European Federation of Pharmaceutical Industries and Associations

EFPIA position on Compliance Check (including validation)

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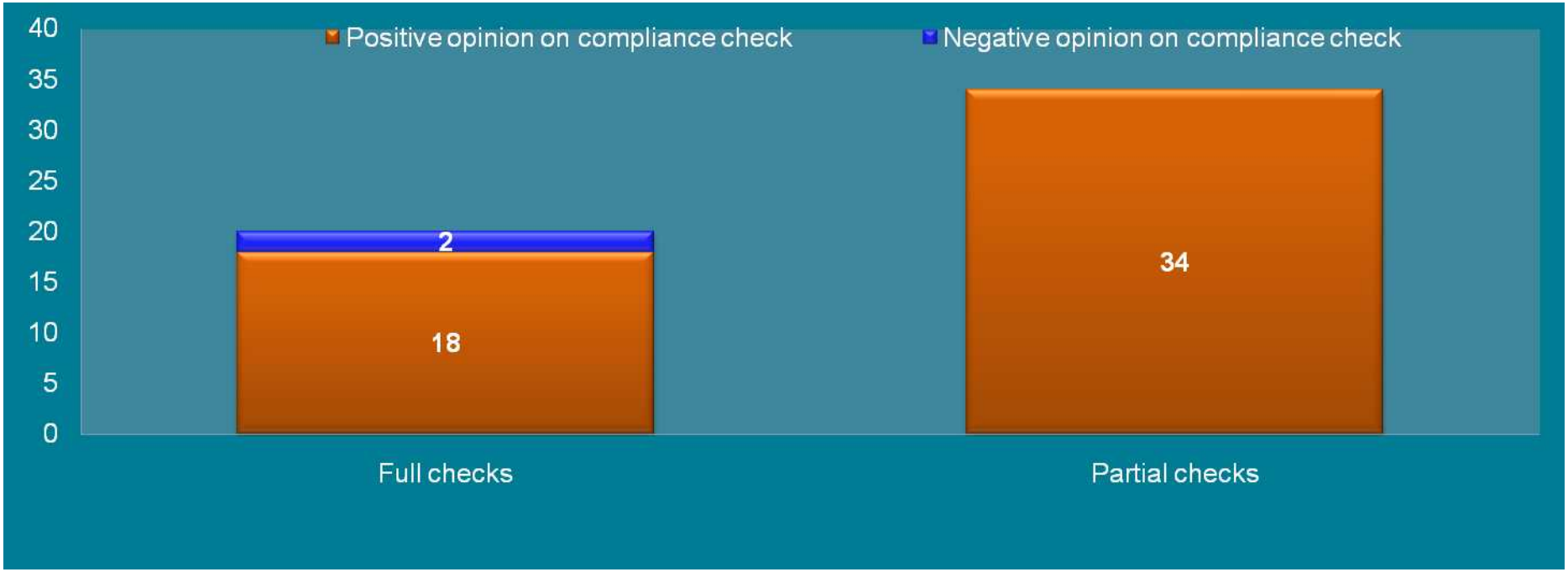
Compliance checks (n=54) based on 169 agreed PIPs



- 2 companies reported a negative opinion on their full compliance checks. EMA/PDCO report only 1 negative opinion. This may indicate that 1 company was able to remedy the issues and reach positive compliance
- Reasons given for negative opinion:
  - Lack of clarity on some key binding elements in the study reports (i.e. clinical endpoints, number of patients, duration of the treatment)
  - CSR and protocol did not contain the same wording as described the PIP decision on key binding elements
- One company reported an initial negative opinion which was converted to a positive opinion after clarification

Key findings – compliance checks

- Survey did not reveal any specific issues to date

- Recent change EMA compliance check guideline*
- Need to closely monitor the implementation
- Industry concerned that interpretation & application of recent amended guidance on partial compliance checks will have a potentially significant impact on regulatory submission strategies, based on limited experiences to date

* Q&A on the procedure of PIP compliance verification : EMA/PDCO/179892/2011 3 March 2011 amending EMEA/553631/2007 dated July 2008

