

Session 2-Product Design

Development of a lower dose paediatric
strength IR tablet

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Focus of this Case Study

- **Design of the Tablet, e.g.:**
 - Selection of excipients
 - Design of the formulation
 - Analytical methods
- **Design and Selection of the Manufacturing Process, e.g.:**
 - Selection of Unit Operations and Equipment
 - Scale-up technical transfer and validation of the batch manufacturing process
- **Development of the Control Strategy, e.g.:**
 - Identification of CQAs
 - Identification of CPPs and critical material attributes

Product Overview



- *“Paediatric Regulation” aims to facilitate the development and accessibility of age-appropriate paediatric medicines. This aim should be achieved without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age groups “*
EMA/CHMP/QWP/805880/2012
- Paediatric formulations are likely to heavily leverage prior knowledge of the original product
- Learnings from this case study are considered widely applicable

Overview



50 mg dose, Immediate release tablet, once daily dosing

API is BCS class 2

Parent Tablet

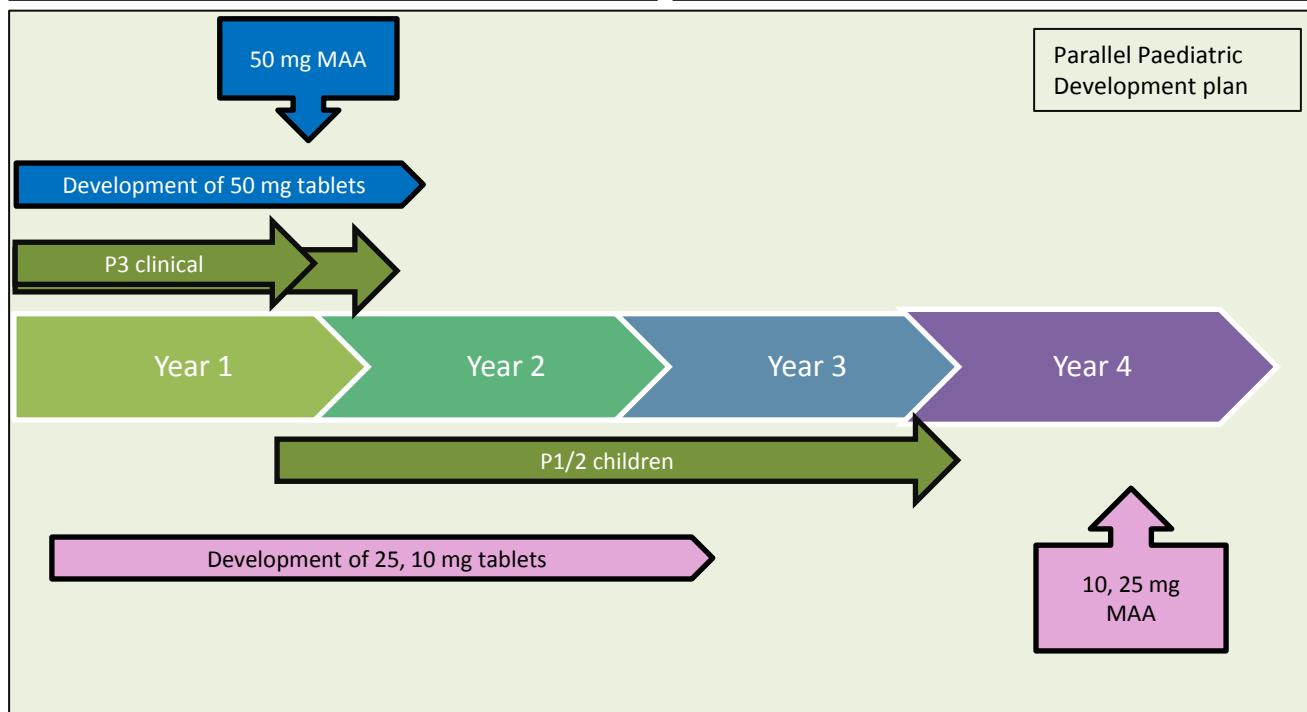
50 mg dose, Immediate release tablet,
once daily dosing

