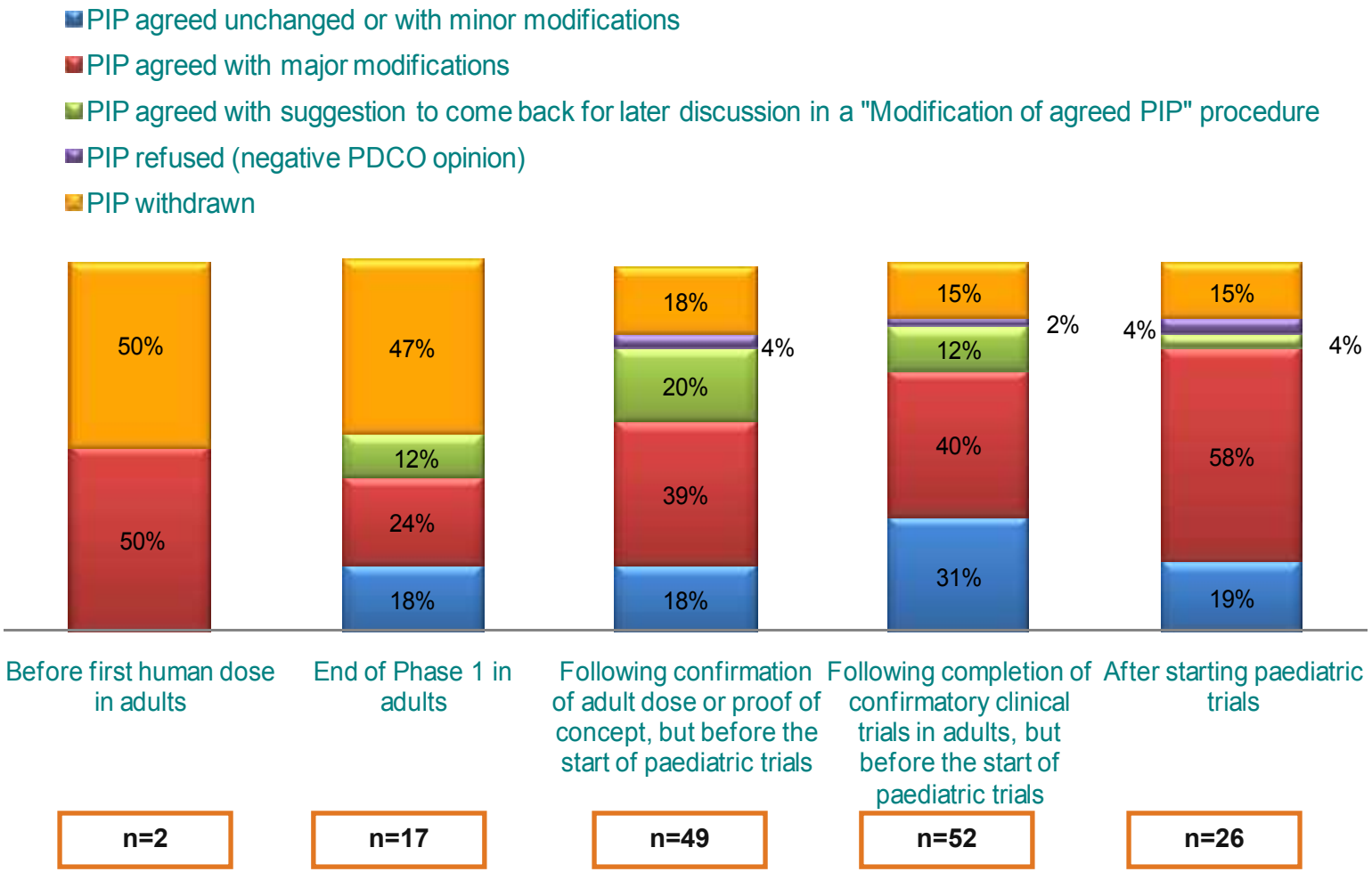
Judith Creba (Novartis Pharma)

Timing of PIP/Waiver application submission

Timing of Art.7 PIP submissions for new medicinal products (information received on N=146 out of 168 submitted PIPs)



Timing and outcome of Art.7 PIP submissions (information received on N=146 out of 168 submitted PIPs)



Key findings on the timing for PIP submission

- Submission timings for Paediatric Investigation Plans (PIPs) vary
  - Majority of PIPs currently submitted following proof of concept (PoC) or confirmation of adult dose
- Submission of PIP before PoC resulted in high rate of withdrawal
- A high proportion of PIPs agreed with major modifications regardless of the submission timing
- Companies obtaining agreement on PIP submitted after PoC, are still requested to come back for later discussion in a modification process

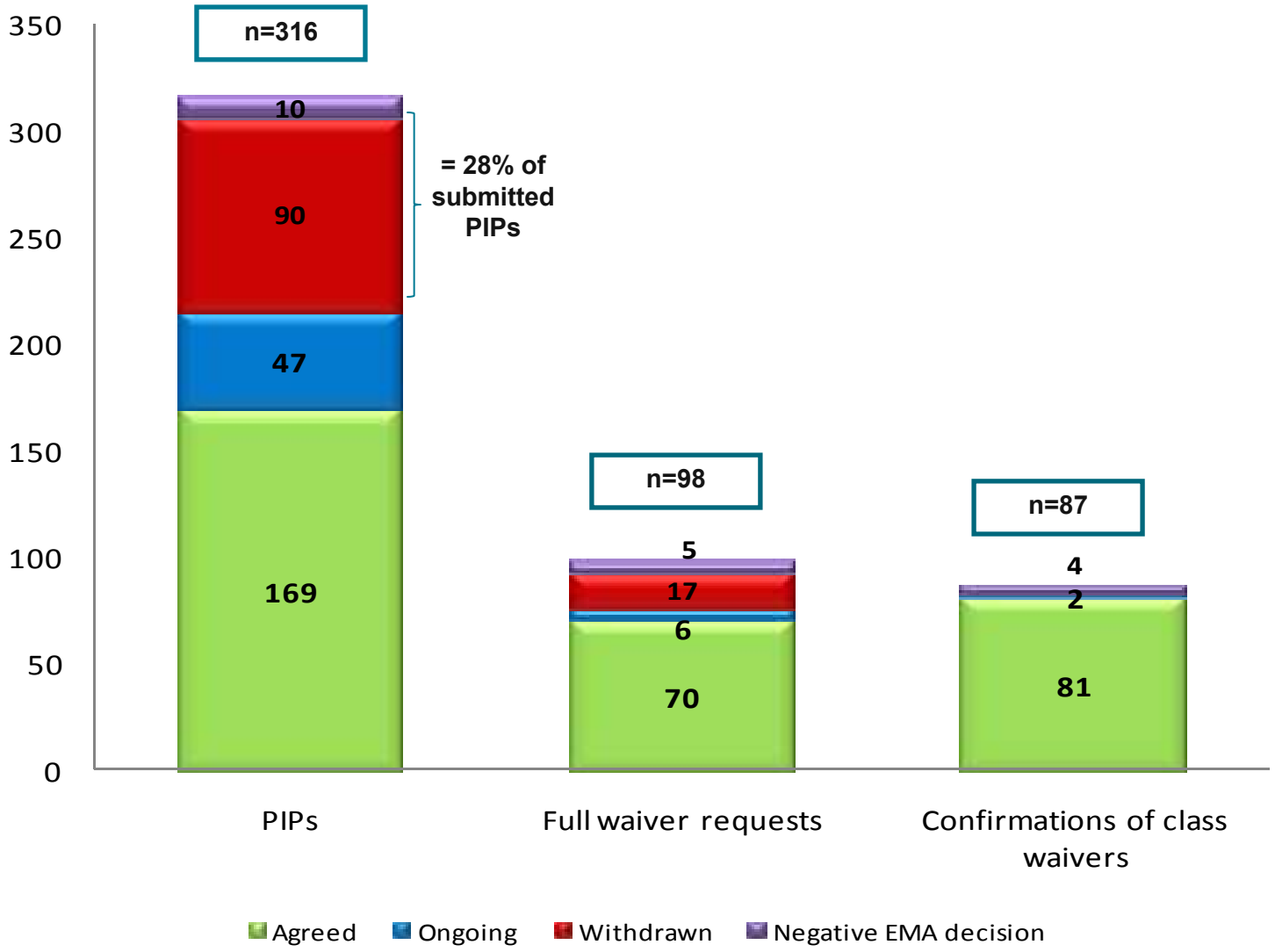
Procedural timelines

- EMA/PDCO respected the legal timelines set out in the paediatric regulation very well (99.8% of cases)
- Companies required longer than the suggested 3-months period to respond to PDCO PIP modification requests (65% of cases)

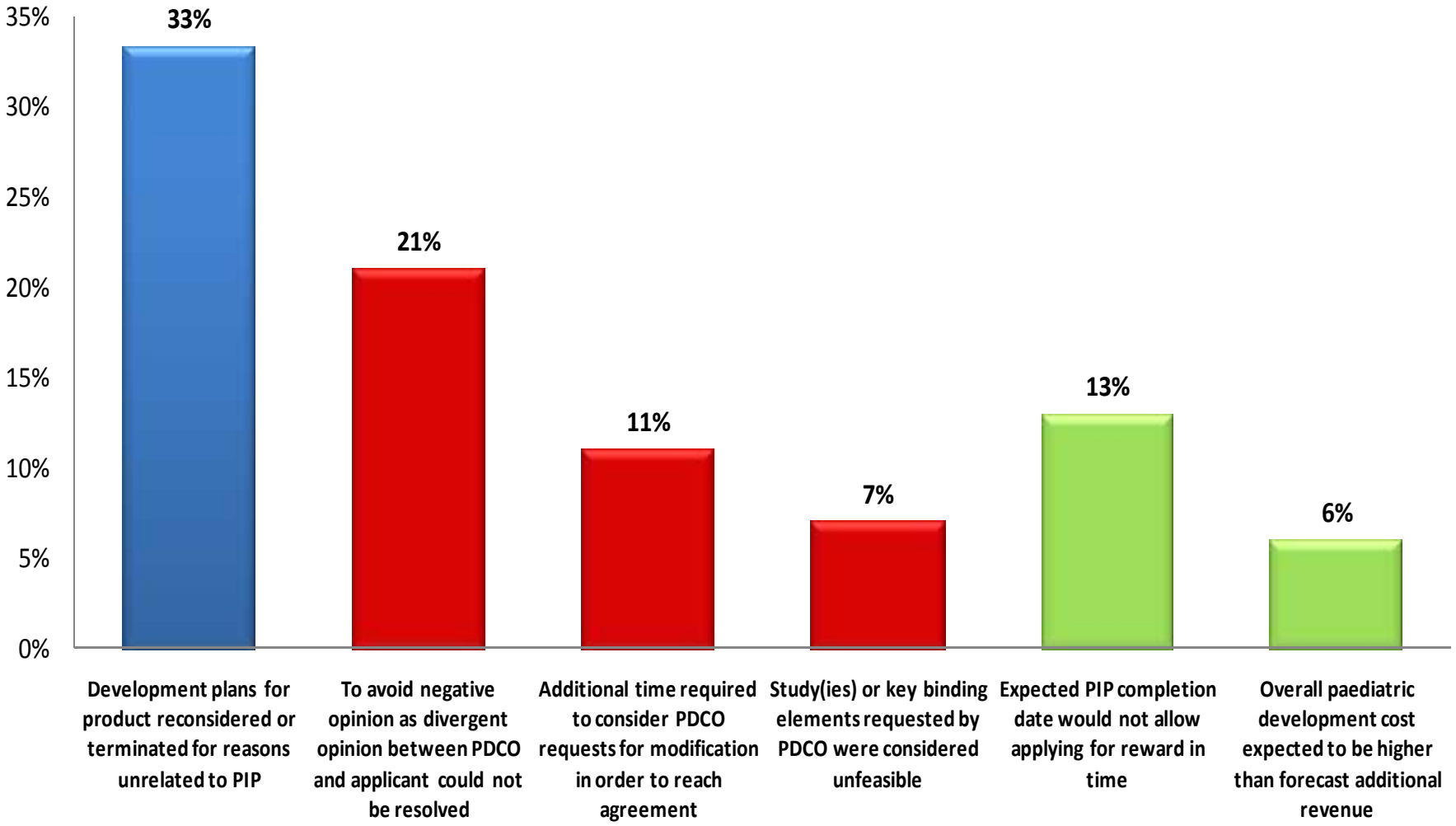
- Reasons why companies need more than 3-months to respond were not collected in the survey, but may include:
  - Evaluation of options to meet complex PDCO requests
    - Need more time to assess study feasibility
    - Waiting for further adult data and impact on development strategy
  - Need for discussion and global development alignment
    - Companies trying to align EU and US paediatric plans
    - FDA feedback may be pending

