EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment of a MAA:

Awareness of the PIP recommendation

Generic applications

Workshop on Paediatric Formulations

For Assessors in National Regulatory Agencies

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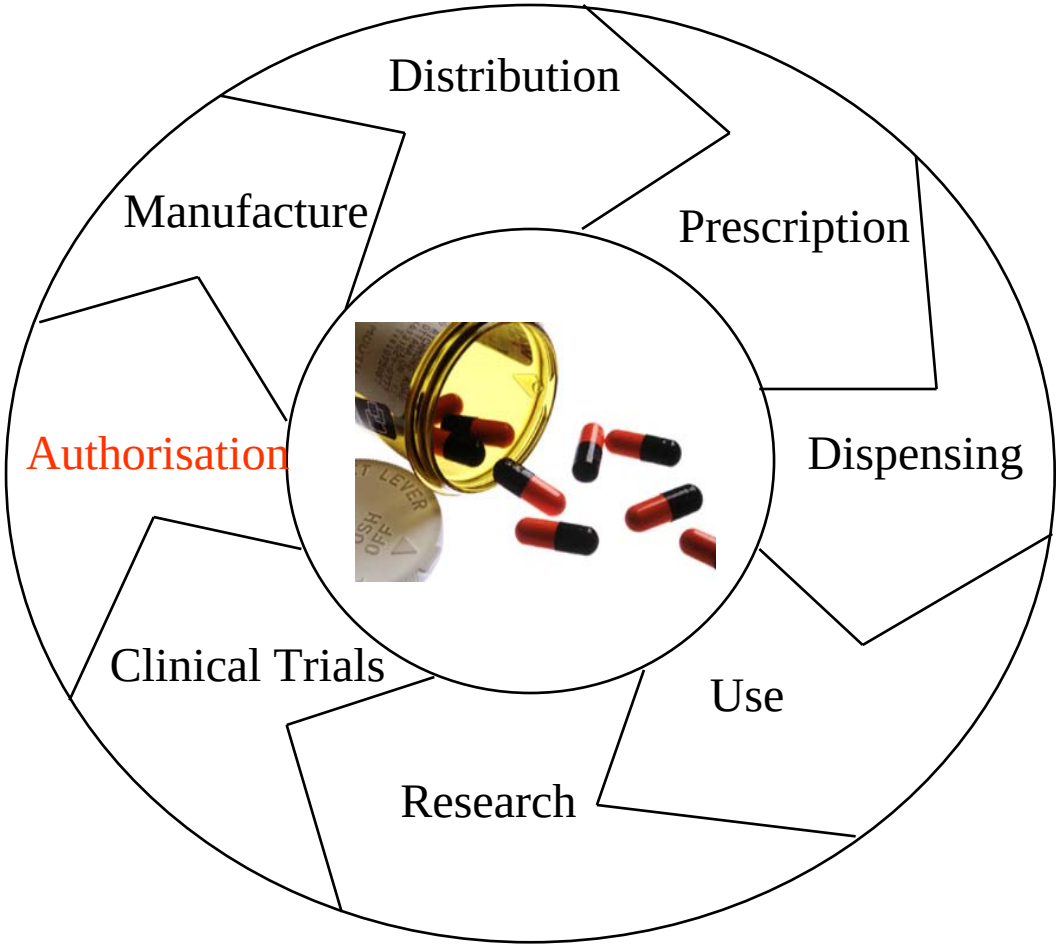
Scientific Administrators/Chemicals/Quality of Medicines

Agenda

- The Life Cycle of the Medicinal Product
- Assessment of Medicines
- Assessment of Generics Applications - Paediatrics
- Critical Points for Paediatric Formulations
- Critical issues during the assessment of paediatric medicines

