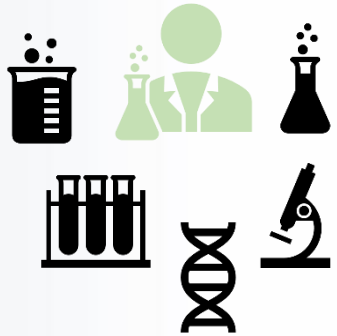
Introduction to Clinical Trial Methodology

Medicinal Product Formulation

Starting from a molecule …

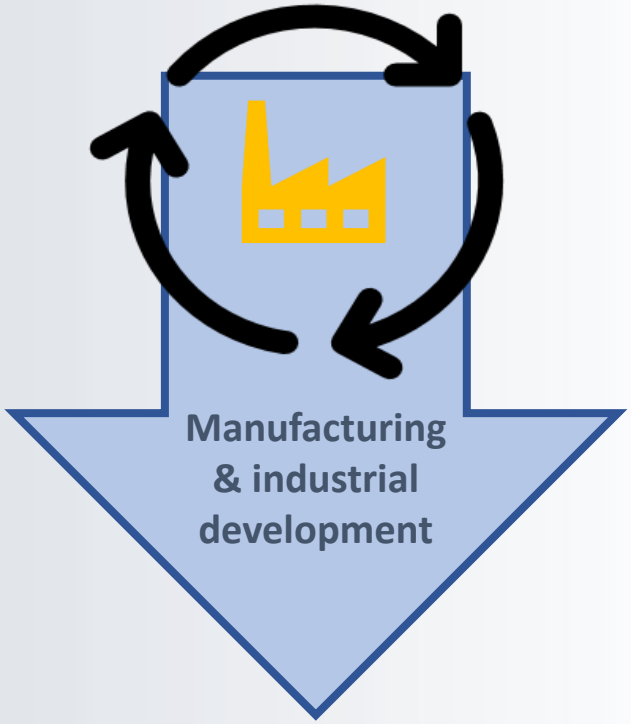
- A long road before clinical studies in humans
  - Research Lab (academy, industry)
  - **Characterization of the molecule, technical ability to produce, pre-clinical tests**



Phase 1 studies
volunteer participants, consented, tight monitoring, specialized clinical centers

Phase 2 and 3 studies.

Efficacy and safety in larger groups of patients



Formulation, form and study design

Development of pediatric age-appropriate dosage forms should be incorporated into the earliest stages of drug development.

- « Formulation » may be mis-leading:
  - Formulation = the composition of a particular dosage form of a medicine for paediatric use.
  - A paediatric preparation = a paediatric formulation in a particular strength

- The study design takes the product (or dosage) form into account
  - Route of administration (oral, IM, IV …), dose regimen,
  - Sample size and definition of treatment arms
    - Is there a need for a placebo controlled study ?
    - Is the comparator the same form as the tested drug ?
  - Needs for data points (adherence, PK over X hours, PD)

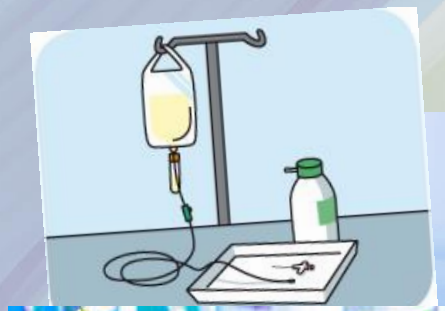
Different forms and different routes of administration.

Could you name some routes of administration ?

Please write your words

Different forms and different routes of administration.

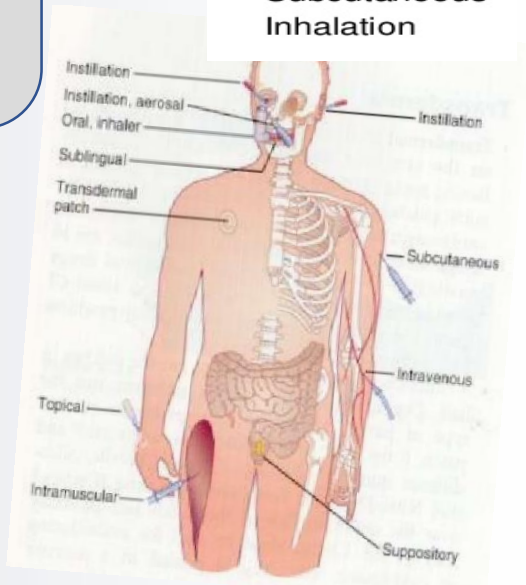
Similar to adults … but children are not only young adults !