Outcome of PIP & waiver requests and analysis of withdrawals

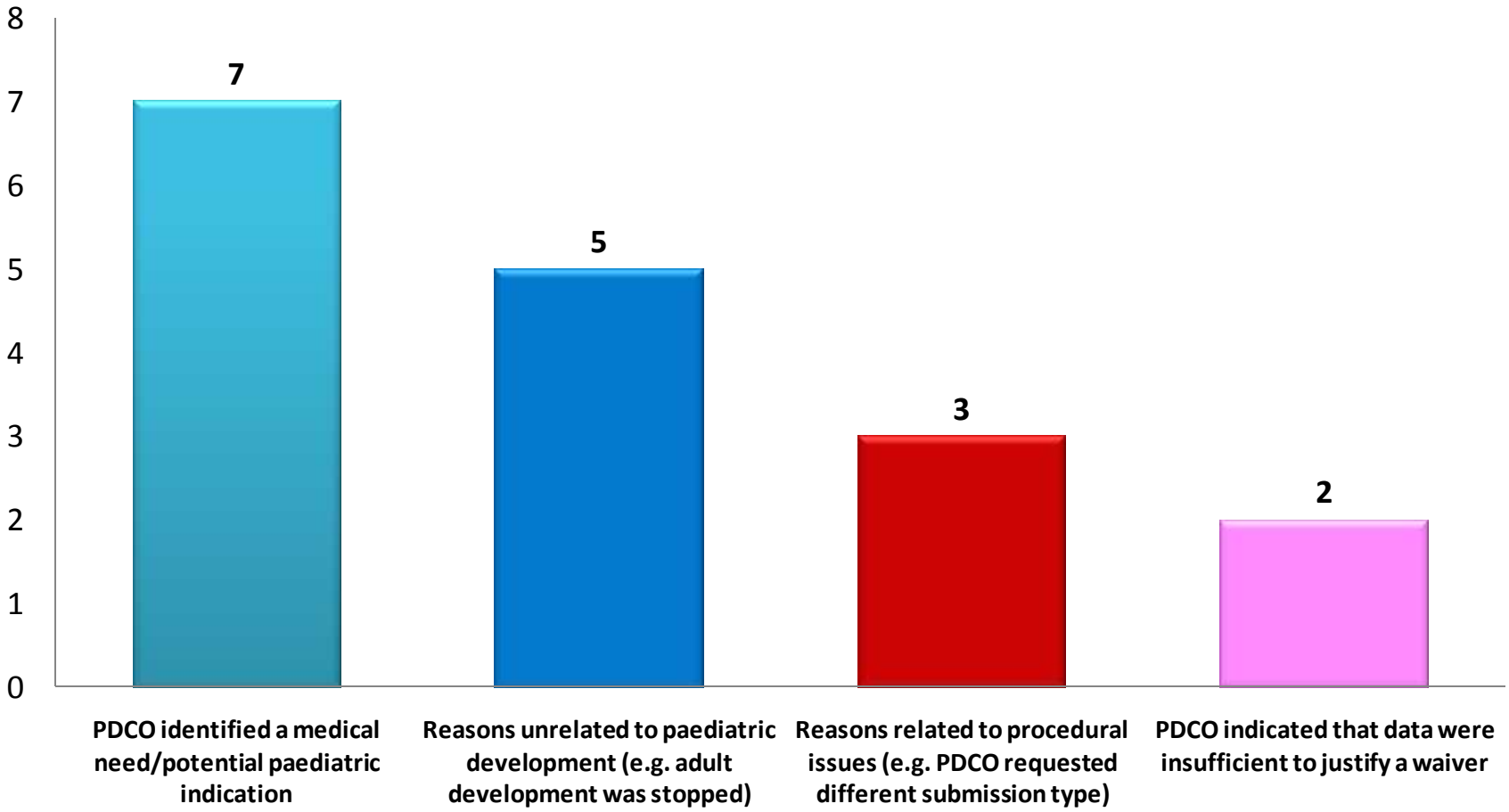
PIPs & waivers requests:
status and outcome of submitted PIP/waiver



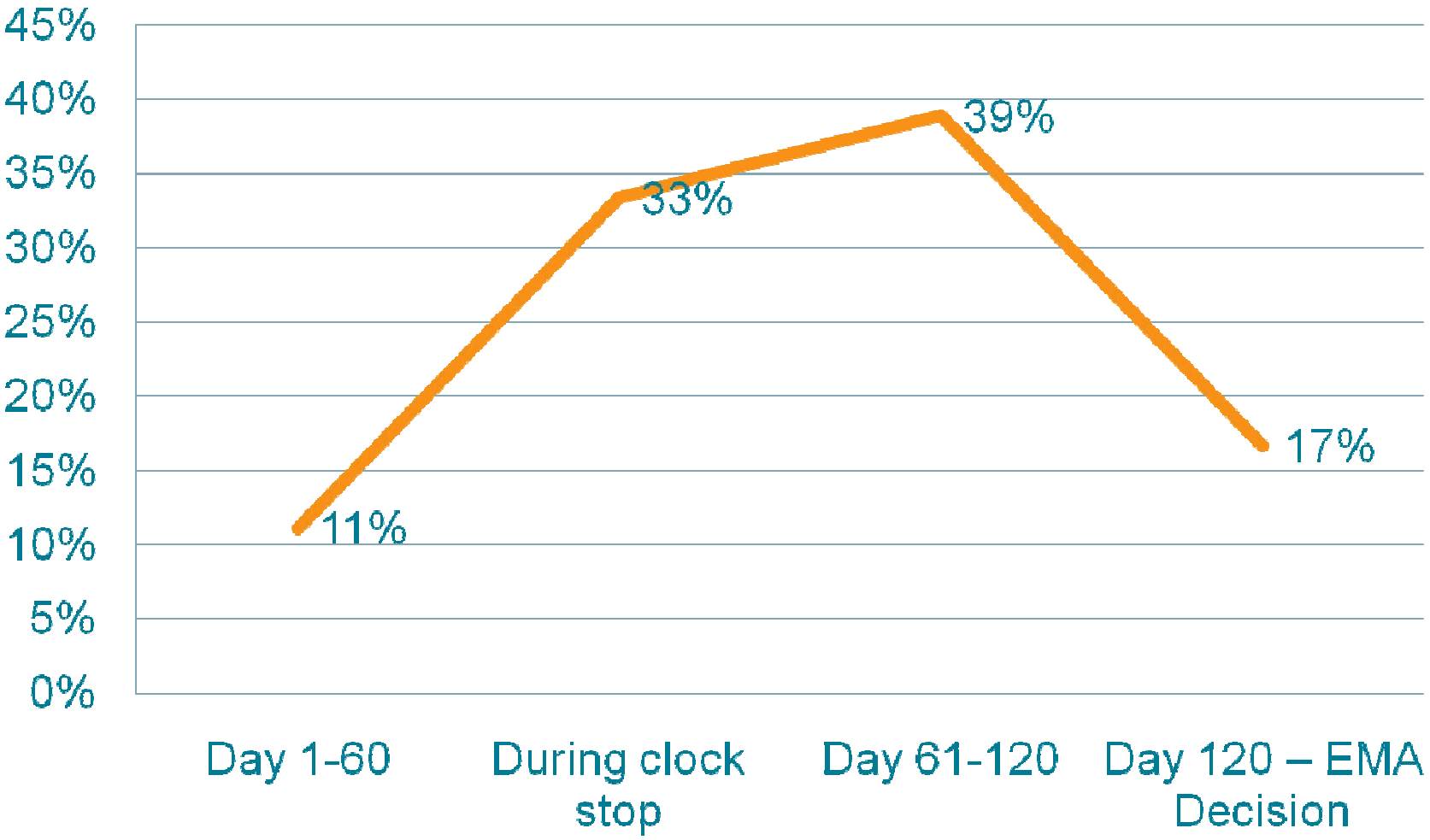
Main reasons for withdrawals of PIPs/partial waiver requests (n=90)



Main reasons for withdrawals of full waiver request (n=17 out of 98)



Timing for withdrawals of PIP/waiver applications (n=90)



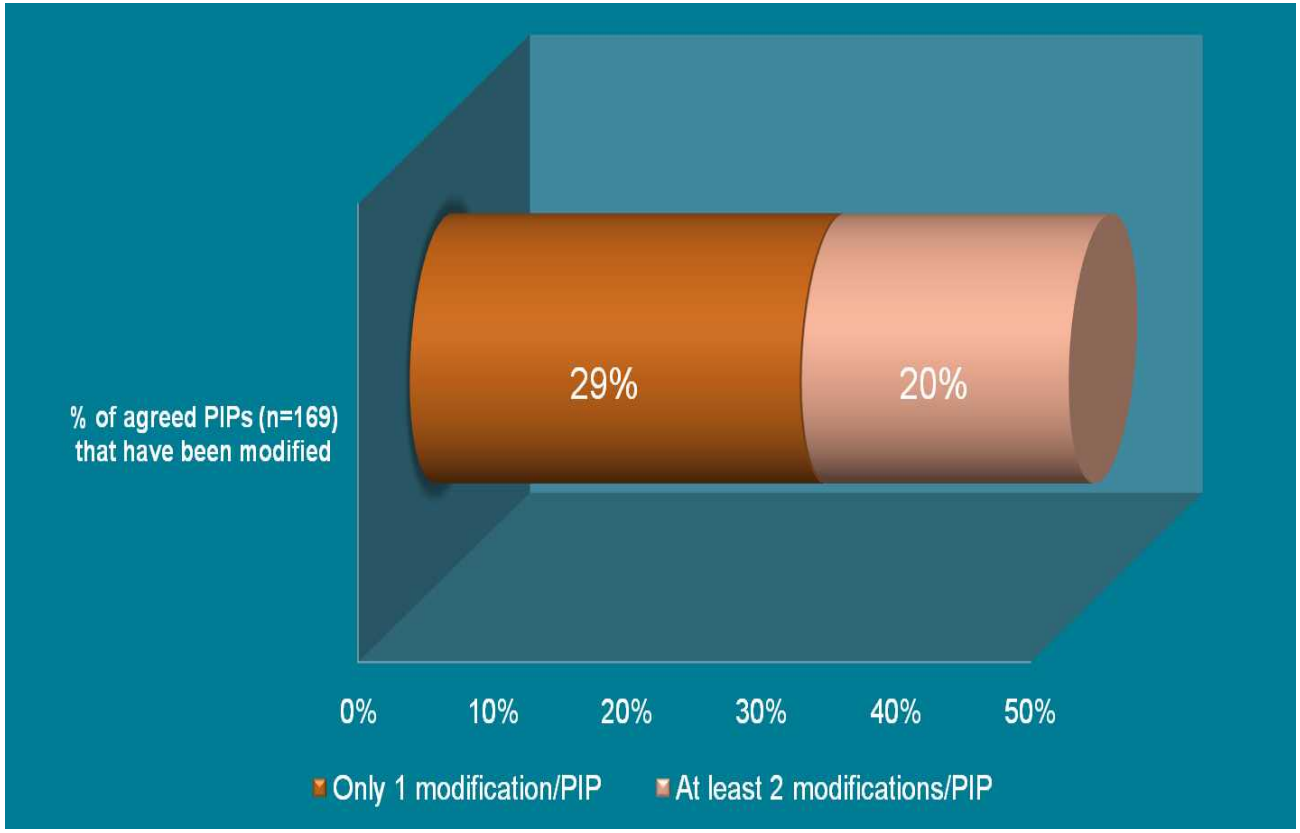
Key findings for withdrawals

- High percentage of withdrawals is of concern
- The majority of PIP withdrawals occur after Day 60 PDCO review:
  - During clock stop and following submission of response (D61) but before Day120
- Main reasons for PIP withdrawals:
  - Termination or reconsideration of project unrelated to PIP
  - Divergent position between PDCO and applicant including feasibility of requests
  - Additional time required to consider PDCO requests
  - Cost/inability to achieve reward
- Main reasons for withdrawals of Full waiver request:
  - PDCO identified medical need
  - Divergent view between PDCO and applicant
  - Termination or reconsideration of project unrelated to paediatric development

Application for changes of agreed PIPs

Applications for changes to agreed PIPs
(N=82 out of 169 agreed PIPs)

- Almost half of agreed PIPs in survey have been modified
- One fifth of agreed PIPs in survey have been modified at least twice (n=33)
- High proportion of requested changes are fully accepted by PDCO



Although companies are submitting PIP applications after Proof of Concept, over half of the agreed PIPs in survey have been modified.