300 mg, coated tablet

Paediatric Tablets

25, 10 mg dose, immediate release
tablet, once daily dosing

150, 100 mg, coated tablets for ease of
use



Overview of the 50, 25 and 10 mg tablets



Granulate
288 mg

- Extra granular excipients
- 12 mg

Granulate
144 mg

- Extra granular excipients
- 6 mg

Granulate
50 mg

- Extra granular excipients*
- 42 mg

Trade-off: reuse of the granule means identical tablet core cannot be used, as the tablet was too small;

* Additional extra granular excipients to add bulk were DC grade intra granular excipients

Example: Comparison of excipient selection and compatibility in P2.2

50 mg tablet

- Discriminating method developed
- Use of well known and understood excipients, controlled to pharmacopeial standards
- Studies on compatibility and stability – Degradation mechanism identified by long term stress storage
- Tablet DOE to understand and develop the pivotal formulation – study of impact on stability, dissolution.....
- Shelf life confirmed in ICH Studies

10, 25 mg tablets

- Discriminating method developed
- Re-use of existing granule
 - *Reference made in P2.2 and other modules to 50 mg granule and formulation comparison*
- Shelf life confirmed in ICH Studies

Rapid development and scale-up of the paediatric tablets

❖ Where was the focus of development? Gr

Trade off: same granule utilised

- Design

- Formulation composition
- Excipient compatibility

Not repeated for 10, 25 mg

- Stability

- Analytical methods - appropriately discriminating for BCS II

Completed for 10, 25 mg

- Impact/suitability of API properties

- Rapid BE and PK Comparison between 50 mg and 10, 25 mg in-vitro & during clinical studies.

- Manufacturing process and Control Strategy

Streamlined for 10, 25 mg

- Selection of the manufacturing process and process equipment
- Identification of CPPs and critical material attributes
- Scale-up, technical transfer and validation of the batch manufacturing process

Trade off: same granule and manufacturing equipment and scale used

Example: Stability of 10, 25 mg Tablets

- Prior knowledge of the 50 mg (stability well understood); 2 year shelf-life should be readily achievable
- Batch Selection:
 - Commercial-scale granulation and compression; pilot scale coating
- Stability conditions:
 - >2 years ambient and 6m accelerated
 - ICH stability was on critical path until change in clinical plan
- Data confirmed assumptions of good tablet stability
- ICH stability package supported the MAA; was it needed?
 - In the future, greater leverage of prior knowledge supported by accelerated stability modelling (ASM)?

Overall Summary

- Ability of leverage prior knowledge of 50 mg tablet was key to rapid development of the 10 and 25 mg tablets
 - Product design, manufacturing process and control strategy
- Learnings:
 - Trade-offs/restrictions in design of the tablet and manufacturing process to ensure prior knowledge was relevant
 - Knowledge of the PK of the 50 mg tablet simplified PK evaluation
 - Referencing prior knowledge from the 50 mg file was a challenge.
 - Relevant additional data (e.g. stability and manufacturing experience) were available from the 50 mg tablet at the time of the paediatric file- how could this be referenced?
 - Could development have been further streamlined based on the prior knowledge (e.g. stability?)

Reflections

• Questions posed by the Case Study

- How was prior knowledge leveraged to facilitate development?
- How was the prior knowledge presented in the submission?
- How can more consistent and extensive use of prior and platform knowledge accelerate development and improve access to medicines?

• Challenges/Answers

- In multiple ways – selection of the granule, scale up, control strategy, PK - generally applicable to PLEs such as paediatric products
- Trade-offs were required to ensure the prior knowledge was relevant – re-use of granule, manufacturing process...
- Some re-use of data where relevant; implied cross referencing
- For rapid development of age-appropriate formulations, it is important that prior knowledge used to support development can be:
 - Clearly identified and referenced in the submission
 - Supported by mechanisms for cross-referral
 - Supported by all available knowledge, including that on the manufacturing site

Joint BWP / QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications

Thank-you!

