Paediatric formulations of antiretroviral therapies

EU Regulatory considerations

Nathalie Seigneuret
European Medicines Agency

How are new medicines authorised in the EU?

Centralised procedure

1 MAA

Max 210 days

1 evaluation by scientific committee (CHMP)

1 authorisation

1 product information (Summary of Product Characteristics, Labelling, Package Leaflet)

20 languages!

However still lack of medicines for children

- Not mandatory to have paediatric data and age appropriate formulation
- No legal force of Guidelines
- Industry not interested in the paediatric market

→ CHMP may impose post-authorisation commitment to get paediatric data and/or age appropriate formulation

In the future…

Draft European Regulation on Paediatric Medicinal Products

- Ongoing discussion at the EU Parliament and the Council
- Expected by end 2006
- Implementation 2007

Outline of the proposed Regulation

Patented medicines

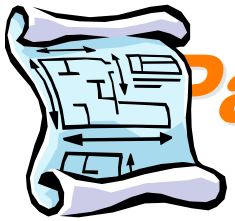
Requirement at a time of applications for new medicines for:

- Data in children (according to Paediatric Investigation Plan (PIP) agreed by Paediatric Committee)
- Or waiver/deferral

Reward for studies conducted:

- 6-months patent extension or 2 years additional market exclusivity for orphan medicines

Outline of the proposed Regulation



Paediatric Investigation Plans

- Measures to assess the quality, safety and efficacy in all subsets of the population

- Any measure to adapt the **formulation** to make sure that its use is more acceptable, easier, safer or more effective for different subsets of the paediatric population.

Outline of the proposed Regulation

Off-patent medicines specifically developed for children:

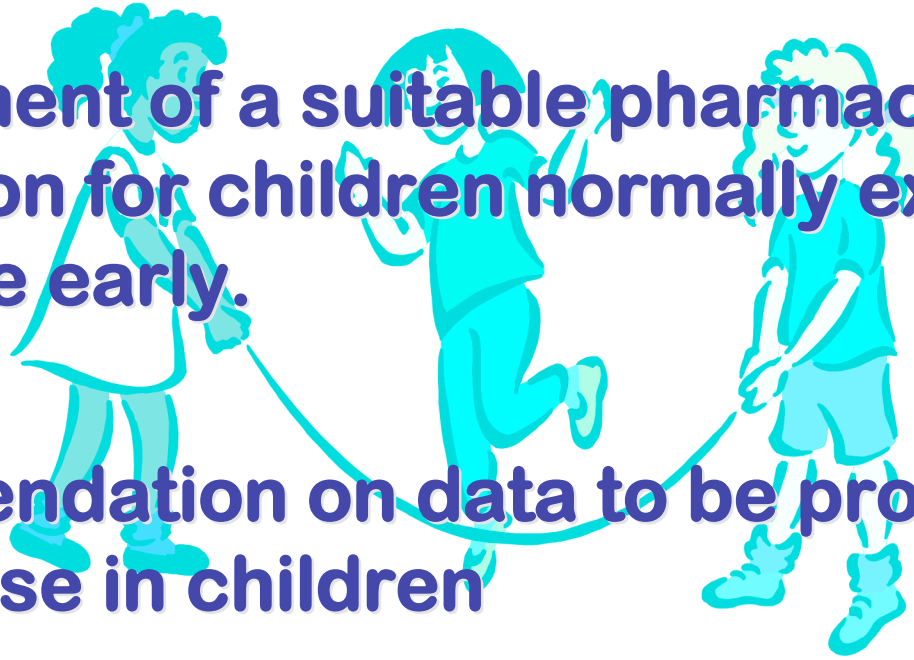
New type of Marketing Authorisation

Paediatric Use Marketing Authorisation (PUMA):

- Enabling 10-years data protection
- Use of existing brand name (brand recognition)
- Only data in children required
- PIP

CHMP Guideline on the clinical development for anti-HIV medicinal products

Children



- Development of a suitable pharmaceutical formulation for children normally expected to take place early.
- Recommendation on data to be provided to support use in children

Currently released for 3 months consultation

Fixed dose combination (FDC)

- No regulatory obstacle for granting MA to FDC
- Potential advantages of FDC:
  - improve benefit/risk assessment
  - or simplification of therapy

For anti-HIV medicinal products

Need for clinical data depending of the nature of the FDC:

- If FDC developed to be used instead of a well-documented "free" combination
- If FDC developed with new posology,

Discussion paper on formulation of choice for children

- under preparation
- will address
  - preferred route of administration dosage form versus age
  - consideration on excipients, preservatives, sweeteners, solvent/fillers, colouring agents (to be avoided)
  - recommendation for manipulation of adults dosage form:

    need for info from manufacturer

Anti-HIV products authorised in EU

Agenerase	amprenavir	50, 150 mg soft capsules	15 mg/ml oral solution	>4 years
Crixivan	indinavir	100, 200, 333, 400 mg hard capsules		>4 years
Epivir	lamivudine	150 mg film-coated tablets	10 mg/ml oral solution	>3 months
Emtriva	emtricitabine	200 mg hard capsules	10 mg/ml oral solution (refrigeration)	>4 months
Fuzeon	enfuvirtide	90 mg/ml powder (and solvent) for solution for injection (refrigeration after reconstitution)		>6 years
Kaletra	lopinavir/ ritonavir	133.3 mg soft capsules	oral solution (each 5 ml contains 400 mg lopinavir co-formulated with 100 mg ritonavir as pharmaco-kinetic	>2 years

Anti-HIV products authorised in EU

Norvir	ritonavir	100 mg soft capsules	80 mg/ml oral solution	> 2 years
Sustiva/ Stocrin	efavirenz	50, 100 and 200 mg hard capsules	30 mg/ml oral solution	> 3 years
Viracept	nelfinavir	50 mg/g oral powder	250 mg mg tablets	250, 625 film-coated tablets > 3 years
Viramune	nevirapine	200 mg tablets	50 mg/5 ml oral suspension	>2 months
Zerit	stavudine	15, 20, 30, 40 mg hard capsules	200 mg power for oral solution (refrigeration after reconstitution)	>3 months
Ziagen	abacavir	300 mg film coated tablets	20 mg/ml oral solution	>3 months

Anti-HIV products authorised in EU

Adults only

Combivir	lamivudine/ zidovudine	150/300 mg film coated tablets		12 years+
Fortovase	saquinavir	200 mg soft capsules (refrigeration)		16 years+
Invirase	saquinavir	200 mg hard capsules		16 years+
Reyataz	atazanavir	100, 150 and 200 mg hard capsules	50 mg/1.5 g oral powder	adults
Telzir	fosamprenavir	700 mg film-coated tablets	50 mg/ml oral suspension	adults
Trizivir	Abacavir/lamivu-dine/zidovudine	300/150/300 mg film coated tablets		adults
Viread	tenofovir disoproxil	245 mg film coated tablets		18 years+

CHMP PAEDIATRIC WORKING PARTY

- Assessment of paediatric needs with help of PENTA
- For HIV medicinal products already authorised in EU, conclusions sent to the companies
- Still under discussion

What are EU initiatives on international cooperation?

- As of Nov 2005, possibility for the CHMP to provide a scientific opinion to WHO on medicinal products not intended for Europe

- Draft legislation under discussion for the compulsory licensing of patents relating to the manufacture of medicinal products for export to countries with public health problems.

Websites

- EMEA www.emea.eu.int (+ links to EU national agencies)
- European Union www.europa.eu.int
- DG Enterprise pharmacos.eudra.org
- DG Research www.cordis.lu