Maintenance of agreed PIPs is resource-intensive

Interaction with EMA/PDCO

Industry experiences

Interaction with EMA and PDCO

Interactions with EMA usually work well: Clarification teleconference following receipt of the Request for Modification particularly valued

Type of interaction	Companies feedback (n=34) (Selection of the highest percentages)
Interaction with the Paediatric Coordinator is satisfactory	15% Strongly agree
	68% Agree
	9% Neither agree nor disagree
It is easy to obtain answers to questions from the EMA staff	12% Strongly agree
	50% Agree
	24% Neither agree nor disagree
The answers obtained by EMA staff are clear, consistent, useful and reliable	59% Agree
	24% Neither agree nor disagree
	9% Disagree
The quality of the Day 60 / Day 120 Summary Reports is sufficient, and it is useful to understand the rationale of the PDCO request for modification / opinion (n=33)	47% Agree
	15% Neither agree nor disagree
	26% Disagree
The teleconferences for the clarification of the Request for Modification are useful to understand the rationale of the PDCO request for modification	21% Strongly agree
	44% Agree
	24% Neither agree nor disagree

Interaction with EMA and PDCO

However, the interactions with PDCO during the procedures could improve

Type of interaction	Companies feedback (n=34) (Selection of the highest percentages)
The interaction with the PDCO is satisfactory	26% Agree
	29% Neither agree nor disagree
	29% Disagree
The interaction with the PDCO Rapporteur is satisfactory	35% Agree
	38% Neither agree nor disagree
	12% Disagree
The interaction with the PDCO Peer Reviewer is satisfactory	18% Agree
	50% Neither agree nor disagree
	12% Disagree
The Oral Explanations are useful to in a way that the issues could be clarified and solved within the ongoing procedure	21% Agree
	44% Neither agree nor disagree
	9% Disagree
	9% Strongly disagree

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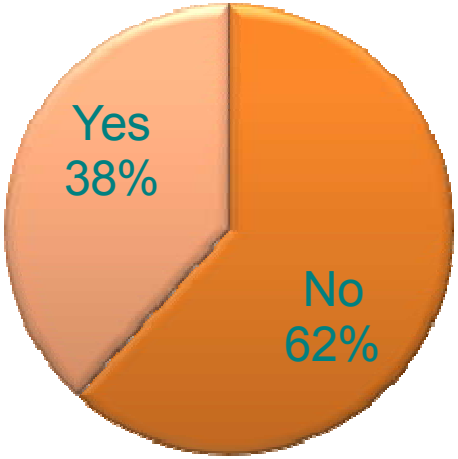
Content and Scope of PIPs

Craig Johnson (Eli Lilly)

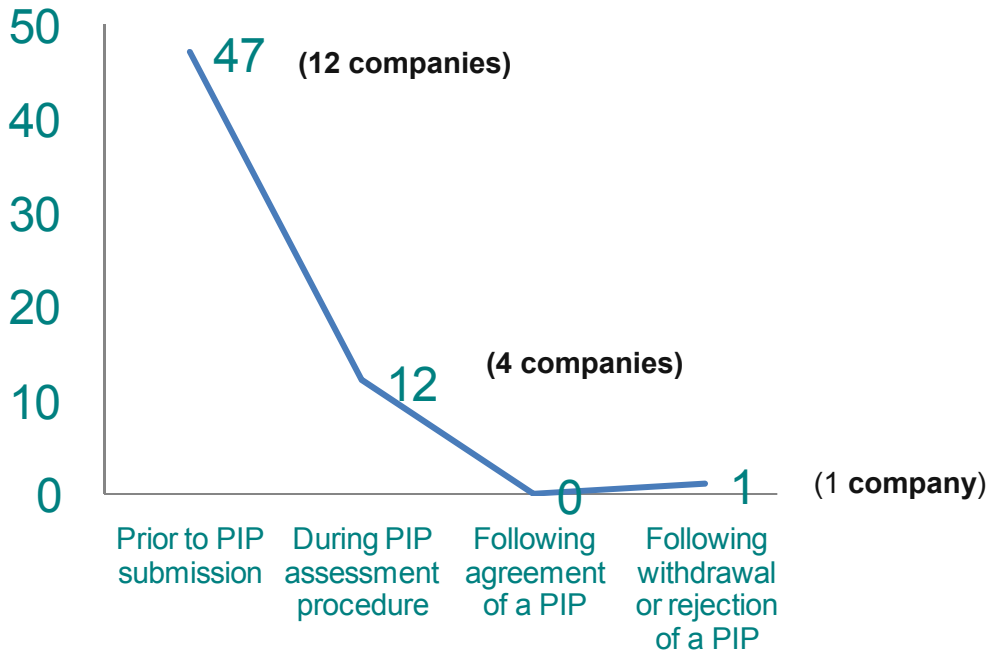
Consistency between PDCO and other EMA assessments

Paediatric scientific advice
(N=34 companies)

Has your company requested paediatric scientific advice from EMA during the period covered by this survey?



Numbers of studies for which advice was requested



Paediatric scientific advice

- 4 companies report that the EMA/PDCO followed the previous scientific advice during PIP assessment in all cases
- 7 companies report the EMA/PDCO followed the previous scientific advice during PIP assessment in some cases
- EMA has made great efforts to ensure a good collaboration with SAWP/PDCO

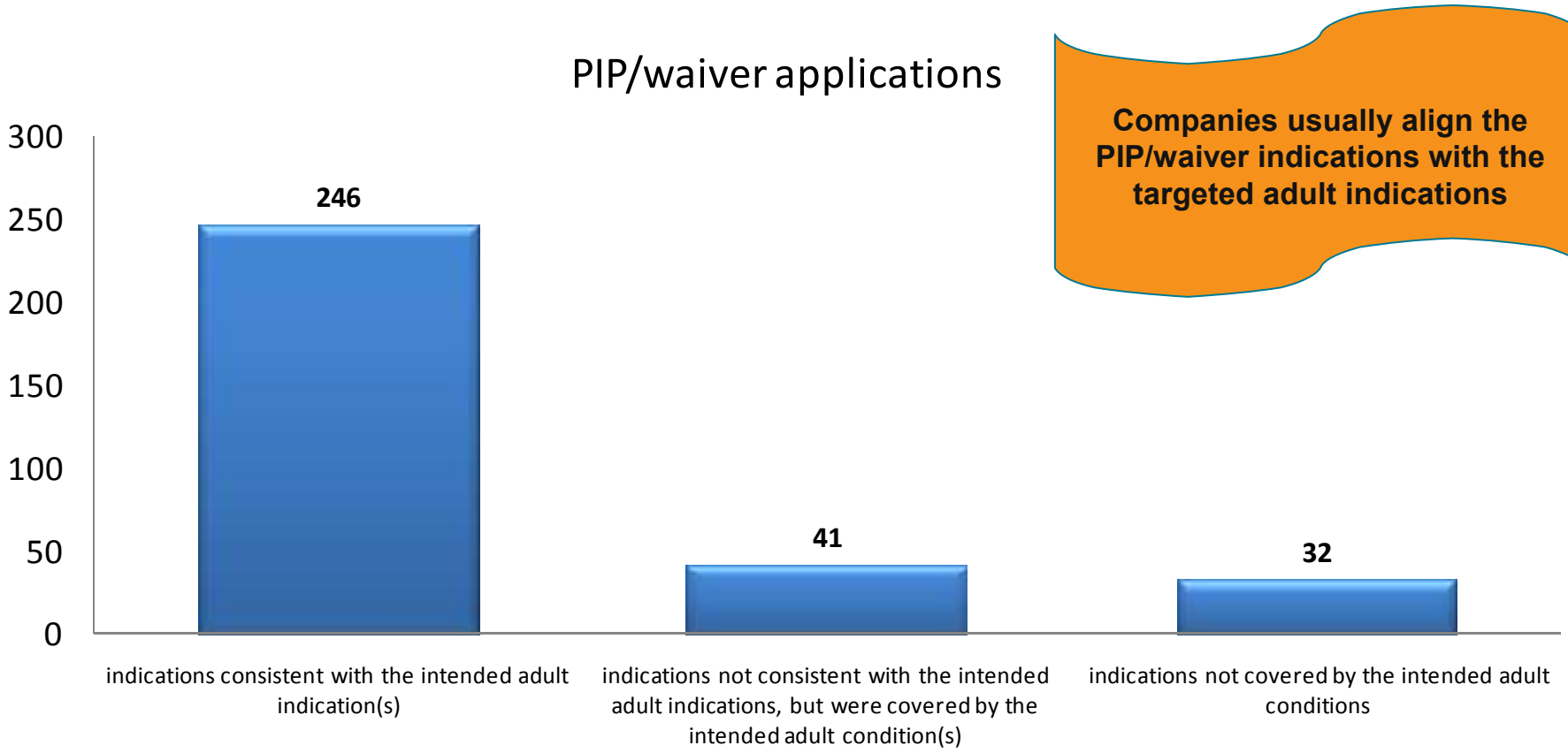
Examples of early inconsistencies between CHMP assessment and Program agreed with PDCO

- During assessment of 3 paediatric MAAs/line extensions/variations, the CHMP or national competent authorities did question/challenge aspects of the methodology or number of studies of the agreed paediatric program
- Reasons for the challenge:
  - Clinical relevance of study questioned
  - Study design features questioned (e.g. practicalities and ethics)
  - Clarification of assessment measures requested

- EMA now ensure PDCO consultation during the CHMP review

Content and scope of PIP/waiver applications

Consistency between adult and paediatric indications in submitted PIPs/waiver (n=414)



Companies usually align the PIP/waiver indications with the targeted adult indications

