Ethical Considerations for Clinical Investigations in Children to Assess the Impact of Placental Transfer of Drugs and Biologics with Immunosuppressive Properties

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FDA Public Workshop: Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products

Disclosure

- The views presented here are personal and do not necessarily reflect the views of the U.S. Food and Drug Administration
- I have no financial conflicts of interest to disclose

Purpose

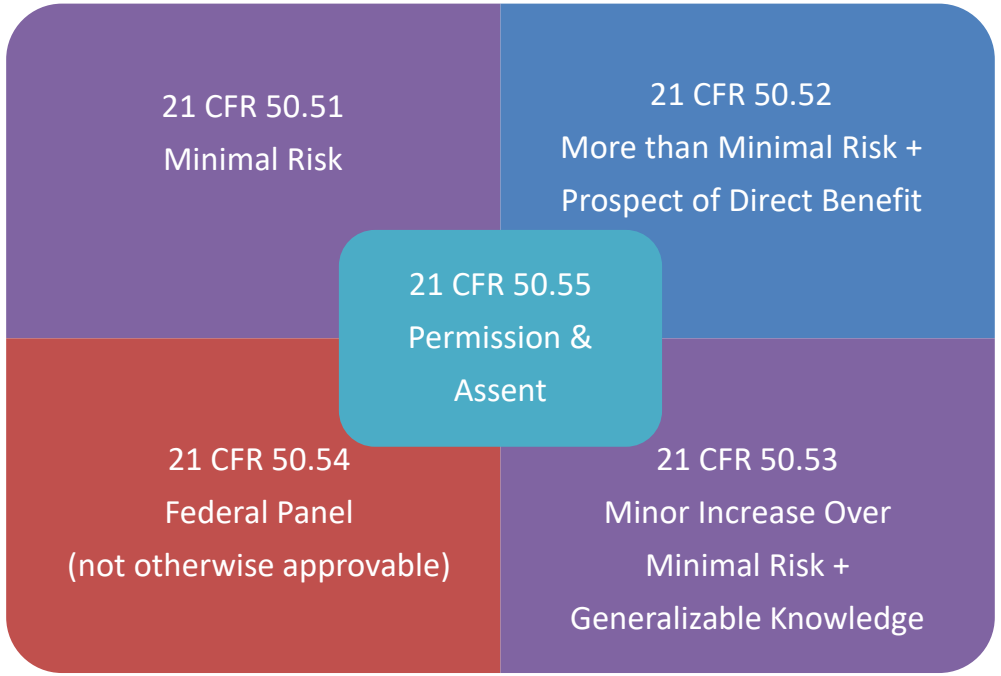
- Provide an overview of FDA's human subject protection regulations that govern clinical investigations involving children, the **Additional Safeguards for Children in Clinical Investigations (21 CFR 50, subpart D)**
- Discuss considerations when interpreting 21 CFR 50, subpart D for pediatric clinical investigations to assess the impact of placental transfer of a drug or biologic with immunosuppressive properties, and ways to minimize risk and burden

Ethical Analysis

- **Ethical Imperative.** Understanding the impact of in utero exposure to immunosuppressive drugs and biologics is imperative to guide health care decisions about use of such products during pregnancy and to inform safety monitoring and vaccination schedules for the infant
- **Scientific Necessity.** The scientific necessity of conducting a study involving children should be considered and any opportunities to answer the scientific question(s) outside of a clinical study in children should be evaluated (e.g., through use of animal models, in vitro studies, pharmacokinetic [PK]/pharmacodynamic [PD] or in silico modeling and simulation)
- **Regulatory Safeguards.** If a clinical investigation involving the infant is necessary, because of in utero exposure to a drug or biologic, then the infant becomes a research subject and, as such, the Additional Safeguards for Children Involved in Clinical Investigations (21 CFR 50, subpart D) apply

Additional Safeguards for Children in Clinical Investigations

21 CFR 50, subpart D



- Research involving children either
  - must be restricted to "**minimal**" risk or a "**minor increase over minimal risk**" absent a potential for direct benefit to the enrolled child [21 CFR 50.51/21 CFR 50.53], *OR*
  - must present risks that are justified by the "**prospect of direct benefit**" to the child; the balance of which is at least as favorable as any available alternatives [21 CFR 50.52]
- **Permission** by parents or guardians and **assent** by children must be solicited [21 CFR 50.55]

Minimal Risk

Minimal Risk (21 CFR 50.51)		
Definition	Interpretation	Examples
Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests	The minimal risk standard should be interpreted as those risks encountered in the daily life of normal, average, healthy, children living in safe environments and indexed to the experiences of children of the same age and developmental stage as the subject population	Single blood draw, physical exam, chest x-ray, surveys

