Small Patients – Big Challenges

PCSIG Webinar

01 Mar 2023 (Virtual)

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Overview

1. Why do we need to test drugs in children
2. Children – what ages? What's special about them?
3. Legislation and regulatory
4. Challenges – parents, enrollment, economic
5. DCT, "patient-centricity", blood sampling
6. Planning for tomorrow……

Why do we need pediatric studies

CHILDREN GET SICK (just like us) - THEY NEED MEDICATION too

2020 → 25% of global pop under 15 yrs (~2 billion)

2000s → <25% drugs labeled for pediatric use
~80% drugs prescribed as "off-label" use

2016 → <50% of new drugs labeled for pediatric use ("off-label")

Pharmacoepidemiol Drug Saf. 2018 Feb;27(2):161-167.

"**Off-label**" use → adult dose adjusted to child's weigh

Why do we need pediatric studies

Off-label use → **Children at risk**

Dose too high → adverse events (AEs)

Dose too low → no therapeutic effect

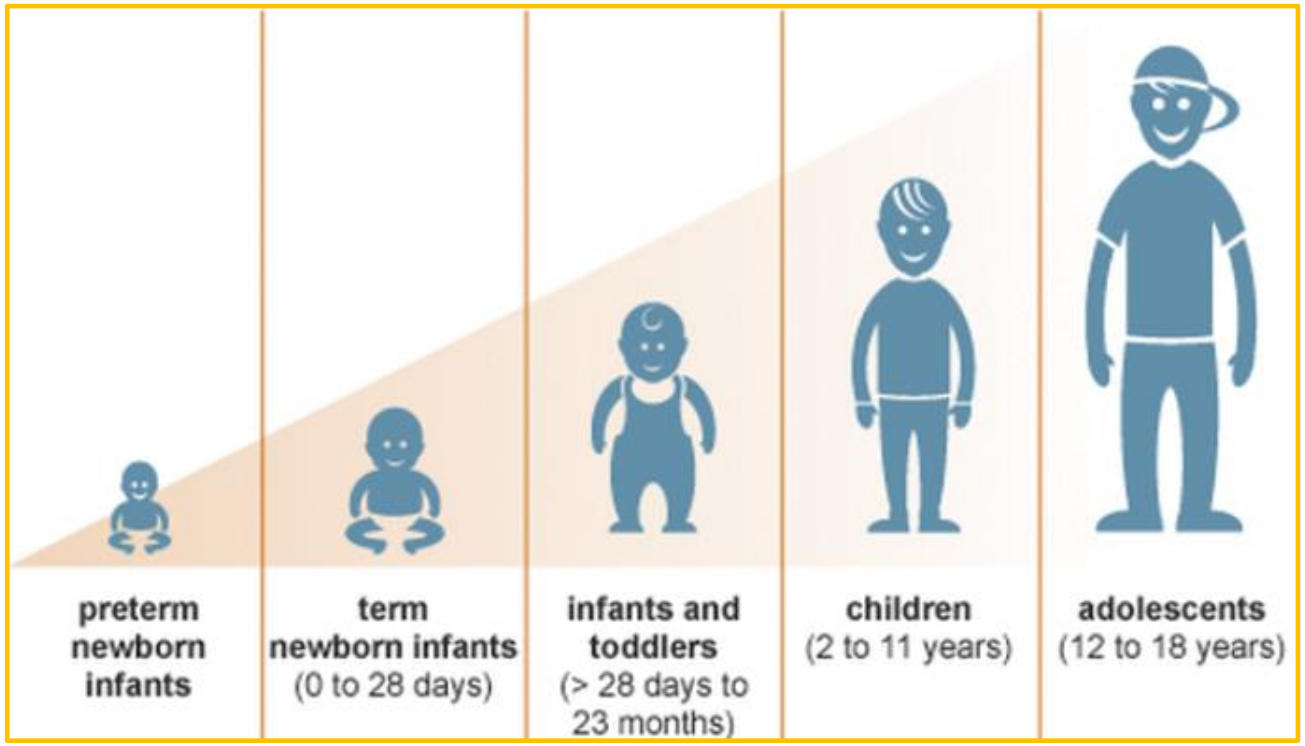
AEs are a common cause, among hospitalized children

Children ➔ “Therapeutic Orphans”