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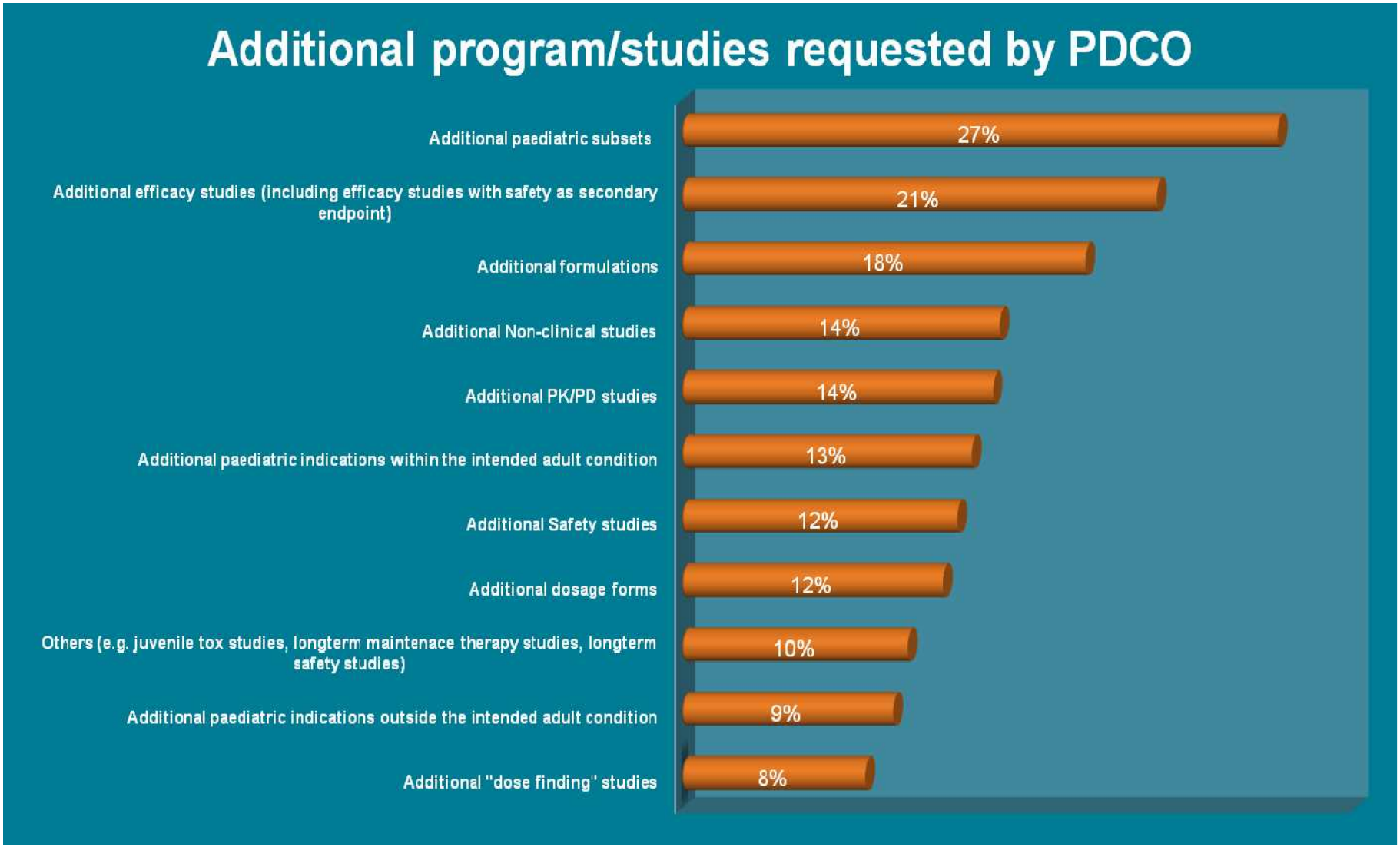
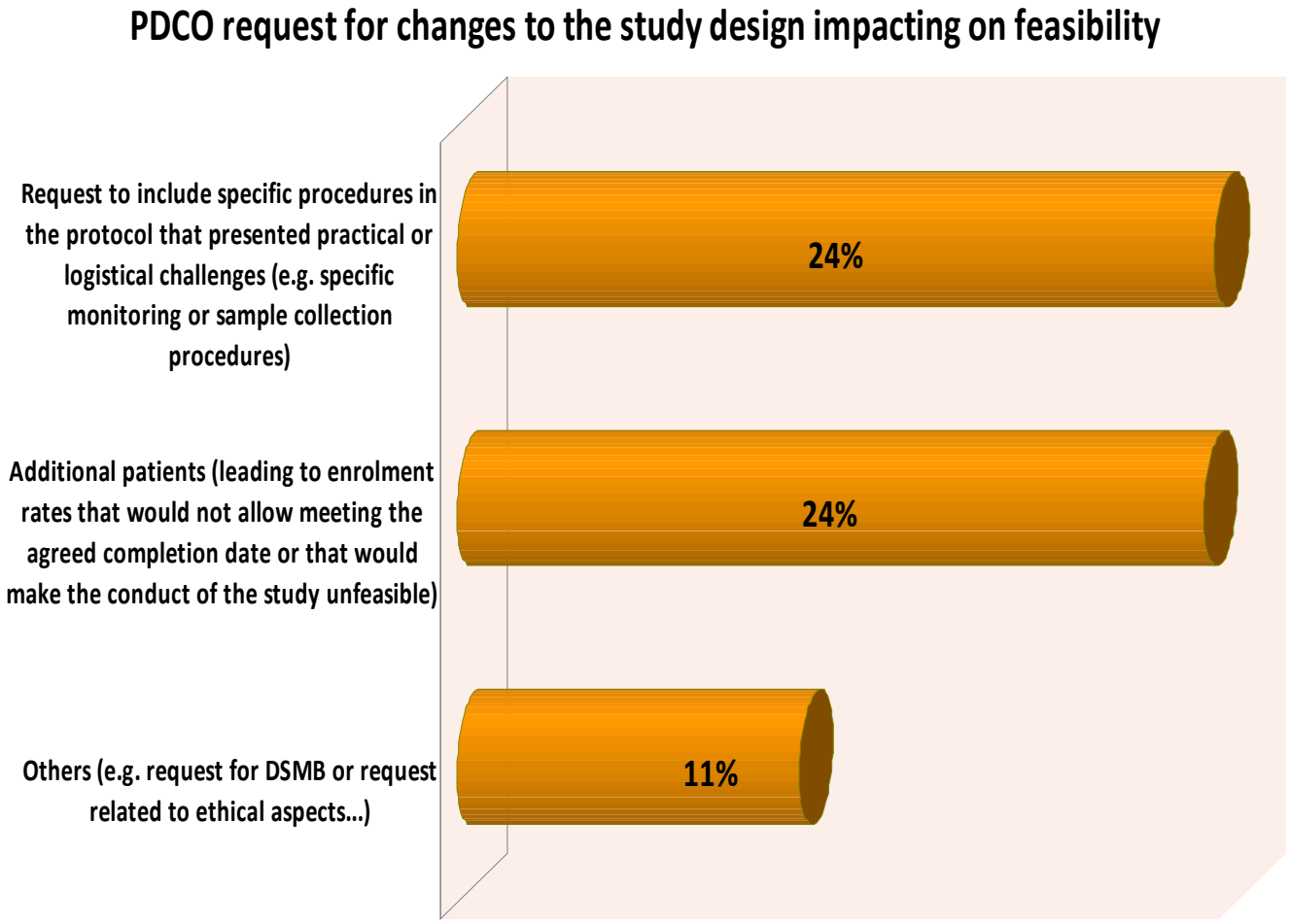
"Detailed target indication language difficult at a point when this is not clear in the development path."

PDCO requests for different development program than initially proposed by companies (n=316 PIPs submitted)



PDCO request for changes to clinical study design that impacted feasibility to conduct studies (n=316 PIPs submitted)



Experiences from individual companies: Scientific issues on study feasibility

"PDCO requested to include a minimum of 50% European patients in trials without scientific/legislative explanations. Such request severely increases complexity of the investigation."

"In some rarer populations, clinical trials in PIPs for multiple compounds will seek to enroll the same rare subjects. The chances of completing one plan properly (instead of multiple failed plans) might increase if PDCO did not demand all potential prospects to be studied at the same time. Feasibility could be further improved if leaner and less intensive studies were required. Fewer study visits and interventions might increase willingness of (rare) patients to participate. PDCO needs to balance what information is a "must have" and what is a "nice to have"."

"The miss-match of expectations between PDCO regarding age groups and indications and applicable regulations in single EU member states leads to major delays to start a trial & partly infeasibilities to conduct the mandated programs."

Key findings on content and scope of PIPs

- Additional PDCO requests are routinely received on company PIP proposals
  - Requests include additional programmes and studies
- High proportion of PDCO requests impact on
  - study feasibility and
  - incur unplanned costs in development

Average paediatric R&D cost reported by one company

- ~ € 200 000 juvenile animal studies
- ~ € 300 000 BE/NA studies related to specific paediatric formulations
- up to € 2 Mio for Phase I
- up to € 40+ Mio for Phase III
  - depending on the original indication the cost of additional Phase I and Phase III studies can be even higher

CTAs for clinical trial protocols included in PIPs

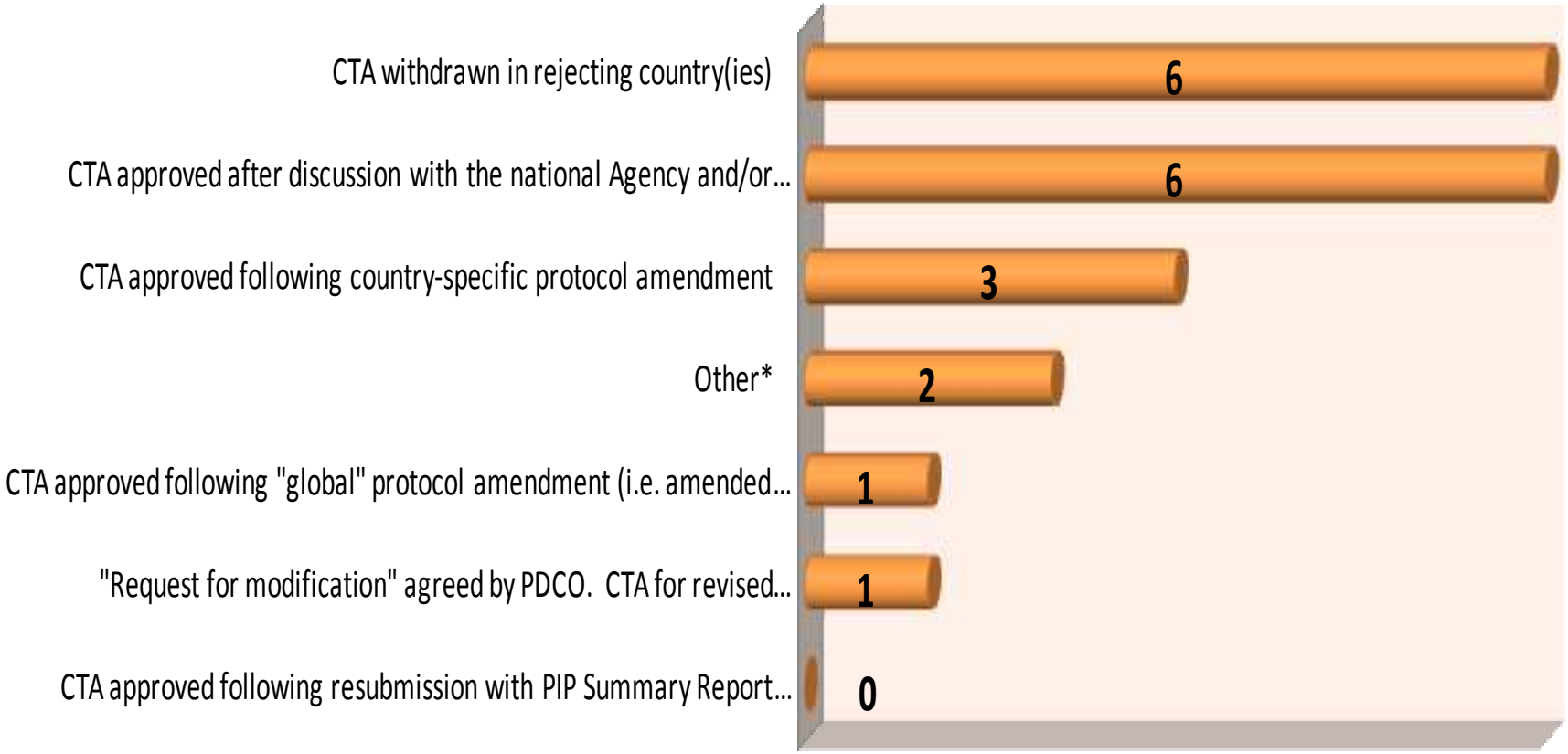
CTAs for protocols in agreed PIPs

- **7 (21%)** of responding companies reported that **14 protocols** which were consistent with an agreed PIP had been rejected or refused by competent authorities or ethics committees during the CTA review process
- Provision of agreed PIP (including the Summary Report) in the CTA made little difference
  - PIP + Summary report provided in 11 of 14 cases
- Countries refusing PIP protocols
  - Mentioned by >1 company: Canada, France, Germany, India, UK
  - Other countries: Argentina, Belgium, Denmark, Italy, Russia, Serbia, Tunisia

Refusal of CTAs for protocols in agreed PIPs

Reasons for refusal of CTAs included:
Push-back on feasibility of conduct
Safety concerns for the use of the compound in children
Refusal to include the paediatric population or part of it
Study design and/or inclusion/exclusion criteria
Ethical concern regarding placebo arm
Ethical concern regarding investigation in low age group
Lowering cut-off age to 6-months via a CTA amendment was not accepted
Continuous glucose monitoring system not approved in the paediatric population (Italy, Argentina)
Actual regulation does not allow clinical trials in paediatric population (Tunisia)

