Novartis TRD pediatric and geriatric network

Pediatric development – industry perspective

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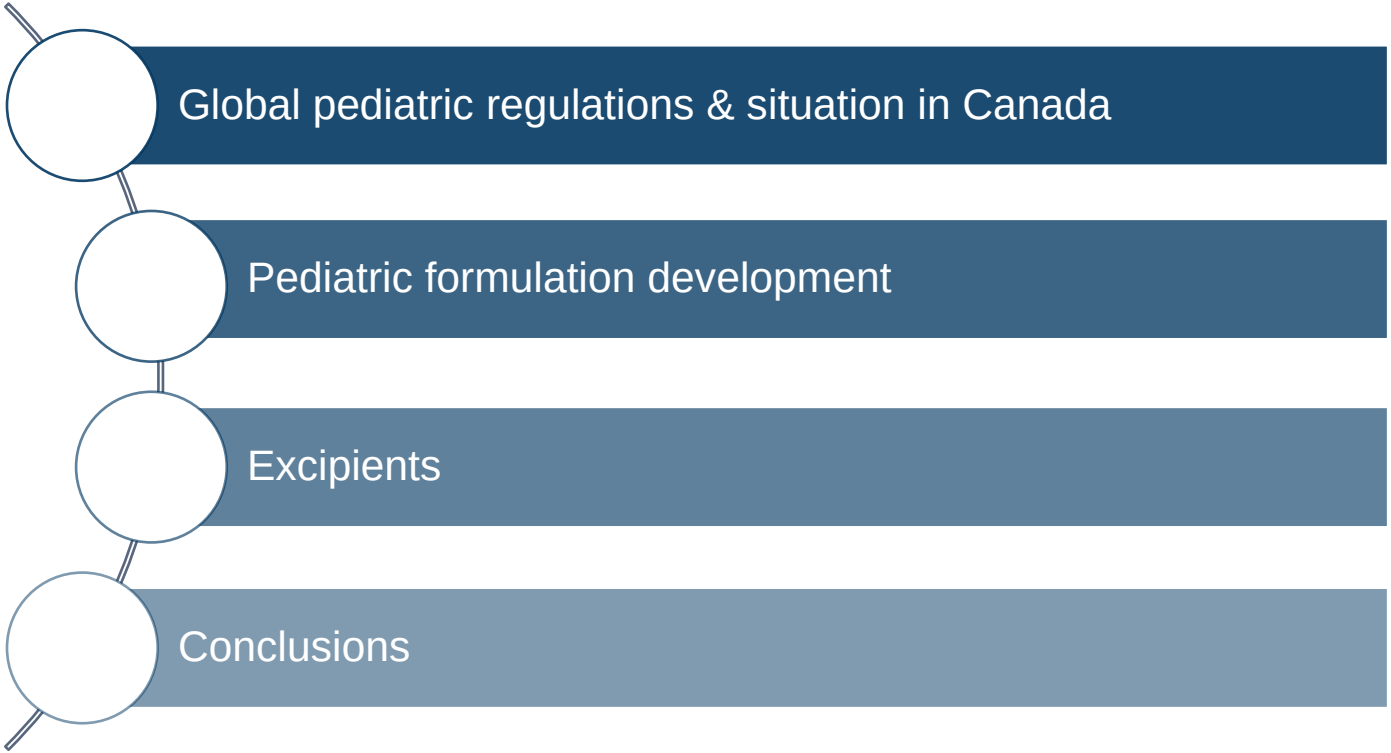
Agenda



Global pediatric regulations & situation in Canada

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Pediatric research policies

Global perspective

US, EU, CH	• Formal legislation mandating pediatric research within an evolving environment • US: PREA (obligation), BPCA (voluntary), FDASIA • EU: Pediatric Regulation
Japan*, Canada*	• Encourages voluntary pediatric data submission with incentives
Australia, New Zealand, Taiwan	• Encourages voluntary pediatric data submission with **no** incentives
China, Turkey, Russia, Asia Region, Latam Region, Middle East & Africa	• No pediatric policy

* Actively considering policy changes which may include obligations; PREA: Pediatric Research Equity Act; BPCA: Best Pharmaceuticals for Children Act; FDASIA: Food and Drug Administration Safety and Innovation Act

Situation for pediatric medication in Canada

In many cases, pediatric formulations that are commercially available in places like the US and EU are simply not marketed in Canada because of

- regulatory requirements that are not practical for small volume products
  - Canadian specific inner labels
  - large numbers of retain samples
- the commercial limitations inherent to a small market