The Life Cycle of the Medicinal Product



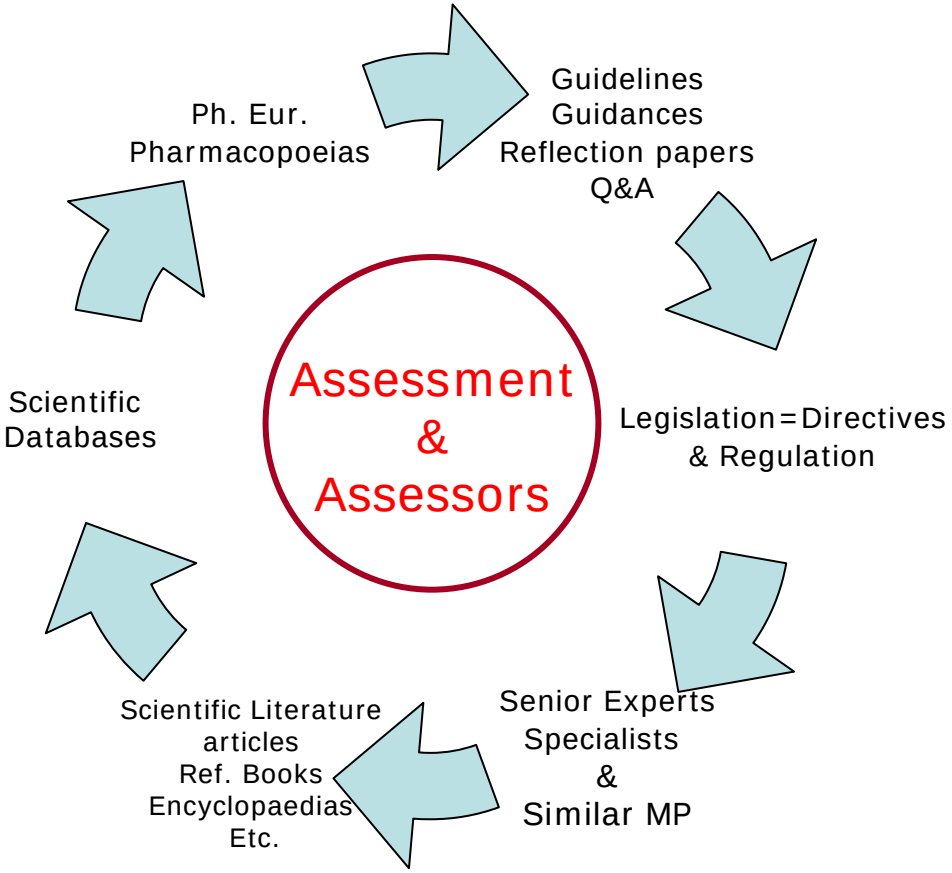
Assessment = Team work

Assessment of Medicines

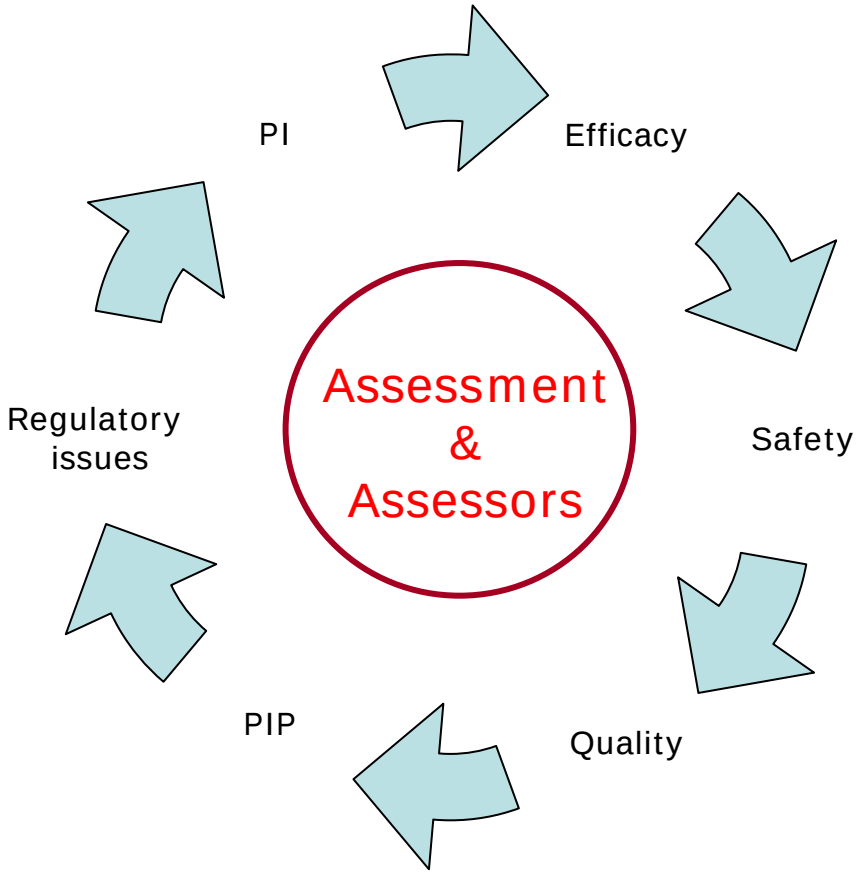
Benefit **Risk**

- Quality
- Safety
- Efficacy
- Risk Management
