Paediatric medicine: Regulations and other influencers

Regulations governing the development of paediatric medicine

In the EU, a single piece of legislation governs paediatric medicines development and the authorisation of medicines for paediatric use. EU Regulations (EC) no. 1901/2006[1] and (EC) no. 1902/2006[2] require that children be included earlier in medicines development: they mandate that a Paediatric Investigation Plan (PIP) be submitted once the first studies in humans are completed, when the understanding of the effect of the medicine is just emerging. The legislation also provides incentives to those who comply with this mandate and submit their PIPs on time.

The US has two pieces of legislation governing paediatric medicines development. The first, the Pediatric Research Equity Act (PREA) (2003), mandates the need for paediatric plans in most cases and requires agreement on paediatric assessment. It covers:

- All age groups,
- Biologic medicines, **and**
- Orphan diseases

The PREA requires that paediatric assessment applies to the treatment of the same disease or indication as in adults. It states that waivers and deferrals can be requested but must be agreed before the licence application is submitted to the U.S. Food and Drug Administration (FDA).

The second piece of legislation, the Best Pharmaceuticals for Children Act (BPCA) (2007), is optional, but completion of the BPCA procedure provides an incentive: an additional 6 months exclusivity (Voluntary Paediatric Exclusivity (PE)) for the medicine during which generics are prevented from entering the market. The outcome of the procedure is a written request from the FDA and must be agreed before paediatric work starts. Once the company agrees, this becomes legally binding. Voluntary Paediatric Exclusivity (PE) legislation provides incentives for those who complete the paediatric studies according to the written request. Biologics are excluded.

All US legislation has a limited lifespan at the end of which it must be re-authorised by the US Congress. The PE legislation was re-authorised the FDA Safety & Innovation Act (FDASIA) in 2002. The FDASIA requires early paediatric discussions with the FDA, typically around the end of Phase II of clinical development.

Outside of the EU, US, and Japan, there are currently no specific paediatric legislative requirements, but this may change in the future. Despite this lack of legislation, some markets do require local paediatric data for marketing authorisation.

Medicines development is no longer possible without considering children, because of such legislation. This has brought paediatric development more in line with adult development and has resulted in increased paediatric development. As a result, more medicines are being developed for children.

Comparison of the EU and US paediatric legislation.

The table below offers a comparison of EU and US paediatric legislation.

Table comparing EU and US paediatric legislation.

	US	**EU**
Legal basis	2 separate processes: Pediatric Research Equity Act (PREA) (requirement) Best Pharmaceuticals for Children Act (BPCA) (incentive)	Unified under the legislation: Paediatric Regulation (1901/2006)
Definition of paediatric population	Less than 16 years of age	Less than 18 years of age
Scope	Required for all new products, active ingredients, indications, dosage forms, dosing regimens, or routes of administration.	Required for all new Marketing Authorisation Applications (MAAs) and changes to patent protected authorised products (new indications, pharmaceutical forms, administration routes).
Confidentiality	Paediatric plans confidential; only summary of paediatric studies are public.	Paediatric Investigation Plan (PIP) decisions are public.

	US	EU
Development	Discussion of paediatric requirements and associated studies are encouraged during development.	Definitive information about the PIP requested early in development procedure.
Biologics licence application (BLA) / New Drug Application (NDA) / Marketing Autorisation Application(MAA)	Filing denied if paediatric data and/or request for waiver and/or deferral of paediatric requirements not included in application (pre-approval of information not required).	Filing denied if MAA does not contain a pre-approved PIP or waiver/deferral.
Procedure	Generally flexible procedure and timelines for obtaining feedback during development.	Rigid procedure with strict timelines.
Reviewing bodies	Paediatric Review Committee (PeRC) recommendations are non-binding; U.S. Food and Drug Administration (FDA) has final say.	Paediatric Committee (PDCO) recommendations are binding and can conflict with Committee for Medicinal Products for Human Use (CHMP).

	US	EU
Investigation of different indications in paediatric population	FDA cannot request paediatric investigation of any indication the applicant is not planning to seek a licence for.	PDCO can request investigation of different indications in the paediatric population than the targeted ones in adults.
Data accepted in the application	US data are required (only special circumstances allow otherwise). Data from outside US can be included as 'supportive' if conducted in line with US requirements.	Worldwide data are accepted.
Post-Marketing	Public assessment of paediatric safety required (Paediatric Advisory Committee).	No public assessment of paediatric safety required.

References

1. European Parliament (2006). *Regulation (EC) No 1901/2006 on medicinal products for paediatric use.* Retrieved 11 July, 2021, from https://op.europa.eu/en/publication-detail/-/publication/f02fd0de-82a9-42d8-9cd1-723176bb5ce0
2. European Parliament (2006). *Regulation (EC) No 1902/2006 amending Regulation 1901/2006 on medicinal products for*

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