Pediatric formulation development

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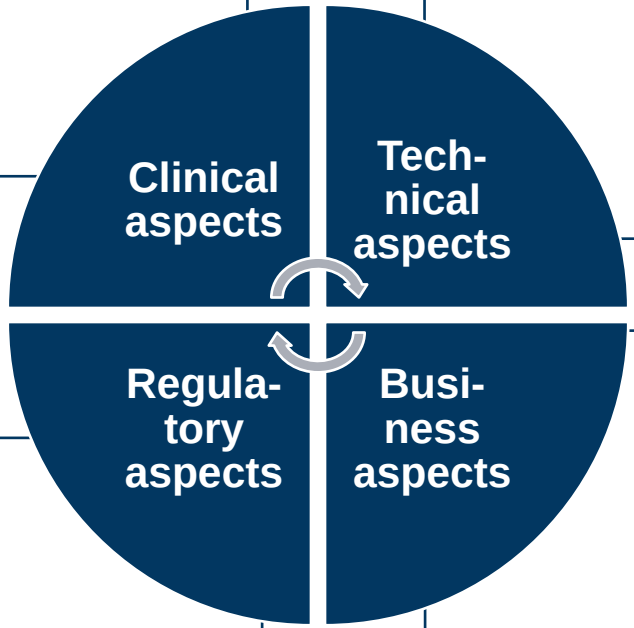
Pediatric drug development aspects

- Dose
- Safety
- Operational aspects etc

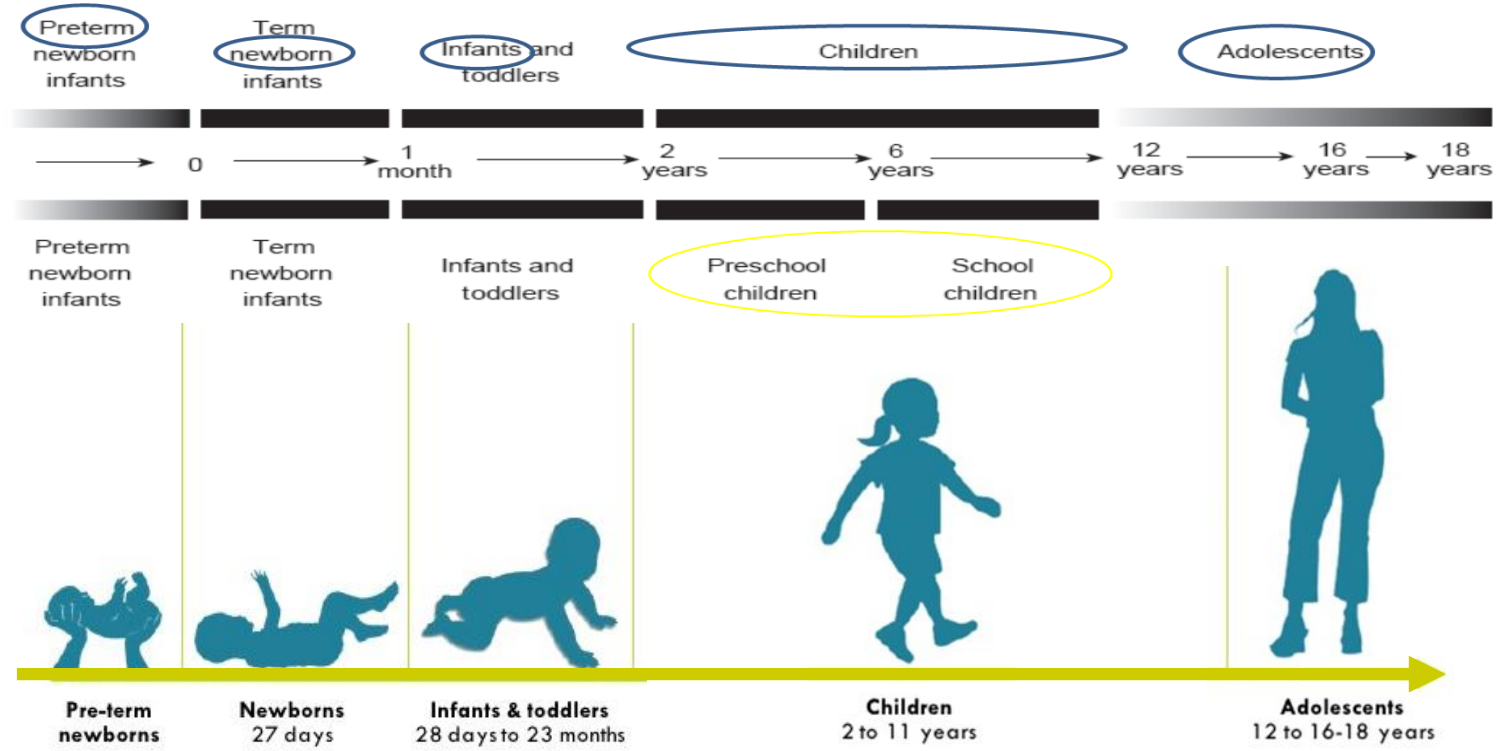


- Specific dosage form/age group
- Acceptabilty & palatability
- Excipients
- Precision of dose delivery/application