Minor Increase Over Minimal Risk

Minor Increase Over Minimal Risk (21 CFR 50.53)		
Definition	Interpretation	Examples
Minor increase over minimal risk should be understood to mean a slight increase over minimal risk that poses no significant threat to the child's overall health or well-being	The intervention or procedure must be likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition	Urine collection via a catheter, bone marrow aspirate with topical pain relief, a single lumbar puncture, a single dose of an investigational drug with adequate safety information

Parent/Child Perspectives are Important

- A **prospective, longitudinal, observational study** involving blood sample collection* and collection of clinical data in infants/children exposed in utero to an immunosuppressive drug or biologic would likely be approvable under 21 CFR 50.51 as minimal risk (assuming acceptable protocol-specified blood sampling limits)
  - An infant exposed in utero to a drug or biological product with immunosuppressive properties is at-risk for a disorder or condition (i.e., immunosuppression and the potential complications of immunosuppression), so these infants could be exposed to a **minor increase over minimal risk** if the research is likely to yield generalizable knowledge of vital importance for understanding the effects of placental transfer of a drug or biologic on infants exposed in utero (21 CFR 50.53)
  - A healthy (i.e., unexposed) infant (e.g., as part of a comparator group) can only be exposed to **minimal risk** (21 CFR 50.51)

*When feasible, individual bloodwork results should be available to inform the parent(s) and the infant's pediatrician about the extent of infant exposure to the drug or biologic

Minimize Risk and Burden

- Blood sample collection for research studies should be **limited to the least possible volume and frequency** required for testing to minimize the risk and burden to the child
  - Consider strategies to limit the necessary blood volume and frequency of sampling, such as:
    - **PK modeling and simulation** to help inform decisions about optimal sampling times
    - **Sparse sampling** (i.e., collecting limited samples from an individual subject and pooling data from multiple subjects)
    - **Micro-volume drug assays** that allow small sample volumes
    - **Dried blood spots** (collection of blood on blotting paper typically requires low blood volumes and may be less invasive)
    - **Scavenged samples** (i.e., samples obtained from surplus blood drawn as part of routine clinical care)

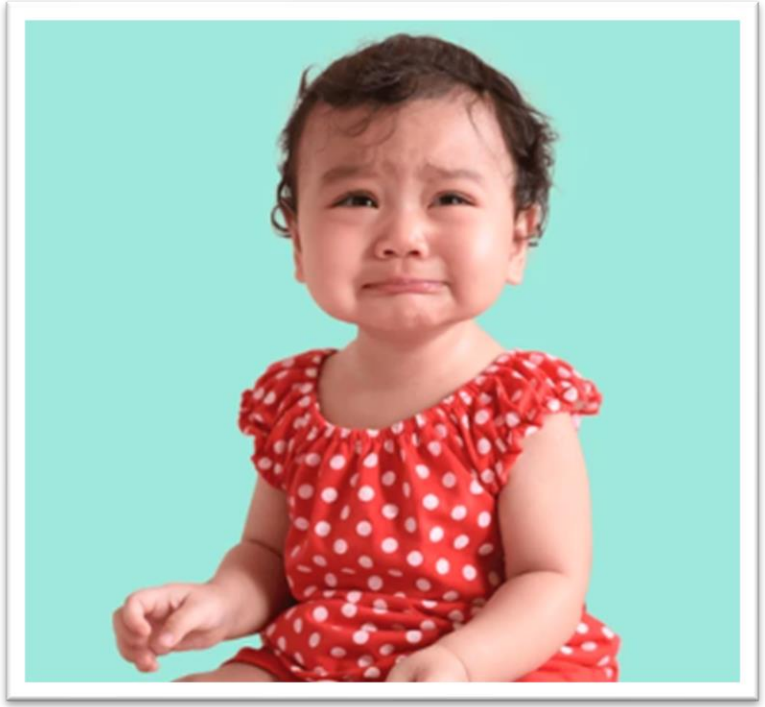
Blood Sample Volume Limits

- Existing guidelines for blood sample volume limits range from **1 to 5% of total blood volume within 24 hours** and **up to 10% of total blood volume over 8 weeks**, and are considered consistent with the limited evidence available on “minimal risk” to children
  - Need to account for blood drawn for research purposes and blood drawn as part of routine clinical care
  - Lower/more restrictive blood volume limits may be necessary for pediatric patients who are critically ill or have other disorders or conditions that may impact their hematologic parameters, or if they will be exposed to an investigational product that is associated with a risk of anemia
    - For example, for a neonate born prematurely, absolute blood volume is low and red blood cells may be replenished more slowly, potentially requiring smaller sample volumes and less frequent sampling