Revised Q&A on PIP compliance verification at EMA

- Q5 - EFPIA member companies are concerned about the inclusion in a partial compliance check of initiation or completion of deferred studies/measures unrelated to the condition which is the subject of the regulatory application in question (but due by that time)

- Clarify the utility of this requirement, given :
  - deferral has been granted and an annual report will be provided on progress of deferred measures
  - Other measures will be checked either at time of next indication submission or during full compliance check

- Purpose of the partial check is to validate an application on a particular condition. Final compliance check provides “full” compliance opinion

Revised Q&A on PIP compliance verification at EMA

- In practice, this may force companies to delay regulatory applications in order to modify PIPs solely in relation to unrelated deferred measures
- “Date of initiation” open to interpretation. Initiation dates may slip for practical and/or administrative reasons – requiring PIP modification if subject to compliance check.
- Clarify utility of checking/enforcing **initiation** dates? **Completion** dates should be the priority and focus with provision of information on paediatrics in line with regulation objectives.

Example

- **PIP with 4 studies:**
  - Adolescents : 2 studies in adolescent population (not deferred),
  - 6-12 year: 2 studies (deferred) – study completion dates February 2011 and June 2011 respectively
- **Partial compliance check submitted in March to meet submission date for pediatric type II variation for adolescent indication**
- **Initial submission of partial compliance check package included:**
  - CSRs for adolescent studies
  - proof that study completion (LPLV) scheduled for end of February had taken place (via letter from investigator)
- **Paediatric coordinator requested that the finalised CSR for study completed in February was provided for partial compliance check** (even if study deferred and not related to adolescent indication) based on the following information from the Q&A on the procedure of PIP compliance just published:
  - Q5: "The partial compliance check will cover all those studies/measures within the condition(s) covered by the Regulatory Application, for which initiation and/or completion have not been deferred, and also those studies/measures which are deferred, but whose initiation or completion was due before or at the time of submission of the Regulatory Application."
- **Issue around definition of study completion date: LPLV or final CSR available?**
  - As per the definition of completion date in the PIP, the date which is tracked in the PIP opinion is not the availability of the full CSR but the LPLV date. However in this case, the company was requested to have the CSR ready by the LPLV.

Short term measures – Proposed changes to EMA guidance

- Proposal for Partial Checks : Do not include initiation/completion of deferred measures relating to other conditions/ study populations not subject of the MAA

Short term measures : Proposed changes to EMA guidance

- Allow for a Compliance check process which does not potentially delay the MAA
  - Propose high level partial check during MAA validation. More detailed review of data during standard MAA review processes. Allows faster, parallel checks & assessments

- Allow flexibility for applicant to demonstrate compliance with key binding elements
  - For example provide expert statement, CSR synopsis or other relevant evidence vs full CSR
  - Potential delay to MAA submission/validation if full CSR required

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Scope of partial check

- Reference Recital (16) of Paediatric regulation
  - ''the existing procedures for the marketing authorisation...should not be changed''
  - ''(from) Recital (11) it follows that Competent Authorities should check compliance with agreed PIP incl any waivers/deferrals at the existing validation step for MAAs''
- Reference Question 17 Q&As
  - The 'paediatric validation is part of the overall validation of the application. It includes the compliance check where necessary & follows the timelines of the MAA or of the variation/extension of the marketing authorisation respectively'

Short term measures : Proposed changes to EMA guidance

- Effective appeal mechanism needed for final compliance check
  - Final positive compliance check results in final PDCO opinion *which is final upon adoption*.
  - Pre-requisite for rewards (SPC extension, orphan market exclusivity extension)

Conclusions & Recommendation

- EFPIA recognises the importance of our commitment to adherence to the Paediatric Regulation
- EMA application of partial check process adds unnecessary complexity, with significant potential to cause delays to MAAs; needs to take account of dynamic R&D processes
- EFPIA proposals seek to enable pragmatic enforceable compliance check processes
- Appreciate & acknowledge the opportunity to take further discussion & dialogue on this important topic with all relevant stakeholders