Enteral
- Oral
- Rectal

Topical
- Otic
- Nasal
- Ophthalmic

Parenteral
- Intravascular
- Intramuscular
- Subcutaneous
- Inhalation



Example from study protocol

Study drug

- **Formulation:**
  - Study drug 300 mg: a 150 mg/mL drug solution in a pre-filled syringe to deliver 300 mg in a 2 mL injection.
  - Placebo matching study drug dosage: identical formulation to the active drug formulation without study drug, in a pre-filled syringe to deliver placebo in a 2 mL injection.
- **Route of administration:** Subcutaneously (SC) injection
- **Dose regimen:**
  - One injection of study drug 300 mg q4w for patients ≥15 to <30 kg at baseline

On top of standard of care medicines.

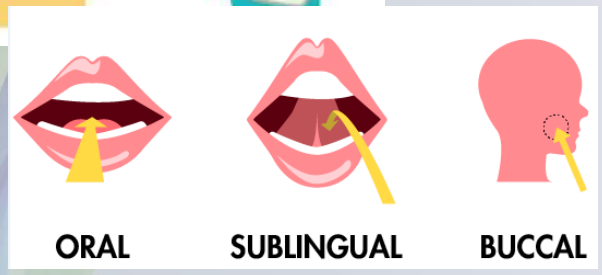
- **Formulation:** Metered dose inhaler or nebulizer solution
- Route(s) of **administration:** inhaled via spacer with face mask, or nebulizer solution by nebulizer
- **Dose regimen:** as needed

- **Formulation:** oral inhalation powder
- **Route(s) of administration:** via diskus
- **Dose regimen:** 50 µg inhaled powder twice daily

- **Formulation:** chewable tablet or sprinkles
- **Route(s) of administration:** oral
- **Dose regimen:** 4 mg once daily

Oral solid preparations

- **Oral solid single-unit dosage** is a stable and easy dosing approach.
- **Oral powders, granules:** greater dosing flexibility.



- Ability to swallow: age, condition, acceptability ...
- Administration through **feeding tubes may be needed for children who are unable to swallow** the available oral medicinal products
- Feasibility of bringing different dosage forms, formulations or preparations to the market (e.g. oral liquid as well as tablets).

Multiple oral solid forms

- **Tabs and Caps**
  - **Tablets:** The size and shape are fundamental to the ability of a child to swallow it. **Alternatives for dosing flexibility include break marks, dispersing or crushing tablets, mixing with food or drinks.**
  - **"Mini-tablets":** the dose is achieved by the intake of one or several small tablets.
  - **Capsules** are usually intended to be taken intact. The acceptability of the capsule size and any associated risks should be considered as indicated for tablets. **Where appropriately justified, hard capsules may also be opened** and their contents taken as such.
- **Oral powders, granules**
  - May be given to children from birth provided they can be administered as a liquid preparation.
- **Oro-dispersible and chewable preparations**
  - Involve oral solid unit dosage forms that are not primarily intended to be swallowed intact.

Oral liquid forms

- Oral liquid dosage forms are normally considered acceptable **for children from full term birth and for pre-term neonates who are able to swallow and accept enteral feeding.**

- **The risks of incorrect or accidental under- or overdosing with the measuring device should be discussed;**
- **Impact of the volume of the dose** on the patient acceptability:
  - small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation allows for better taste masking.
- **Packaged with an appropriate measuring device, unless demonstrated that they are widely available;**
- **Preserved oral liquid preparations will generally be considered acceptable for children from birth provided that the preservatives (and any other excipients) can be considered safe**

Oral liquid forms (2)

- **Oral suspensions:**
  - Quality attributes include physico-chemical characteristics of the suspension: viscosity, foaming, air entrapment, sedimentation and sticking to the primary container and to the measuring device.
  - The risks of under- and overdosing to the child as a result of **inadequate shaking** should be discussed.

- **Oral drops:**
  - Will only be considered acceptable for paediatric medicines containing **active substances with a wide therapeutic window**.
- **Effervescent, soluble and dispersible preparations,**
  - The suitability of effervescent preparations for use in children **may be restricted by the relatively large volume of liquid needed for dissolution** and the high electrolyte content. The potential risks when administered without prior dispersion or dissolution should be considered.