Howie SRC, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bulletin of the World Health Organization, 89:45-53.
Veal GJ, 2014, Blood Volumes in Pediatric Clinical Trials: A Review of Current Regulations and Guidance for Research Studies, Clin. Invest, 4:1005-1011

Limiting Burden

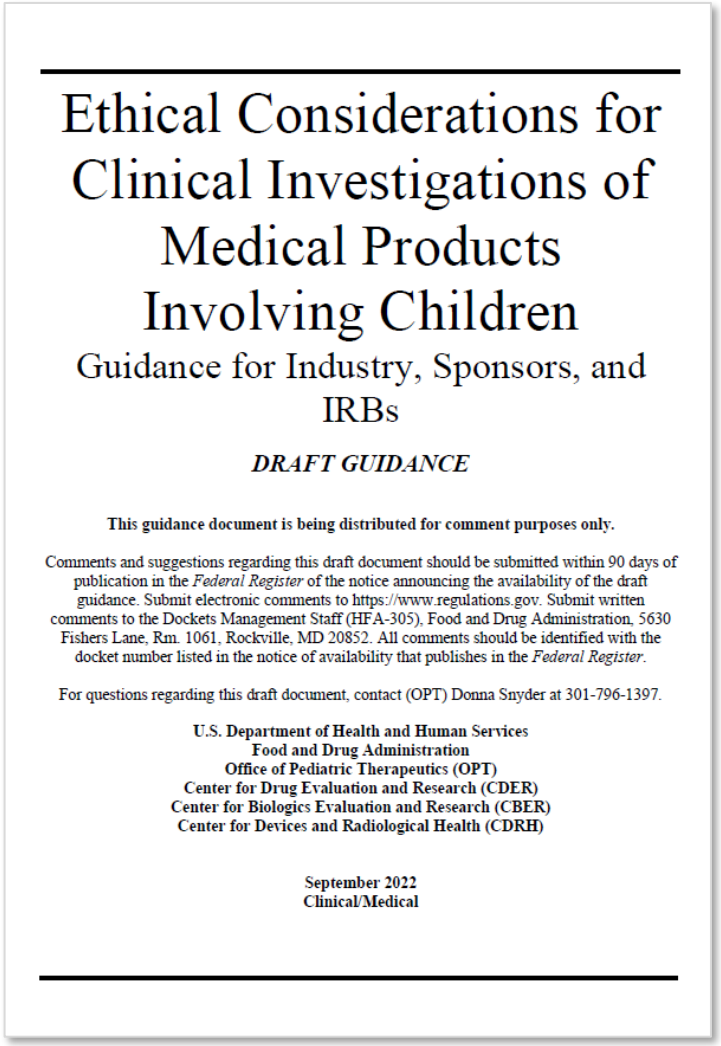
- Well-trained phlebotomist experienced working with children and using techniques to optimize venipuncture success (e.g., illuminators)
- Limit discomfort and pain (e.g., employ a child life specialist, perform blood draws in a comfortable room, use indwelling intravascular catheters)
- Time blood draws for research with those needed in clinical care (**"opportunistic" sampling**) to reduce the number of needle sticks or draws from an indwelling catheter



Summary

- **Ethical Imperative.** Understanding the impact of in utero exposure to immunosuppressive drugs and biologics is imperative to guide health care decisions about use of such products during pregnancy and to inform safety monitoring and vaccination schedules for the infant
- **"Low" Risk Studies.** A prospective, longitudinal, observational study involving blood sample collection and collection of clinical data in infants/children exposed in utero to an immunosuppressive drug or biologic would likely be approvable under 21 CFR 50.51 as **minimal risk** (assuming acceptable protocol-specified blood sampling limits) or could be approvable under 21 CFR 50.53 as a **minor increase over minimal risk**
- **Minimize Risks.** Study risks and burdens (e.g., related to blood sample collection) require careful consideration and need to be minimized

Resources



Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Guidance for Industry, Sponsors, and IRBs