Children are not small adults

- Many changes occur in children as they grow and develop
- Affect ADME properties – especially drug clearance (biotransformation, elimination)
  - A: Physiological changes in GI track ➔ affect absorption of PO drugs
  - D: Changes in body water/fat, protein binding
  - M: Changes in drug metabolizing enzymes (Ph 1 & 2) - CYP3A4 increase gradually with age, ~50% of adult activity by one year of age.
  - E: Renal function – GFR reaches adult values by 8-12 mths.
- Different safety concerns
  - May need a different dose (higher or lower than adult)
  - Higher dose in pediatrics = flucanazole, daptomycin, micafungin
- Therefore, drugs used in children must be studied in children

Who are pedatric patients



ICH Guideline E11		FDA	
Preterm newborn infants		-	
Term newborn infants:	0 to 27 days	**Neonate:**	Birth to 1 month
Infants and toddlers:	28 days to 23 months	**Infant:**	1 month to 2 years
Children:	2 to 11 years	**Children:**	2 to 12 years
Adolescents:	12 to 16-18 years*	**Adolescent:**	12 to <16 years
* dependent on region			

Action: Legislation

1997: Best Pharmaceuticals for Children Act (**BPCA**)

2003: Pediatric Research Equity Act (**PREA**) ➔ reauthorized in 2007 and made permanent 2012

2016: RACE for Childrens Act – update of PREA – require pediatric oncology based on molecular target (and not indication)

BPCA ➔ financial incentive (VOLUNTARY) ***(pediatric act)***

PREA ➔ allows FDA to require pediatric studies (MANDATORY) ***(pediatric rule)***

FDA: A Pediatric Study Plan (PSP) is MANDATED.

Failure to include a PSP with submissions is a reason for Refusal to File.

EMA: An approved **Pediatric Investigation Plan (PIP)** is **required at the time of submission**.

Legislation

Since BPCA & PREA became law:

- ~50% of drugs approved for pediatric use (up from 25% in 2000)
- Over 300 pediatric label changes

2012 to Apr 2019:

48 products studied under BPCA

219 products studied under PREA

But..Pediatric trials are “difficult”

2016 Harvard Univ study:

- **550 pediatric studies** conducted between 2008-2011 (total of 77,500 children participated).
- more than **40%** never finished (terminated) or finished and never published
- questions the value of the trial and its participants

- Biggest reason for trial failure: **inability to enroll**

FDA 2018: FDA patient-focused drug development (PFDD) efforts - a systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. Includes gaining the perspective of youth and parents or caregivers.

EMA 2019: The European Paediatric Regulation (EC) No 1902/2006 as amended, includes a European Medical Agency (EMA) responsibility to consult the views and opinions of children and young people.

Challenges for pediatric trials

1. Trial design: tailor to the needs of children & their families:
2. Dose: easy dosage form, liquid, tablet, fast disintegrating, taste masked,
3. Enrollment and Consent (**emotions**):
   - Convincing a parent → experimental drug is "better"
   - Worry that child may get enrolled in placebo group
   - Fear of side effects → impacting child's growth & development
   - **Trial procedures, blood volumes**
   - Multiple Clinic visits (travel, out of state)
4. Financial:
   - Finding time and money
   - Single parents, multiple kids
   - Time off from work, school
   - Travel to clinic, transportation *(in midst of pandemic)*
   - Reimbursements

Challenges with blood/PK sampling

1. Complicated dosing schedules:
   - Timing of clinic visits *(to accommodate sampling times)*

2. Requires multiple clinic visits:
   - Spend entire day in the clinic *(to accommodate the sampling times)*

     Additional time for travel to and from the clinic

3. Requires larger blood volume samples:
   - Problematic in the youngest cohorts
   - 2 mL of blood per PK time point (6-10 timepoints?).
   - **This is in addition to all other standard safety draws**.

Hinder recruitment

Reason for drop-out

It's time to stop the bleeding!!!

Blood Volume Limits: blood loss should not exceed 3% of total blood volume over four weeks
should not exceed 1% of total blood volume at any single time

	Whole blood volume (mL/kg)	Mean body weight (kg)	Whole blood volume (mL)	3% (mL)	1% (mL)
Newborn, 1 day	83	3.45	287	8.6	2.9
Infant, 3 months	87	6.15	535	16.1	5.4
Infant, 6 months	86	7.85	675	20.3	6.7
Infant, 12 months	80	10.1	808	24.2	8.1
Children, 6 years	80	20.6	1648	49.4	16.5
Children, 10 years	75	32.6	2445	73.4	24.5
Adolescent, 15 years	71	54.3	3855	115.7	38.6

Adapted from: Zisowsky, Jochen et al. "Drug Development for Pediatric Populations: Regulatory Aspects." *Pharmaceutics* vol. 2,4 364-388. 29 Nov. 2010