Special Oral administration

- **Administration through feeding tubes,**
  - Oral medicinal products for patients who are tube fed due to their condition or age-related limitations e.g. pre-term neonates, **unable to swallow but able to receive enteral feeds**.
  - The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be considered during pharmaceutical development.

- **Oro-mucosal preparations,**
  - Their correct use and acceptability will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time (eg mouthwashes or dental gels)

Parenteral administration

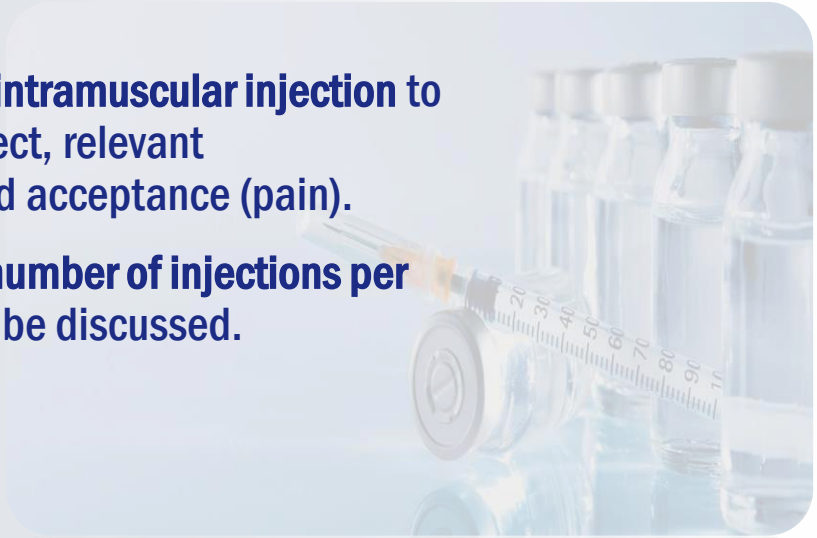
Most commonly used route of administration for active substances for children who are seriously ill and for clinically unstable term and preterm neonates.

- **The route of intravenous administration (central or peripheral),** site of injection, the injection volumes, the rate of administration, and, if relevant, the needle thickness and needle length should be described and justified.
  - Where appropriate, **the use of micro-needles or needle free injectors** could be considered, especially for medicines requiring frequent or long treatment period.

- In cases where parenteral administration is required for children in out-patient settings, **it should be demonstrated that the parenteral preparation is suitable for administration by the child itself or its adult caregiver.** This is especially important in cases where administration may also be necessary in situations where a trained caregiver is not present.

Parenteral administration (2)

- **The choice of an intravenous, subcutaneous or intramuscular injection** to be justified in terms of the intended clinical effect, relevant characteristics of the active substance and child acceptance (pain).
- The age and weight of the child, the **maximum number of injections per day and the duration per treatment** should also be discussed.



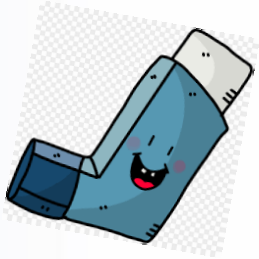
- **The volume should be justified according to the target age group(s).** Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml, however lower volumes are warranted for neonates and infants.
- **Neonates** may only accept very small volumes of medicines in order to avoid volume overload and to allow sufficient room for essential fluid nutrition.

Other routes of administration

- **Nasal preparations**

  - Normally considered suitable for children of all ages. Suitability of administration for **local and systemic treatment**, patient acceptability in relation to the palatability and sensation on product administration.

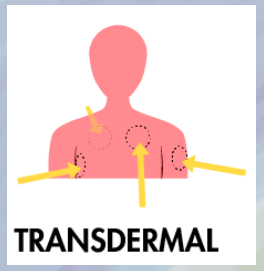
- **Oral inhalations:**
  - Pressurized metered dose inhalers may be applied to children from birth if in combination with a specific spacer system and face mask.



- **Rectal preparations:**
  - Suppositories and liquid rectal preparations should take into account the age and size of the child.

