EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Completion of the development of a formulation: Requirements for compliance check vs. requirements for Marketing Authorisation

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Workshop on Paediatric Formulations

For Assessors in National Regulatory Agencies

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An agency of the European Union

Agenda

- The Paediatric regulation – New requirement;
- Compliance Check;
- Pharmaceutical Formulation Development;
- PIP - Quality studies requested;
- Requirements for Marketing Authorisation;
- Conclusion

PIP

- The Paediatric regulation – New requirement (PIP or proof of having a waiver or deferral):
  - New medicinal products
  - Authorised Medicinal Products covered by patent:
    - New indication;
    - Route of administration;
    - pharmaceutical form;
- PIP – any time
  - Authorised Medicinal Products - Off patent

Compliance Check

- Compliance?
  - The paediatric development must be in compliance with agreed PIP: Measures & Timelines
  - “Black or white” = Yes or NO
  - No room for negotiation
  - **Compliance ≠ Assessment**
  - **Compliance is needed.**

Compliance Check

- Compulsory for Validation:
  - New MAA;
  - New indication;
  - New route of administration;
  - New pharmaceutical form;

- **Lack of compliance before validation?**
  - **Refusal of validation**

Compliance – Partial Check

- Compliance for ongoing PIP = Partial Check

  – Submission before all PIP is completed:

  - Compliance checked for the applied indication;
  - Compliance for measures that should have been completed by that time (Old policy);
  - Checked studies ongoing (New policy);

Pharmaceutical Formulation Development

- Pharmaceutical Formulation?
  - Process in which active substance and excipients are combined
- Formulation Studies?
  - Objective: Selection formulation & Pharmaceutical form
  - Developing a stable formulation and acceptable for the patient
  - Choice of excipients
  - Compatibility studies
  - Characterisation of the active substance (Physical & Chemical properties)

Pharmaceutical Formulation

- Formulation Studies?
  - Disintegration studies
  - Dissolution studies
  - Several factors:
    - Particle size
    - Polymorphism
    - pH
    - Solubility
    - Bioavailability

Compliance Check - Quality

- How to demonstrate that the pharmaceutical development has been done?
  - Submission of overall summary (Module 2):
    - **Section 2.3.P.1 -** Description and composition of the drug product
    - **Section 2.3.P.2 -** Pharmaceutical Development
    - **Section 2.3.P.3 -** Manufacture
    - **Section 2.3.P.5 -** Control of drug product (including specifications)
    - **Section 2.3.P.7 -** Container Closure System
    - **Section 2.3.P.8 -** Stability

PIP - Quality studies requested

- Case A
  - Age appropriate liquid formulation – February 2009 - Compliance Check OK
- Case B
  - Development of age-appropriate dispersible or orodispersible or granule formulation –January 2011;
- Case C
  - Development of prolonged-release granules– December 2013;
- Case D
  - Development of paediatric age-appropriate strengths of film-coated tablets – January 2017

PIP - Quality studies requested

- Case E
  - A formulation age appropriate for paediatric patients less than 6 years (a powder for reconstitution, oral solution, oral granules, dispersible tablets or mini-tablets) – January 2011
- Case F
  - Development of an age-appropriate inhalation device – December 2017.
- Case G
  - Development of an Intravenous formulation – December 2017.

PIP - Quality studies requested

- Case H
  - Development of age-appropriate oral or parenteral formulation – December 2012
- Case H
  - Development of age-appropriate oral suspension – April 2014
- Case J
  - Development of chewable tablet formulation, in 100 and 250 mg strength - June 2014

PIP - Quality studies requested

- Case L
  - Studies to establish the minimum quantity of preservatives.
- Case M
  - to assess the bioequivalence of oral suspension to the tablet formulation.

Conclusion on Quality studies requested

- Development of age-appropriate:
  - Liquid formulation (e.g. oral solution)
  - Orodispersible tablets
  - Granule formulation (oral granules)
  - Mini-tablets
  - Prolonged-release granules
  - Powder for reconstitution
  - Intravenous formulation
  - Oral Suspension
  - Chewable tablet

Conclusion on Quality studies requested

- Other Quality studies requested
  - "Appropriate" paediatric strengths;
  - Age-appropriate inhalation device;
  - Other Age-appropriate deliver devices & dosing device;
  - Minimum quantity of preservatives;
  - Minimum quantity excipients;
  - Critical excipients to be avoided and replaced;
  - To assess the bioequivalence of new formulation & old formulation;
  - Size of the tablets;
  - Palatability – Studies to be performed;

Conclusion on Quality studies requested

- Other Quality studies requested
  - Compatibility issue (content/container)
  - Accuracy (syringe with small volumes, droppers)

Requirements for Marketing Authorisation

- Stable formulation and acceptable for the patient
- Compliance with the relevant Legislation
- “Compliance” with the relevant Guidelines / Guidances / Reflection papers … or Justification
- Full Dossier

Conclusion

- The paediatric development must be in compliance with agreed PIP
- Compliance is needed
- Compliance ≠ Assessment
- Development of age-appropriate formulations
- Level of information for Marketing Authorisation ≠ Compliance check

Questions and Answers