Typical Blood Test MINIMUM Vols:
- CBC 0.5 mL (no repeat testing)
- CMP 0.5 mL (no repeat testing)

Additional tests:
- C-reactive protein (CRP)
- Liver panel
- 3-5 different disease related tests

- Additional blood draws at screening

- PK draws (1 mL x 8 draws = 8 mL)

Average Adult (180 lbs): ~ 5.7 L of blood

Risk due to blood draws

- Show symptoms or signs of anemia
- Drop in hemoglobin levels (i.e. below 8 g/dL)
  - Require volume replacement and/or iron supplementation
  - Require blood transfusion
- Higher risk for infants (body weight of less than 3 kg)
- Infections: multiple needle pricks or accessions to central lines/catheters

Additional caution: Children with conditions associated with inhibition of erythropoiesis

- Patients with bone marrow dysfunction, severe sepsis, anemia
- Patients undergoing chemotherapy

“NEEDs” from a pediatric at CHOP

- “simplified approaches that avoid the use of central lines (which can increase the risk of infection)”
- “minimise the blood sample volumes and the pain incurred during the sample collection”
- “where appropriate, sampling should be performed in outpatient locations that are more convenient to the patient”

Notes from discussion with Dr Athena Zuppa, CHOP, 12NOV2018

Focus on the PATIENT

Need to design trials with the patient at the center……

How do we do that?

We need a partnership with the patients & parents

- Ask the patients (& parents) for their input
- Involve them in study design
- Accommodate their needs (parents/caregivers)
- Patient Convenience & Engagement

Ask the patient….

International Children's Advisory Network Fourth Annual Research & Advocacy Summit Edinburgh Scotland July 12, 2018

- 32 participants
- age range 10-22
- Europe (n=12) North America (n=17)
- Most are teens/youth with chronic health conditions

HOME SAMPLING Feed Back

- **Convenience**
  - No school hours missed
  - Fits my busy schedule
  - Time saving
  - Less travel
- Responsibility for your own care
- Smaller blood volume
- Easy, quick
- **Privacy:** people ask why I missed school

Wickremsinhe E, Short M, Talkington B, West L. Do-it-Yourself Blood Sampling for Pediatric Clinical Trials. Applied Clinical Trials, 2020: 29(3):20-25.

What Covid has done…

Techniques/technologies were available… but organizations were “slow” or hesitant to adopt

Accelerated and focused the need to “decentralize” (patient centric)

Ensure patient safety, continue on-going trials, initiate new trials

“Experienced” audience: All of us…… patients, caregivers, parents, guardians, you and me

Microsampling – slow uptake by industry

- It's not a panacea – "one size does not fit all"
- Disruptive technology – it's different to status quo, resistance to change time tested approaches, "gold standard"
- But CoVid studies – using home sampling (micro sampling)

Covid pushed patient-centric sampling over the hill…. It's all downhill now ☺

Microsampling – challenges

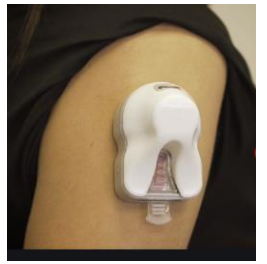
- Easy to use: to collect
- Generate data: equivalent to plasma
- Scalable: handle large number of samples
- Implementable globally: multiple clinical sites
- Implementable at home
- Compatible: current workflows, automation
- Savings (trial cost, healthcare cost)












What is blood collected/used for?

CBC & CMP
(central/local lab)

PK: drug conc
(BioA lab)

Other labs/panels
(central/local lab)

Standard Biomarkers
(central/special lab)

Disease markers
(central lab)

Special biomarkers
(BioA/special lab)

Diabetes - glucose
(home test)