Actions & outcomes after refusal of “PIP” CTAs



*Other: Investigators would not take part in the study (placebo control deemed unethical) so no CTA made; Limitation to certain paediatric subsets)

Key findings on CTAs

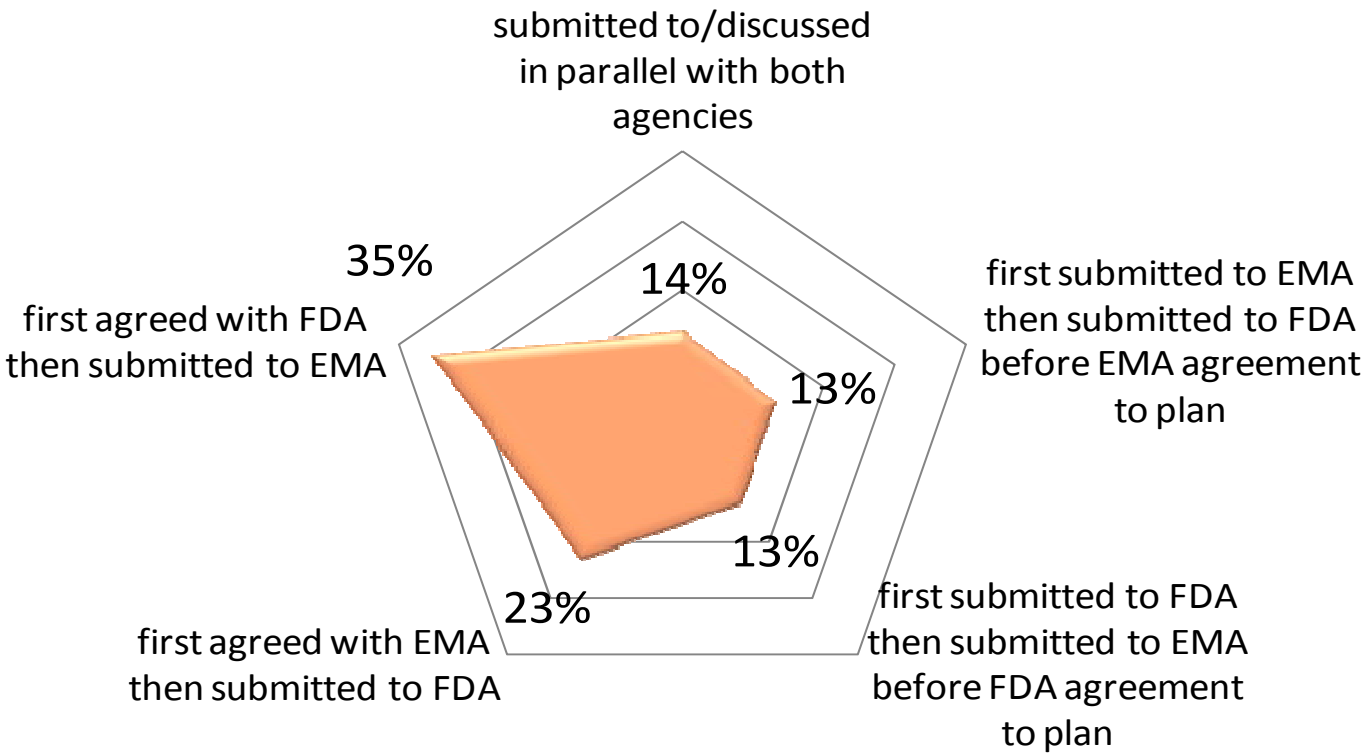
- Providing the agreed PIP and Summary report did not help avoid CTA rejection or refusal
- Need for close collaboration between PDCO member and the Clinical Trial assessors at the national competent authority level
- EMA/PDCO need to raise awareness on paediatric development questions
- Countries outside EU refuse PIP protocols, highlighting the complexity in the management of global paediatric trials

Interaction with EMA and FDA

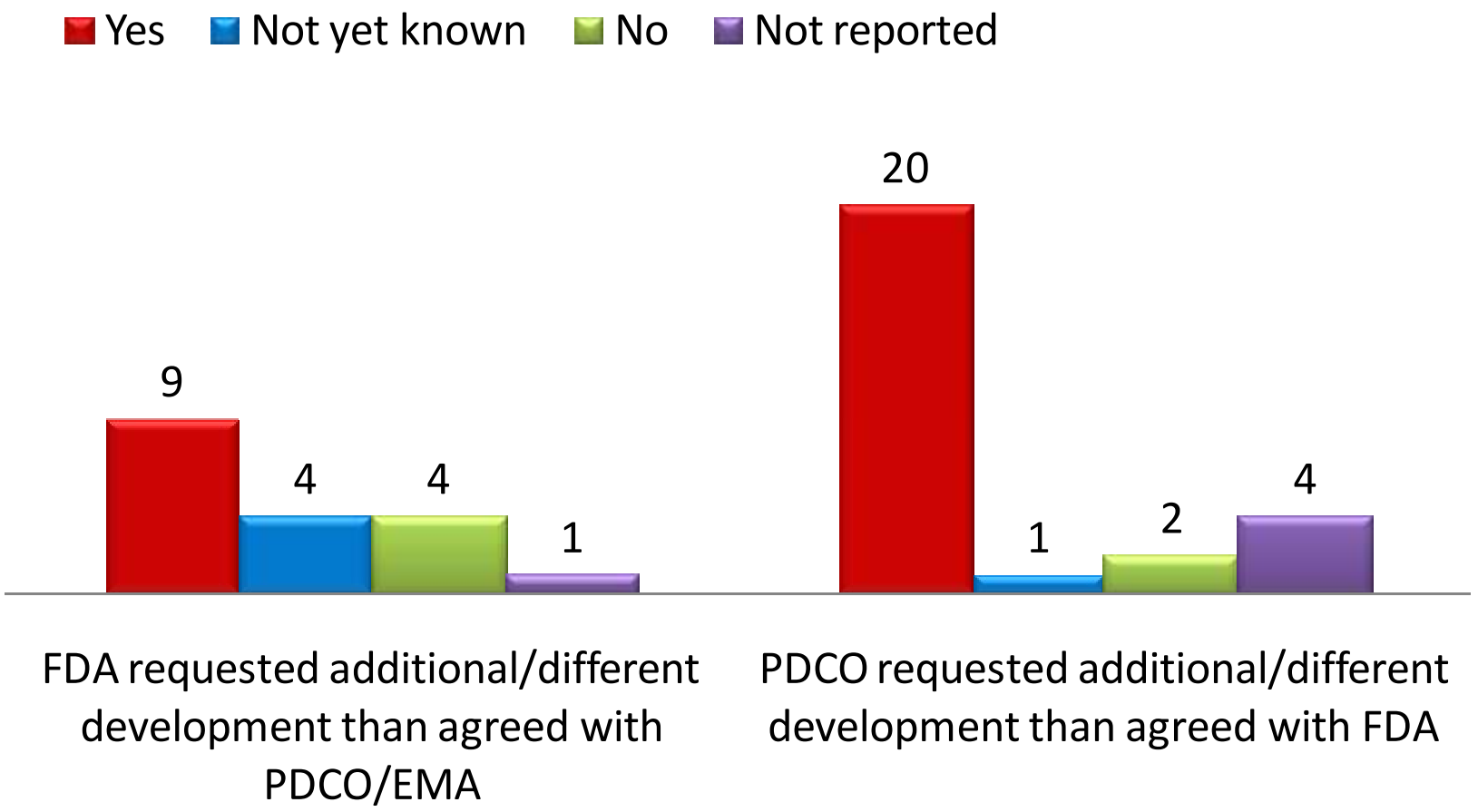
Global paediatric development program

Identical paediatric development program proposals submitted to EMA and FDA

Of the 77 identical paediatric development plan proposals, how many were:



FDA/EMA requests for changes to identical paediatric development program proposals (N=27 from EMA, N=18 from FDA)



Key findings on interaction with EMA and FDA

- Companies carry-out global development and strive for alignment of paediatric development programmes between US and EU
- Companies may opt to submit Paediatric plans in parallel to EMA and FDA to facilitate Inter-Agency discussion
- Higher rate of requests from PDCO for changes to FDA-agreed paediatric plans
  - Possible reflects early experiences with the EU Regulation, but need for continued monitoring

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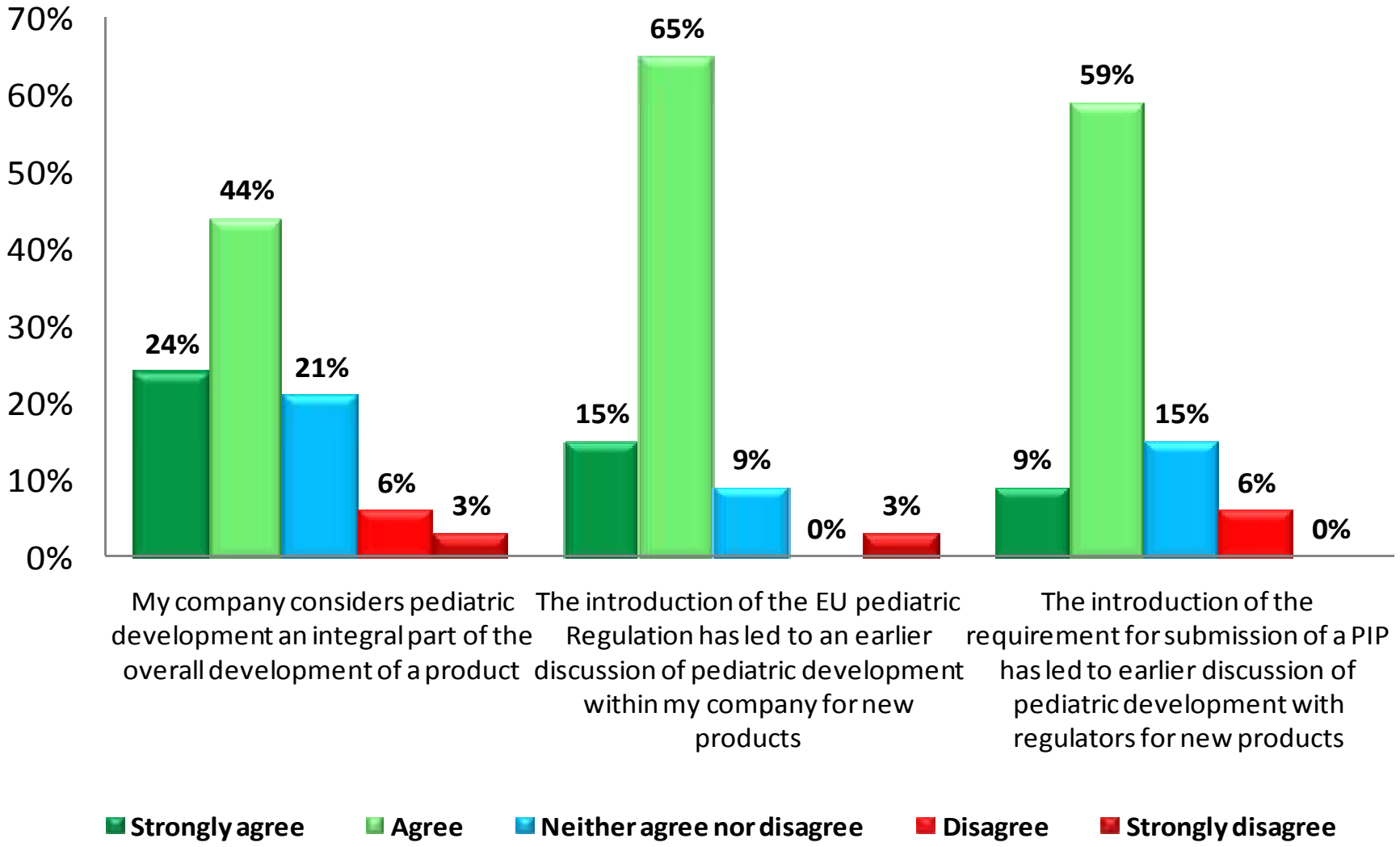
Impact on Drug Development and Marketing Authorisation

Angelika Joos (Merck Sharp & Dome)