- Ped development plans required in EU & US to submit the adult form

- Usually low volume products
- Payers only willing to pay more for an advantage in efficacy or safety, or for an unmet need

Pediatric age groups



Parenteral dosage forms

Oral dosage forms

Pediatric formulations need to fulfill additional requirements

Need for a **specific formulation** and dosage form per pediatric subsets/age groups

- Potential limitations to **excipients** and their exposure levels
- **Acceptability of dosage form** (e.g. size of tablet/ volume of administration) and **palatability** (might need taste masking)
- **Precision of dose delivery** and/or dose accuracy covering all indicated pediatric age ranges

Parenteral dosage forms – pediatric formulation strategy

Goal	• Define a standard approach for all parenteral categories (in early and late stage) • Introduce pediatric approach already in an early stage of formulation development • Ensure seamless transition from early phase development through to commercialization
Technology	• For parenteral products, pediatric indication uses the same drug product formulation as is used for the adult population with adjusted strength/injection volume.
Benefits	• Ensure pediatric patient access to new medicine • Be aligned with current HA requests • Enlarge patent protection for unauthorized and/or patented medicines • Reduce development in terms of timelines and costs

Parenteral dosage forms

Administration considerations for preterm and term newborn infants:

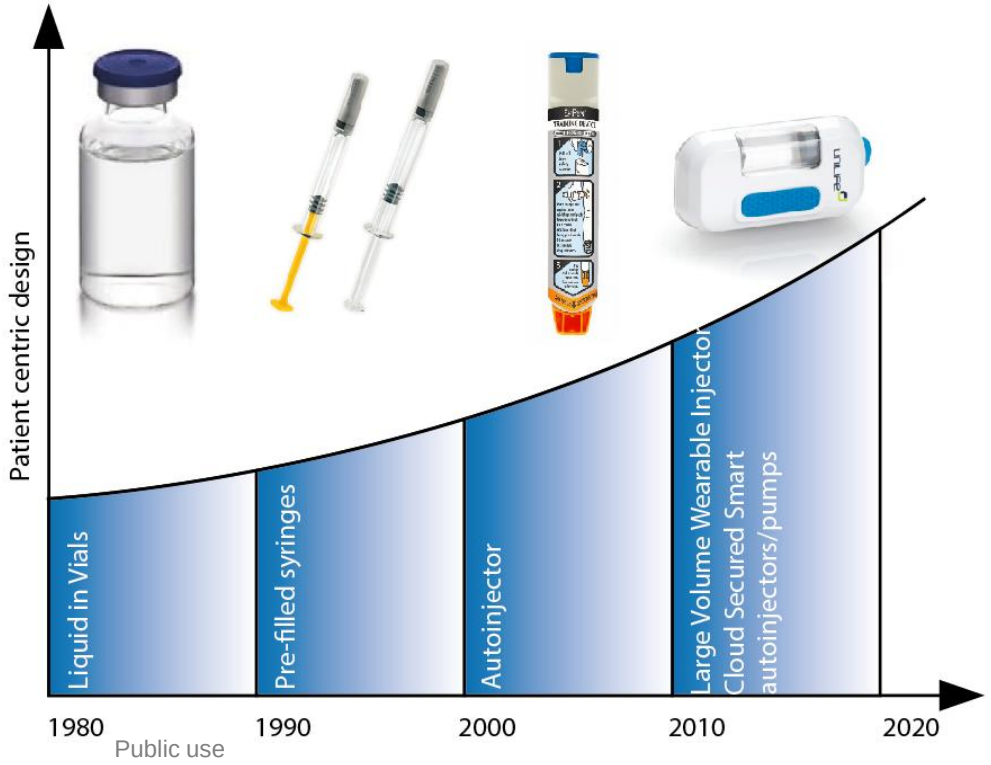
- Needle size (smaller outer diameter since less injection pain tolerance)
- Administration volume (limited for local administration, e.g. s.c. or i.m. (<1mL))
- Administration speed (less injection pain tolerance)
- Preferred option to develop needle-free system

Formulation considerations:

- Restriction of functional excipients/DS depending on age group with special consideration for neonats due to different metabolism
- Drug concentration vs. restricted local administration volumes
- Osmolality and pH (more physiologic since less injection pain tolerance)

→ WHO Guidelines for pediatric medicines

Device selection for parenteral dosage forms



Intended use aspects must be considered:

- HCP admistration in clinic vs patient / caregiver administration at home
- Pediatric self-administration vs caregiver administration
- Patient profile e.g. age, weight, dosing considerations, injection site
- User profile e.g. size, strength, cognitive ability, emotional maturity, motivation
- Training, supervision and support

Oral dosage forms – pediatric formulation strategy

Goal	• Define a standard approach for oral dosage forms • Introduce pediatric approach already in an early stage of formulation development • Ensure seamless transition from early phase development through to commercialization
Technology platforms	• Powder/granules for suspension/solution (neo-nates to 12 years) • Multi-particulates (6 months to 18 years) • Mini-tablets (> 12 months to 18 years) • Small standard tablets & capsules (6-18 years)
Benefits	• Existing PK/PD data can be used if adult blend / granule or formulation & dosage form are the basis for pediatric formulation.

Oral dosage forms – formulation considerations

- Restriction of functional excipients/DS depending on age group
- Taste assessment/taste masking
- Drug concentration vs. administration volumes

→ WHO Guidelines for pediatric medicines

The reconstitution model (versatile)

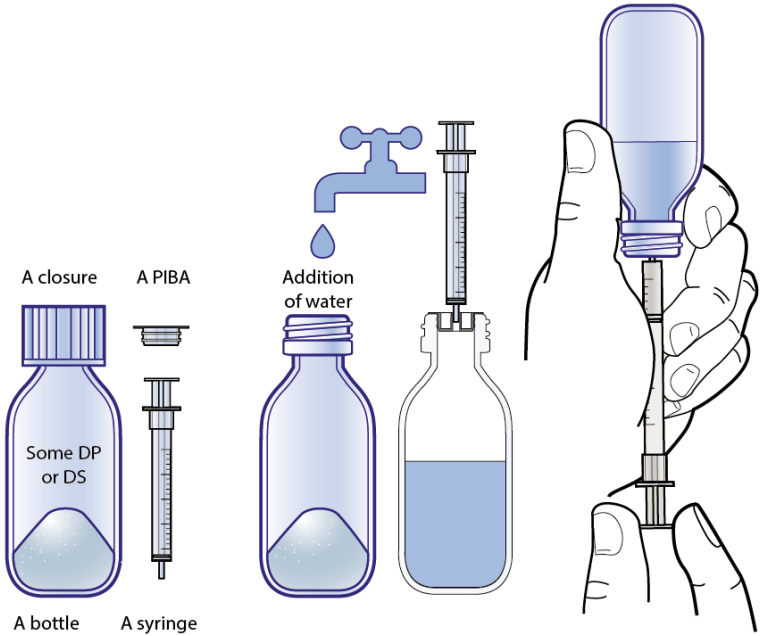
- Children population requires packaging adaptation. In most of the cases the patient is not the device user and the reconstitution, dosage and administration trigger a lot of stress to parents.

- Oral syringes are the most common devices to support liquid administration, they propose flexible dosing adaptation to a wide patient population using a unique DP bottle.

About oral administration

Powder in Bottle, stick packs

Liquid form provide dosage flexibility, beyond oral solution, reconstitution options using oral syringes are proposed.



Excipients

Excipients - general considerations

- «Children are not small adults»: PK/PD different, immature organs/metabolic pathways
- Excipient regulatory/safety assessment is **product specific** and depends on:
  - daily intake
  - target population (age, comorbidity, medical conditions due to existing treatments or disease)
  - country/market
  - indication
  - chronic or acute use
  - route of administration

Critical excipients

- Examples of critical excipients:
  - (Co-)solvents: Alcohols, Glycols (renal toxicity!)
  - Surfactants, Buffers, Antioxidants, fillers
  - Preservatives (parabens, sodium benzoate)
  - Taste masking agents (sweeteners, flavours, coatings)
  - Colorants

- Example of adverse events with Propylene Glycol:
  - Non mature metabolic pathway can lead to accumulation and potential adverse events in children below 4 years

Conclusions

Collaboration is key to overcome the hurdles in pediatric drug development

Any ideas/suggestions to:

- simplify the regulatory pathways with respect to regional requirements/label requirements e.g. as done with inner label for Gilenya
- overcome the commercial limitations inherent to a small market e.g. US kit can be marketed in Canada as well

Thank you

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