Other routes of administration (2)

- **Cutaneous and transdermal:** patches and medicated plasters
  - Developmental changes in **barrier function of the skin**, (eg thickness, hydration, changing ratio of Body Surface Area to weight) should be considered.
    - Developed for use **without need for cutting** to achieve a smaller dose.
    - Use of excipients known to sensitize the skin (e.g. some surfactants and adhesives) should be justified.
    - **Application sites** which cannot be easily reached by the child are preferred in order to prevent the child from removing the patch or medicated plaster.

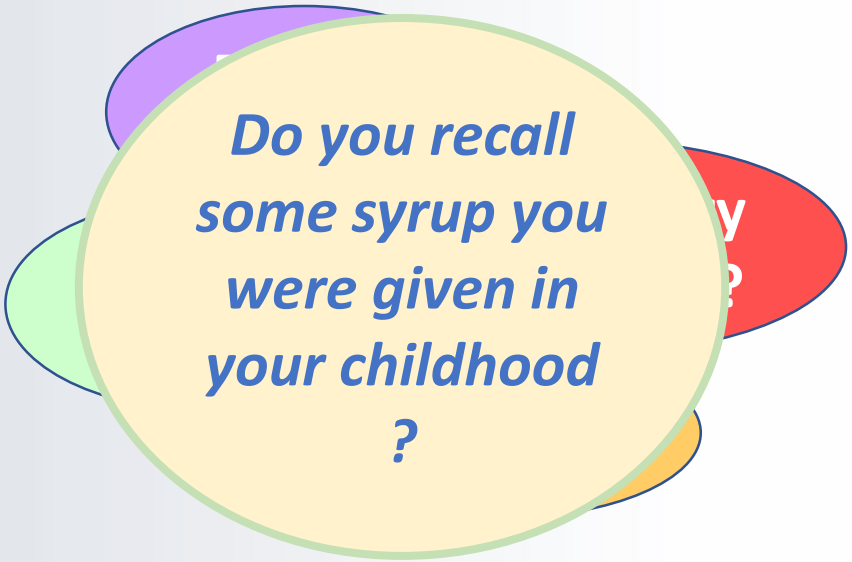


- **Eye and ear preparations**
  - In the absence of better alternatives, they should be considered acceptable dosage forms for children of all ages.
  - Preservative free containers should be considered, especially for neonates or if long term use is necessary.

Excipients in the formulation

- The intake of an excipient may result in a **different exposure in children to that in adults**, or in children of different ages.
- A **conservative approach** should be followed **in case of limited safety data** relevant to the use of an excipient in a specific age group.
- **Allergies** can arise in early childhood and children may be more easily sensitized than adults.

- **Colouring agents**
- **Flavours**
- **Preservatives**
- **Sugars and sweeteners**



Modification of the form

Every modification is to be verified with respect to its potential impact on the safety and efficacy of the medicinal product.

May include patient acceptability, dosing accuracy, compatibility with the proposed vehicle(s) (e.g. in-use stability studies) and the volume or amount to be used, a bioavailability or bioequivalence study comparing the modified and not modified preparation, and any safety risks for the person who will modify the preparation

- **Modified release preparations**
  - **Prolonged release formulations can significantly reduce the dosing frequency and can be beneficial for compliance** (at school or during the night). Should not be restricted to the oral route of administration.
  - In **oral modified-release preparations**, attention will go to the physiological conditions related to the age of the child, e.g. gastric pH and gastro-intestinal motility and their variability since these characteristics could have an impact on the drug absorption.

One step backward …

Is the medicine well designed, acceptable and usable ?

Appropriate Form	Route	Should take into account, justified	Acceptability
X		Age of children, Developmental physiology	Palatability, swallowability, Appearance, Pain and discomfort, Dose and regimen, Convenience of use (preparation, device, administration)
X		Condition (disease)	
X	X	Dosing including regimen (including duration of treatment)	
X	X	Environment (including child and caregiver's behavior), User aspect	
	X	Active substance	
	X	Administration (measuring, device)	
	X	Stability / preservation	

From adherence to behaviour

In paediatric population, acceptability has a significant impact on patient adherence, and consequently on efficacy and safety.

A drug may be efficient and safe but not accepted thus loosing its added therapeutic value ?!

- **Field of assessments and innovations**
  - Drug accountability, collection of reasons for non compliance …
  - Completion of diaries (electronic or paper)
  - Specific questionnaires (quality of life)
  - Behavioural studies: environment of children life (school, lifestyle)

Patient Reported Outcomes or quality of life questionnaires completed or answered by the **patient / Caregiver / Parents**