Impact of paediatric regulation on drug development and MAs

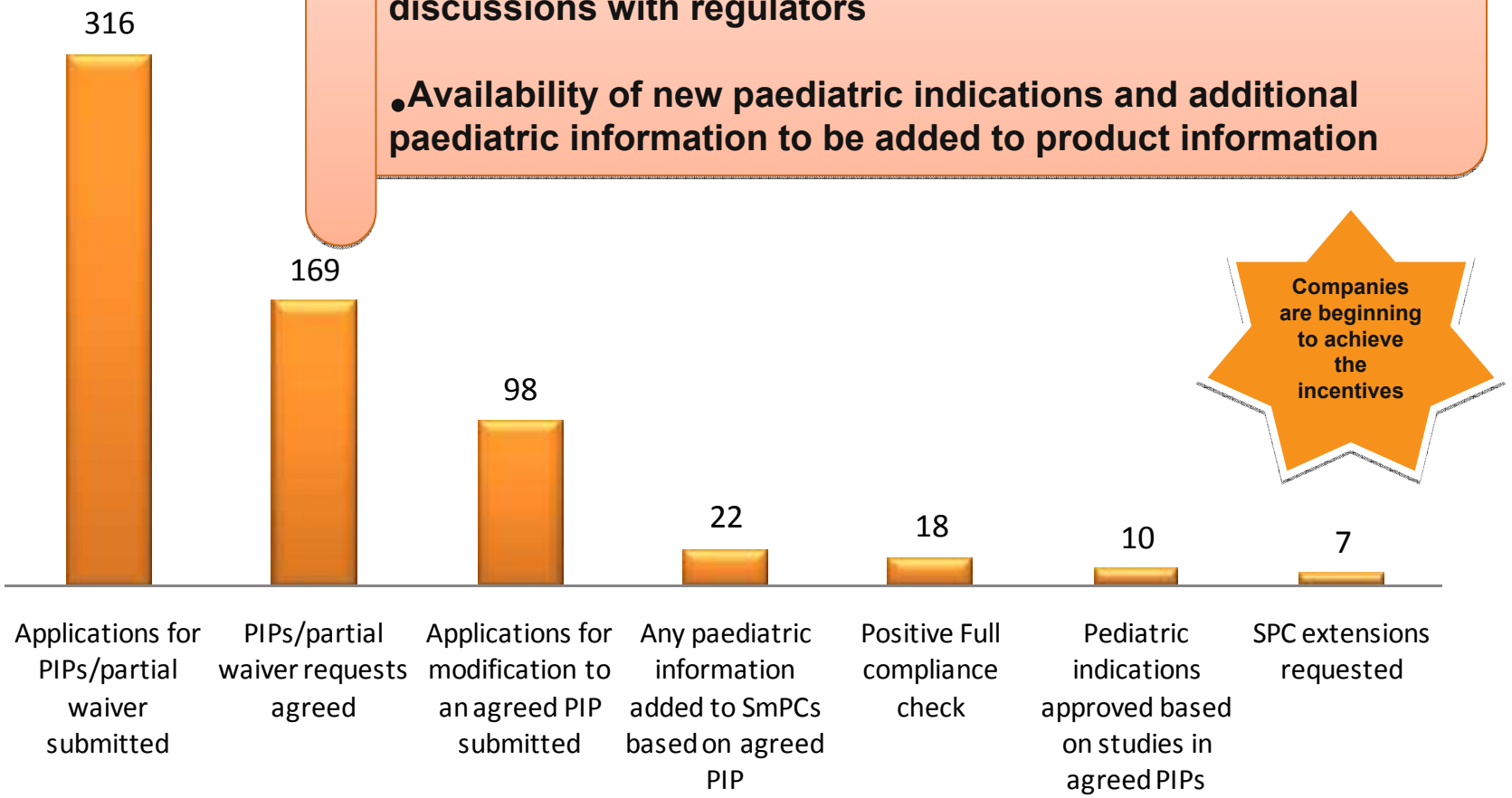
Impact of paediatric regulation on drug development (n=34)



Overall impact of the Paediatric Regulation to June 2010

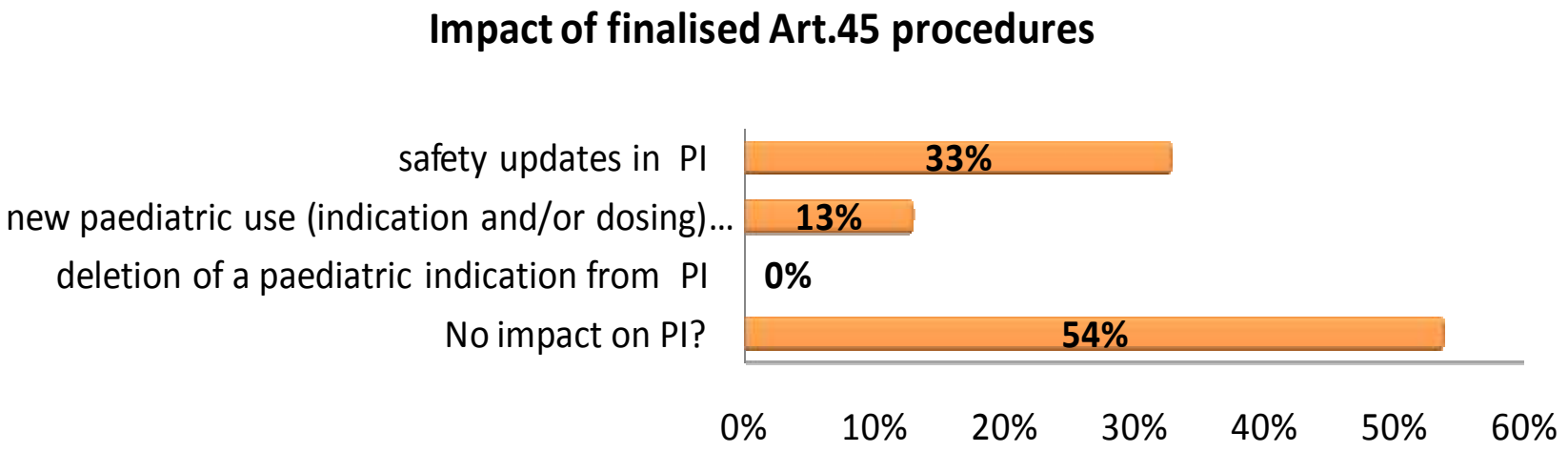
Paediatric Regulation has increased industry focus on paediatric development and results are starting to be seen:

- **Increased dialogue and integration of paediatric development into product development together with earlier discussions with regulators**
- **Availability of new paediatric indications and additional paediatric information to be added to product information**



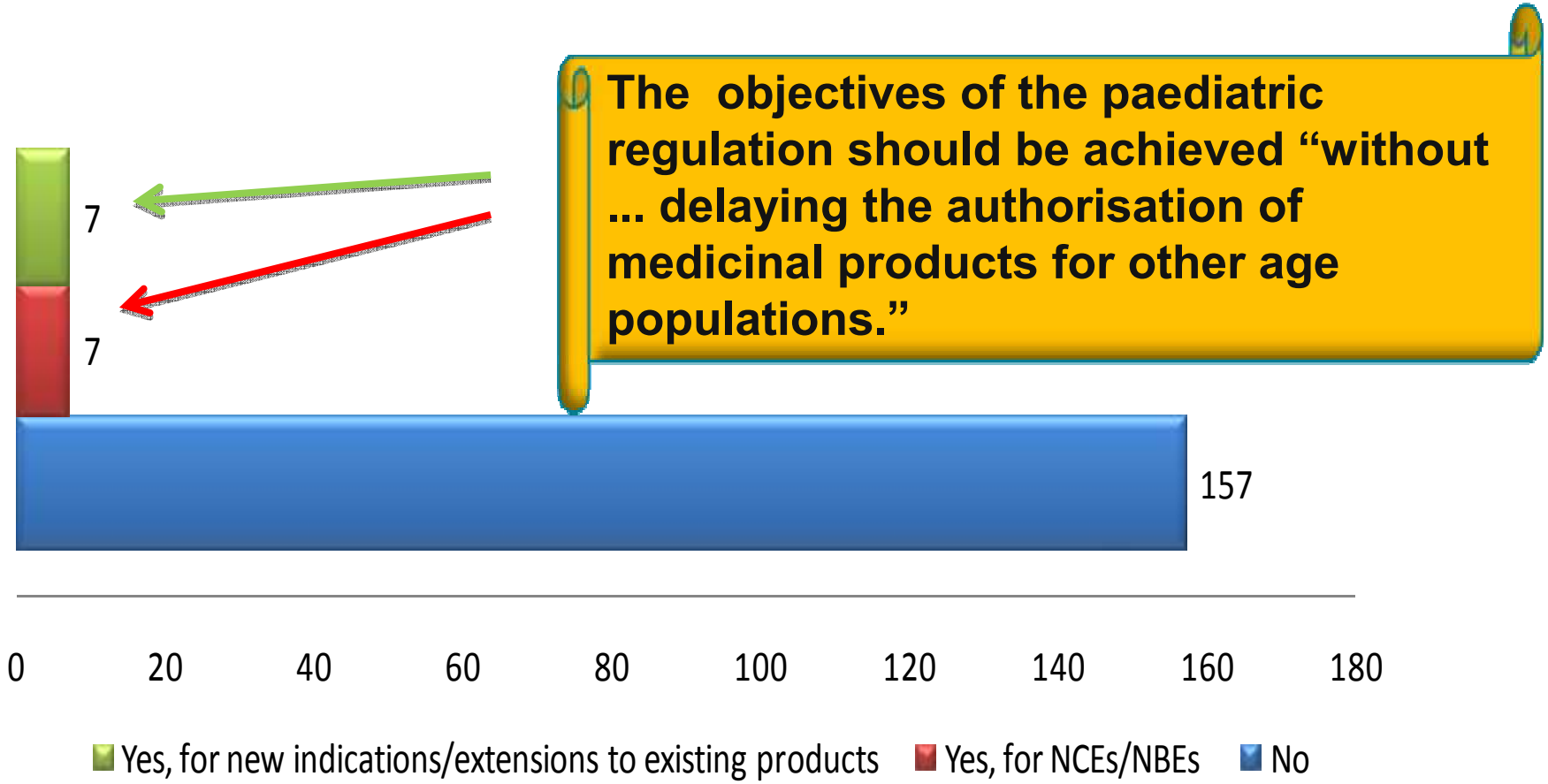
Overall impact of the Paediatric Regulation to June 2010

- **111** Art.45 procedures initiated – **54** finalised
- Of finalised procedures, 25 (46%) have resulted in revised product information