DRAFT GUIDANCE

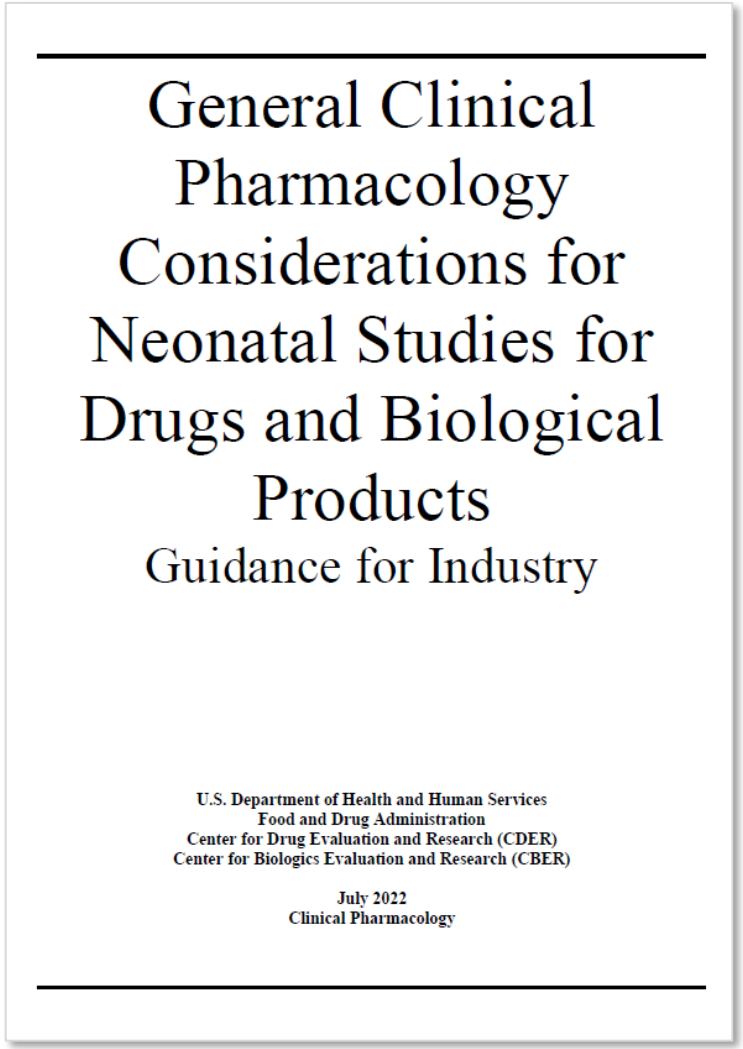
This guidance document is being distributed for comment purposes only.

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 (OPT) Donna Snyder at 301-796-1397.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2022
Clinical/Medical

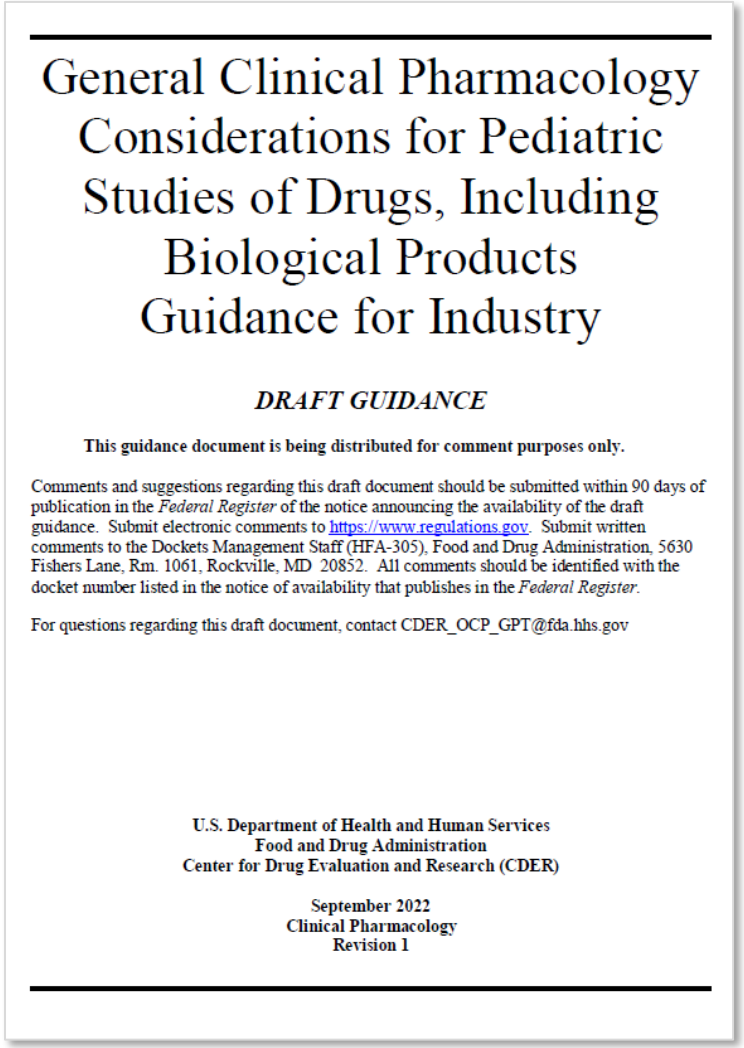


General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products

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



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

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Revision 1

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Thank you for your time and for all you do for children