Vacutainers….. 1947 by Joseph Kleiner
DBS….. 1960's by Dr Robert Guthrie

ICH
harmonisation for better health

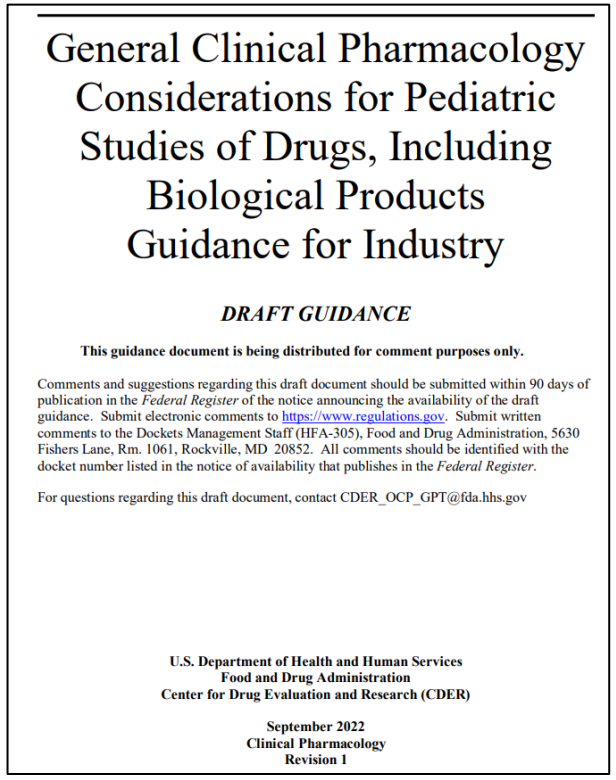
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Final version
Adopted on 18 August 2017



General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products
Guidance for Industry

DRAFT GUIDANCE

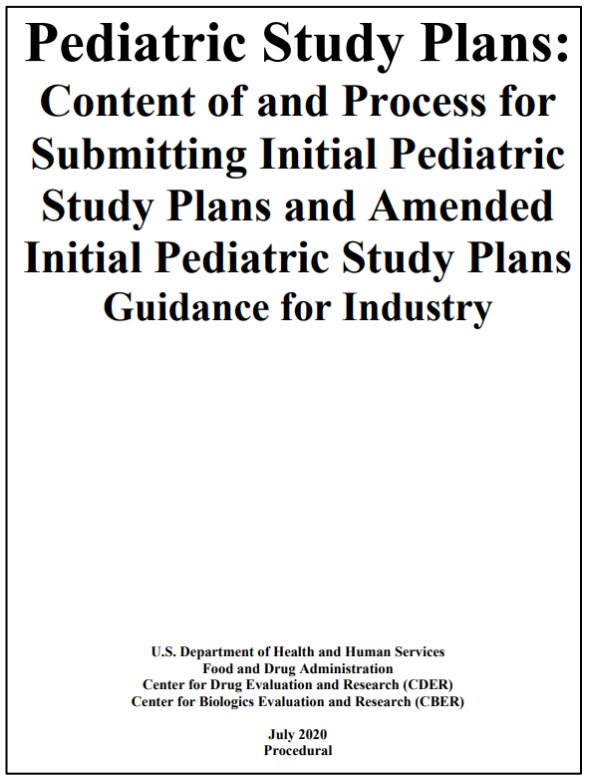
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact CDER_OCP_GPT@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

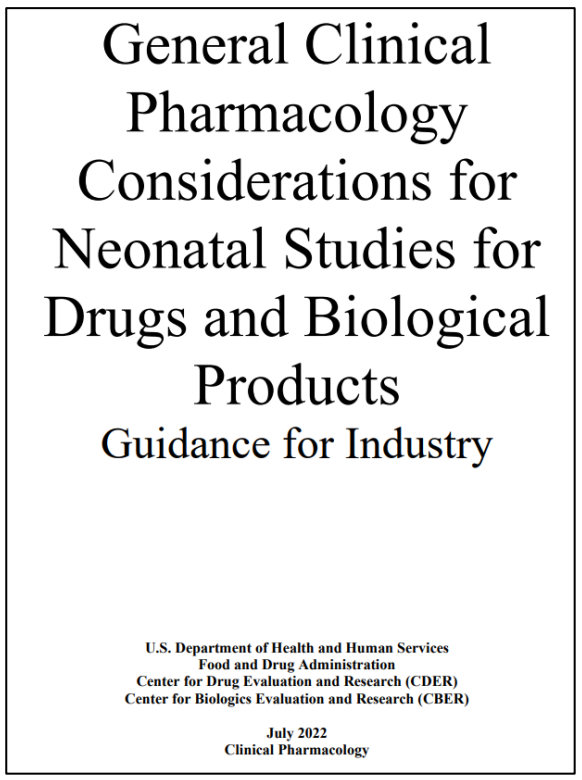
September 2022
Clinical Pharmacology
Revision 1



Pediatric Study Plans:
Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2020
Procedural



General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2022
Clinical Pharmacology

We must plan for tomorrow …

- The children's needs are urgent and real (and global)
- Need to take bold steps
- What's keeping you from adopting pediatric patient friendly techniques and technologies?

PCSIG SWAT TEAM?

Thank You

Happy to answer your questions

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