Impact on development in adults

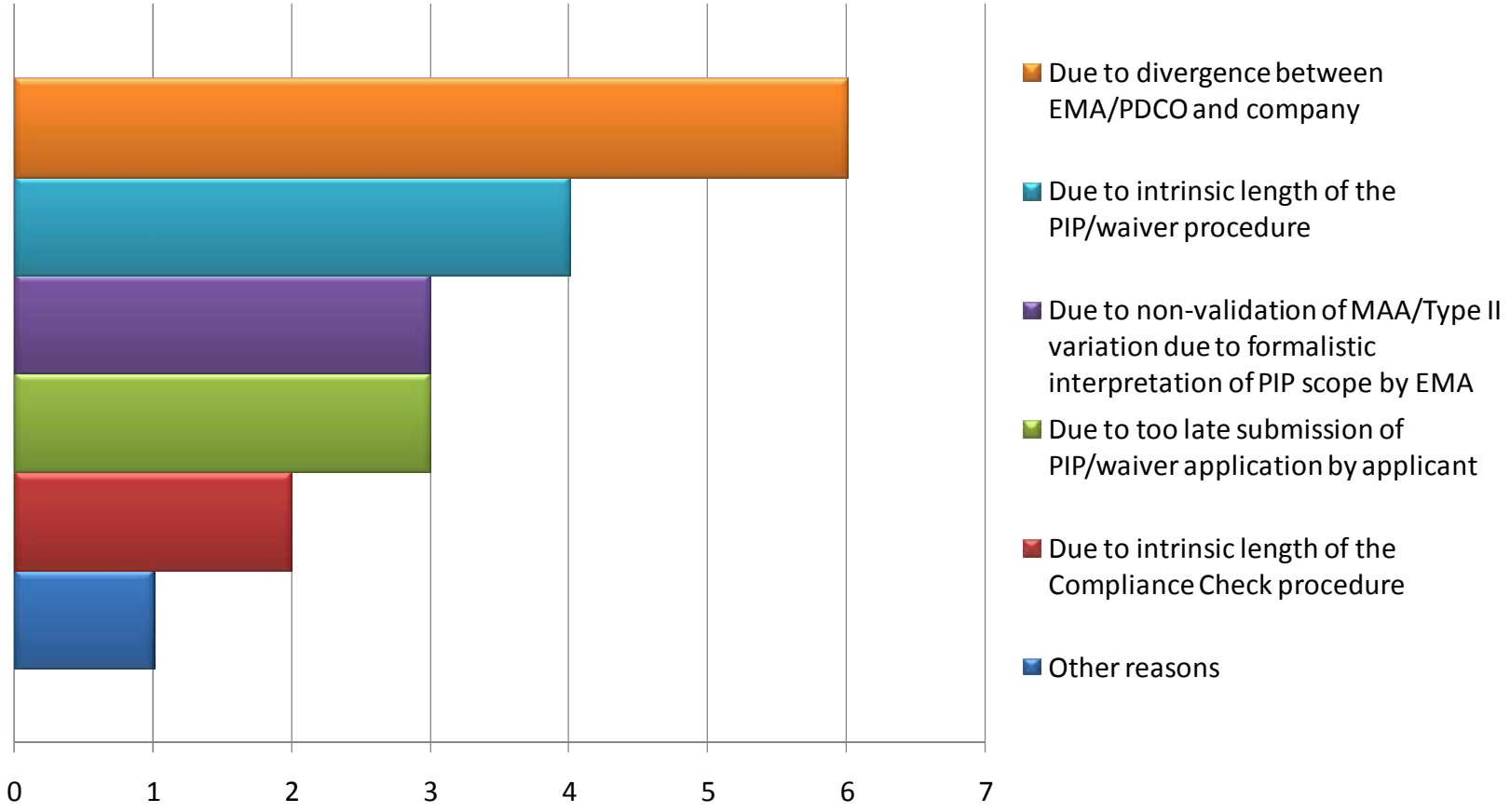
Has the development in adults of any of your company's products been delayed or abandoned in expectation of or as a consequence of additional costs and requirements associated with paediatric development?



The objectives of the paediatric regulation should be achieved "without ... delaying the authorisation of medicinal products for other age populations."

Postponement of submission of a Marketing Authorization application, or a variation, for a new adult indication due to requirements of the paediatric Regulation (N=159)

139 (=87%) of 159 MAAs or variations for a new adult indication were not postponed due to requirements of the paediatric regulation.
However, **19 MAAs or variations were postponed**:



Key findings on the impact on development and Marketing Authorisations (MAs)

- Paediatric Regulation has increased awareness and early discussion of paediatric need and development
- Paediatric development has become more embedded into companies development plans
- Paediatric Regulation has impacted R&D productivity
  - Development programmes (including adult programmes) have been negatively impacted
    - New marketing authorisation/line extensions delayed or postponed due to
      - Divergence between applicant and EMA/PDCO
      - Length and timing of PIP procedure including compliance check
      - Non validation of MAA/Type II variation

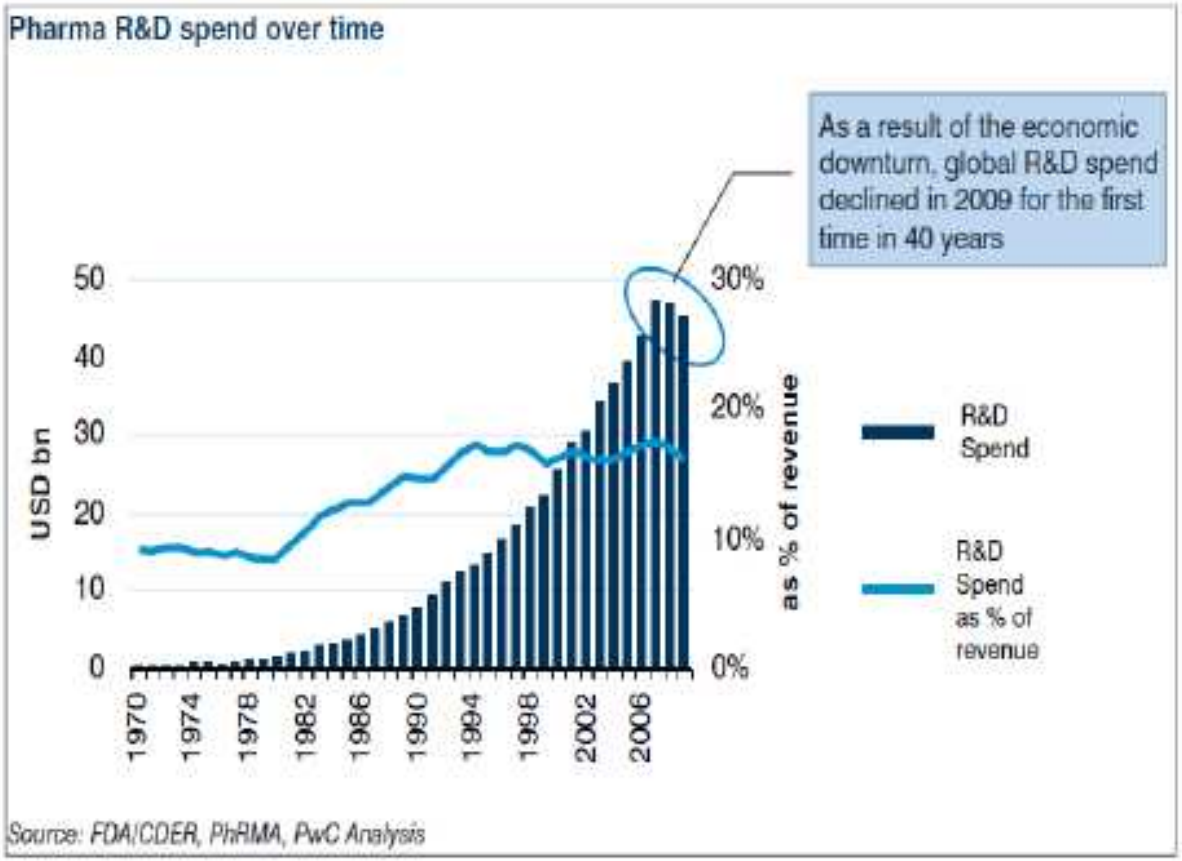
Impact of the Paediatric Regulation on company resources

Reality check

- Perception:
  - Companies can carry the majority of the R&D bill as they have larger resources compared to Academia

- Reality:
  - Companies R&D budget is a fixed number
  - The additional cost for one program will necessarily draw resources from another program, even from adult development
  - **It is necessary to focus on the "real" need**

Progression of R&D spend



Regulation impact on resources

- Complexities of paediatric clinical development may increase per patient cost due to:
  - the additional safety issues
  - extensive interactions with IRB
  - the provision of not only consent forms but assent and even parental permission
  - requirements to establish surrogate endpoints that don't exist for adults
  - formulation issues
  - operational issues where there is a very low patient to site ratio for recruitment

Source:

Some examples of paediatric R&D cost reported

- € 50 to €100+ Mio for an entire paediatric program including toxicology, CMC, end point validation, pharmacology, PK/PD studies, safety and efficacy studies, long term safety studies, epidemiology, operations management, regulatory and legal aspects costs
- Some specific examples for studies requested by PDCO:
  - Juvenile animal studies reported by most companies
  - € 80 Mio (FDA program) vs. € 111 Mio (PDCO program)
    - longer duration of trial, additional active comparator trial
  - € 1 Mio for additional study required by PDCO, not required by CHMP

Average paediatric R&D cost reported by one company

- ~ € 200 000 juvenile animal studies
- ~ € 300 000 BE/NA studies related to specific paediatric formulations
- up to € 2 Mio for Phase I
- up to € 40+ Mio for Phase III
  - depending on the original indication the cost of additional Phase I and Phase III studies can be even higher

Additional resource cost of new Regulatory PIP process to 34 EFPIA companies

Overall:

- **Regulatory: € 3.28 - € 131.2 Mio (Median: € 32.8 Mio)**
- **Other functions: € 16.4 - € 360.7 Mio (Median: € 98.4 Mio)**

- Calculation Basis:
  - 414 procedures = 316 PIPs and 98 waivers
  - Estimated required Full Time Equivalents (FTE) per PIP procedure
    - 0.1 - 4 FTE for Regulatory (Median 1 FTE)
    - 0.5 - 11 FTE for other functions (Median 3 FTE)
  - 1 FTE = 220 working days x 8 hours x 45 €* = 79200 €

* http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pd, page 22f

Resources invested in process without obvious Paediatric benefit

Overall: € 5.84 - € 136 Mio (Median: € 39 Mio)

- Calculation Basis:
  - 90 PIPs and 17 waivers withdrawn
  - 16 of 171 development programs with PIPs completely stopped in later phases of development due to unrelated quality/safety/efficacy issues of the compound
  - 0.6 - 14 FTE per procedure (Median 4 FTE)
  - 1FTE = 220 working days x 8 hours x 45 € = 79200 €

In perspective of:

- €30 Mio was set aside as the EC contribution for research activity in the field of off-patented medicines in the FP 7 first call
  - The limit of the EC contribution to a Paediatric research project has been set at €6 Mio per project*.

*ftp://ftp.cordis.europa.eu/pub/fp7/health/docs/paediatric-research-initiatives-2009_en.pdf
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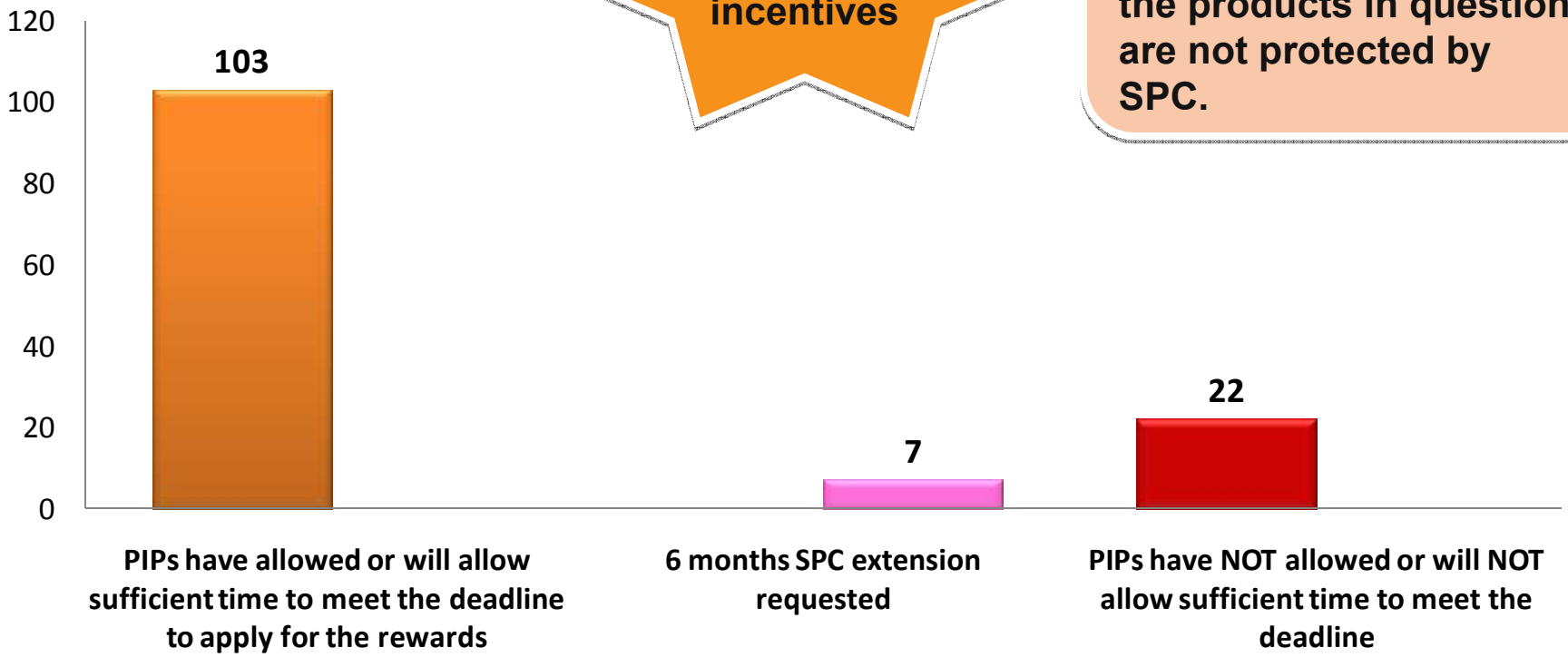
Key Findings