- *"PIP Recommendation"*

Assessment of Medicines



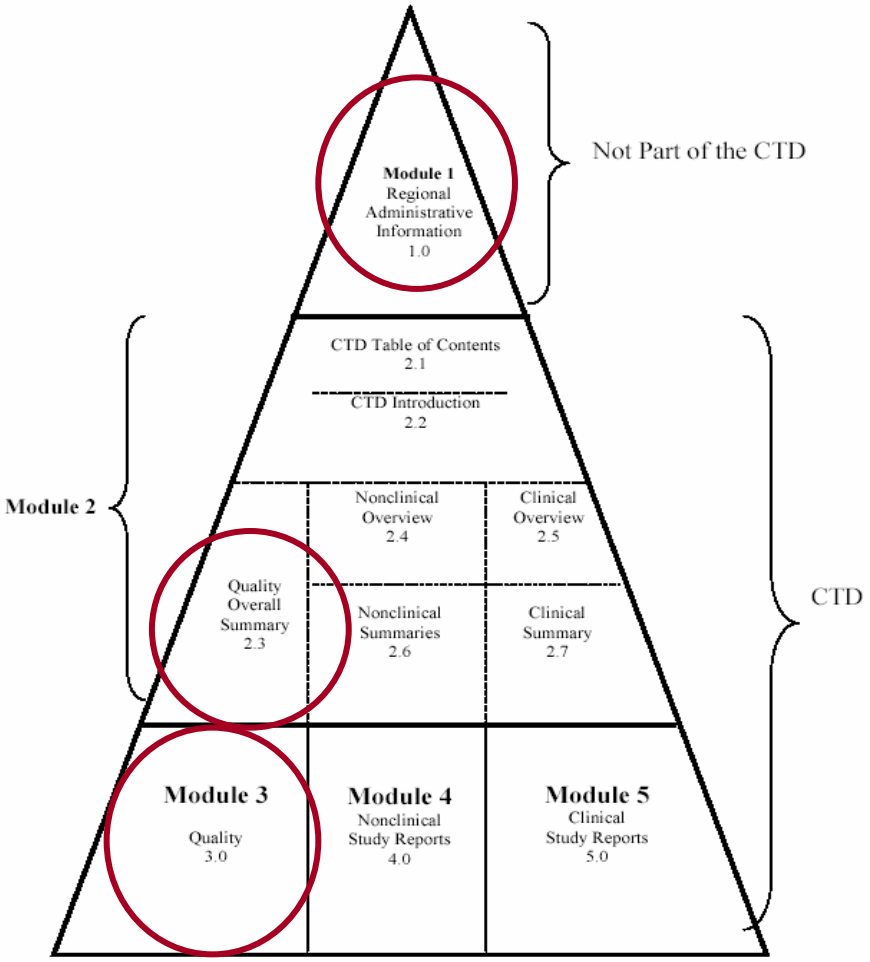
Assessment of Medicines



MA – CTD format

Module 1 = PI + PIP Recommendation + ….

Diagrammatic Representation of the Organization of the CTD
Common Technical Document