- Paediatric Regulation has had a significant impact on R&D and regulatory resources
  - Additional PDCO requests routinely received on company PIP proposals
  - Withdrawal of PIPs/abandoned development programmes results in wasted resource
  - Actual management of regulatory procedure is resource intensive
    - Initial submission plus downstream modifications
- This impact needs to be considered in context:
  - Paediatric development and clinical trials are more expensive per subject than adult development
  - R&D budgets are defined - increased costs for one project due to uncertainty and cost of paediatric program will impact delivery of this and/or other projects
  - Global project viability may be at greater risk due to significant increase in development costs in some situations

Paediatric Rewards and Regulatory procedures

Number of agreed PIPs which will allow sufficient time to meet the deadline to apply for the reward (n=169)

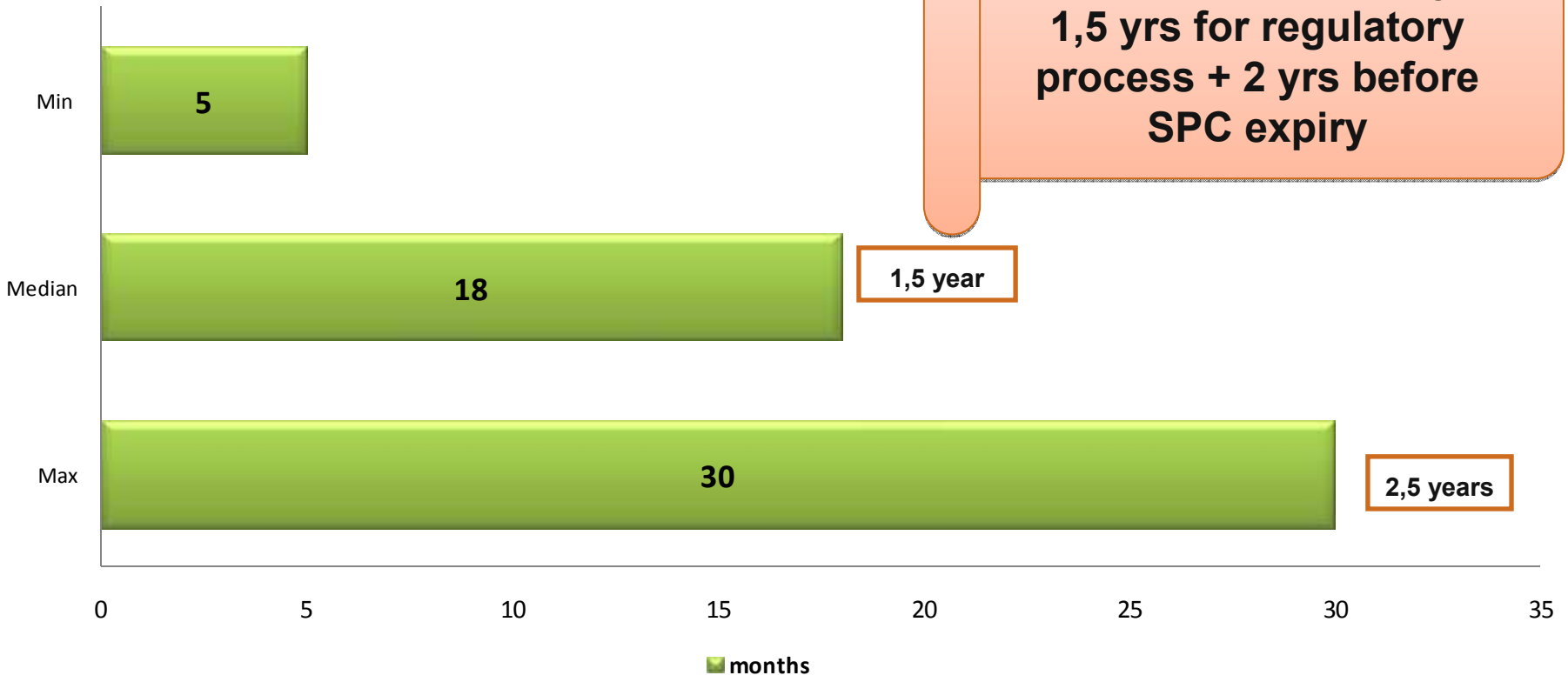


Companies are beginning to achieve the incentives

A not insignificant number of PIPs will not lead to rewards, either due to timing constraints, or because the products in question are not protected by SPC.

Timing for Regulatory procedures: Interval between the last patient last visit (LPLV) of the last paediatric study and the first request for SPC extension (n=5 products reported)

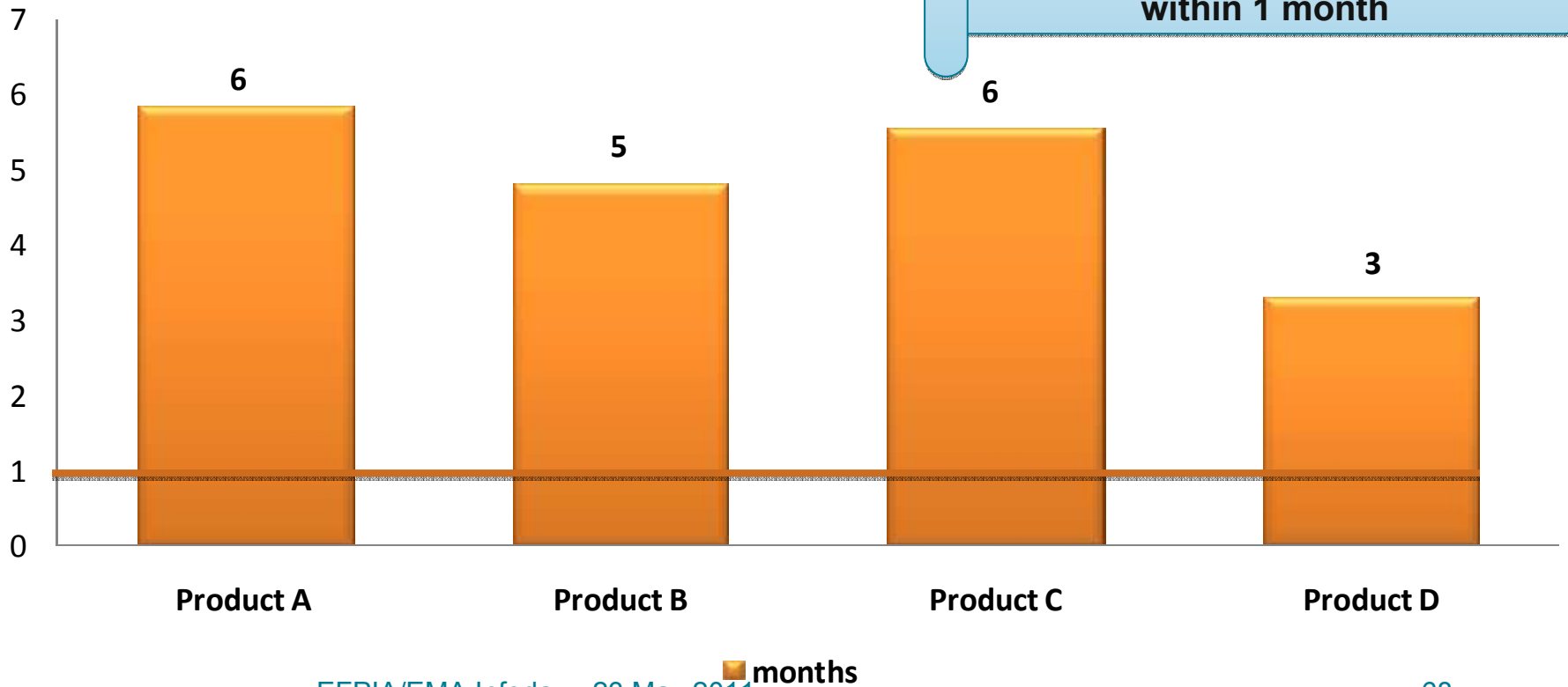
Companies need to complete the PIP 3,5 yrs before the SPC expiry = 1,5 yrs for regulatory process + 2 yrs before SPC expiry



Time needed to receive updated product information with PIP results in all 27 Member States (data from 4 non-centrally approved products):

- For a further 8 medicinal products, there is a risk of not meeting the deadline for applying for SPC extension due to likely or possible delays in updating the product information in the Member States.

According to Art 28(5) of Directive 2001/83/EC and Art 34(3) for referrals, the national decision on the product information should be adopted within 1 month



Key findings on regulatory process and rewards

- Companies are beginning to achieve the incentives
  - Applications for SPC/exclusivity extensions are now being made
    - Companies need to complete the PIP 3.5 years before the SPC expiry to meet the deadline for the rewards
    - Risk that companies may not achieve rewards
      - » Timing of completion of PIP commitments needs more flexibility
      - » delays in timely update of the product information in all member states for non-centrally approved medicinal products need to be addressed

European Federation of Pharmaceutical Industries and Associations

Conclusion and Recommendations

Angelika Joos (Merck Sharp & Dome)

Conclusions

- Extensive survey data from 34 companies on 316 PIPs
  - Survey presents early experience with the Paediatric Regulation (3.5 years experience Jan 2007- June 2010)
- Industry has embedded paediatric development in its development process, this has had a significant impact on R&D resources
- Some beneficial results for paediatric patients have been realised so far:
  - 22 SmPCs with updated paediatric information based on agreed PIPs
    - 10 paediatric indications approved based on agreed PIPs
  - Article 45: 25 procedures resulted in revised SmPCs

Conclusions

- Some companies are beginning to realise the incentives
- Signals in survey already highlight some areas for future work e.g.
  - Ideal timing/content/scope of PIPs
  - Reducing high number of withdrawals/modifications
- These signals should be addressed now without waiting for formal revision of the legislation
- Some proposals how to approach these are oulined on next slides and include:
  - Short-term measures – changes to PIP process
  - Mid-term measures – changes to the Commission Guideline
  - Long-term measures – changes to the Regulation

Recommendations

Short-term measures: Proposed changes to the PIP process

- Allow for a clock-stop at Day 90 of the PIP procedure
- Allow for optional interactive discussion meeting with PDCO on Day 90
- Allow for a clock-stop during the modification process
- Facilitate more direct discussions between PDCO Rapporteur(s) and sponsor, where required

Short-term measures: Update of Regulatory guidance

- Definition of condition vs. indication for the scope of PIP
- Facilitate early joint discussions between regulatory experts, academia, learned society and the pharmaceutical industry
- Build consensus on most appropriate paediatric plan per indication, balancing unmet or critical paediatric needs and current practical/feasibility limitations
- Build paediatric requirements into the regulatory therapeutic guidances as soon as possible
- Publish available data and regulatory guidance related to epidemiology for known disease areas in order to avoid duplication of efforts

Mid-term measures: Proposed changes to the Commission guideline

- An initial PIP should generally be submitted and discussed with Regulators once “Proof of concept” in adults is established/reached
- Limit the initial PIP to “high-level” information and agree paediatric needs, target indication, target population, formulation and projected timeline depending on development milestones
- Include commitment to come back with detailed study design proposals before paediatric studies are started

Long-term measures: Proposed changes to the Regulation

- Limit the scope of mandatory paediatric development to the corresponding adult indication and defined critical unmet medical needs
- Align the submission of Paediatric Clinical Trial Study reports to authorities with the general 12 months submission deadline for CTs.
- Special consideration needed for the application of the regulation to Orphan medicinal products and vaccines
- Reflection on adequacy of rewards and incentives should be initiated

Industry embraces paediatric development !

But we feel constrained under the current system!