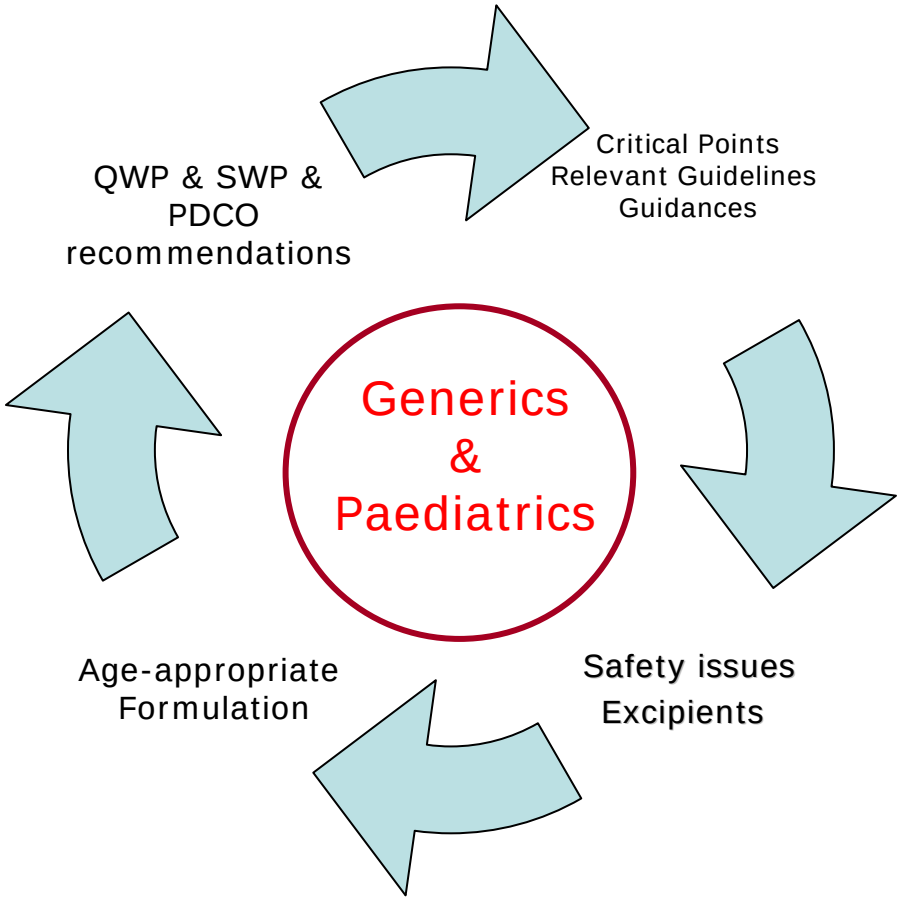


NTA, Vol. 2B-CTD, foreword & introduction, edition 2001

EU - Generics

- Same active substance
- Same quantity of active substance
- Same pharmaceutical form
- Bioequivalence demonstrated
- **No PIP**

Assessment of Generics Applications-Paediatrics



Critical Points of the Paediatric Formulations (reminder)

- Routes of administration
- Appropriate dosage forms i.e.
  - Development of specific paediatric form
  - Extemporaneous preparations
  - Size of the tablets
- Excipients / Safety issues i.e.
  - Preservatives
  - Antioxidants
  - Colorants
  - (…)
- Delivery devices
- Taste and palatability

Case 1 – Oral solution

- Strength: 50 mg/ml
- Age group: 0 - 18 years

Case 1 – Oral solution

Preservative system

Name of ingredients	Unit formula / 100 ml	Function
Potassium sorbate	0.500 g = 0.5 %	Preservative
Sodium methyl parahydroxybenzoate	0.300 g = 0.3 %	Preservative
Sodium propyl parahydroxybenzoate	0.090 g = 0.09 %	Preservative

Case 1 – Oral solution

Major objections:

- Day 120 - The preservative system is complex and insufficient development pharmaceutics work has been performed …
- Day 180 - … Justify the inclusion of **Propylparaben** in the formulation …
- **Ground for re-examination:**
- **Inclusion of Propylparaben**

Case 1 – Oral solution

Applicant's position:

- Exposure to propylparaben should not be considered as a cause for concern since it will be a limited exposure

CHMP's position:

- …despite propylparaben not being used in food it can be said that propylparaben is widely used in medicines / paediatric population
- **FUM: To assess the potential risk of propylparaben on the reproductive system of the neonatal rat.**

Case 2 – PIP - Oral suspension

- Strength: 40 mg/ml
- Age group: ≥ 2 years

Case 2 – PIP - Oral suspension

Preservative system

Name of ingredients	mg / ml	Function
Potassium sorbate	1.34 = 0.134 %	Preservative
Sodium methyl parahydroxybenzoate	1.20 = 0.120 %	Preservative
Sodium propyl parahydroxybenzoate	0.300 = 0.03 %	Preservative

Case 2 – PIP - Oral suspension

Conclusion from the PDCO Formulation Working Group:

- The applicant should investigate alternative preservative systems / free from propylparaben

Case 3 – Film-coated tablets Age-appropriate formulation

- Active substances: A / B (Fixed Combination)
- Strength: 40 mg / 320 mg & 20 mg / 160 mg & 10 mg / 80 mg
- Age group: ≥ 6 Months (crushed tablets)

Case 3 – Film-coated tablets Age-appropriate formulation

Peer Review:

- The Film-coated tablets only recommended for children ≥ 6 years old
- Development of an age appropriate formulation is needed
- crushed tablets is not acceptable

Day 120 LoQ

- …an update should be provided on the development of the age appropriate formulations as proposed in the PIP

Case 4 – Generic MAA - Film-coated tablets

- Active substances: A / B (Fixed Combination)
- Age group: ≥6 years

Case 4 – Generic MAA - Film-coated tablets

Major objections:

- **Reference Product =** breakable
- **Generic ≠** not breakable
- **Day 120 –** Generic should be breakable since a half-dose is recommended for children in the SPC.
- **Clock stop - Ongoing**

Case 5 – Generic MAA - Film-coated tablets

- Strength: 150 & 300 mg
- Age group: ≥6 years

Case 5 – Generic MAA - Film-coated tablets

Major objections:

- **Reference Product =** breakable + Oral solution
- **Generic ≠** not breakable
- **Day 120 –** Generic should be breakable since a half-dose is recommended for children in the SPC.
- **Responses to Day 120:**
  - Breakable tablets
  - An oral solution is available

Conclusion

- Keep in mind the PIP recommendation
- Keep in mind Critical Points for Paediatric Formulations
- Assessment = Team work

Questions and Answers