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IRB Reviews, Pediatric Research Regulations, And Updates to Scientific Considerations (#1)

FDA has issued two new draft guidances, both of which address numerous ethical and regulatory aspects of research involving children as the participants.

We present here what we consider to be the key highlights that will likely impact IRBs that review such research.

However, the two guidances (together totalling over fifty pages) obviously contain more details than we can present in a single HRR.

Therefore, we will describe additional highlights in future HRRs as time and IRB-related events permit.

We note that neither guidance explicitly describes recommended IRB actions for pediatric research, beyond a few practical resource citations which we will quote for IRBs' use.

Instead, dozens of references to "safety and efficacy" requirements abound throughout the two guidances.

"Safety and Efficacy" Are Basic IRB Topics

As IRBs know well, subject safety and study efficacy are both integral research requirements that justify human subject participation in any experiment.

This is particularly true of vulnerable populations such as children. Therefore, we will describe the guidances' proposals that affect "safety and efficacy."

Both guidances were published in the May 18 FEDERAL REGISTER. The first guidance is titled "Pediatric Drug Development: Regulatory Considerations -- Complying With the Pediatric Research Equity Act [PREA] and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act [BPCA]."

> "This draft guidance, when finalized, is intended to provide recommendations to [the drug research] industry on complying with the pediatric study requirements under the Pediatric Research Equity Act (PREA), and to describe the process for qualifying for pediatric exclusivity and the protections that pediatric exclusivity offers under the Best Pharmaceuticals for Children Act (BPCA).

Combining discussion of PREA and the BPCA together in regulatory guidance em-

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, or missing words. However, we will on occasion insert words or edit text and/or formating in brackets [ ] to make the material easier to read.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued in subsequent issues are marked at the end of the article with **{TBC}**.

ALSO IN THIS ISSUE

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phasizes the sponsor's need to consider both laws when developing pediatric drugs and biological products" (88 Fed. Reg. 31764, May 18).

The second guidance is titled "Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations."

"This draft guidance addresses selected clinical, scientific, and ethical issues involved in developing drugs, including biological products, for pediatric use when such drug products are subject to the Pediatric Research Equity Act (PREA) and/or the Best Pharmaceuticals for Children Act (BPCA)" (88 Fed. Reg. 31766, May 18).

Opportunity to Give Feedback to FDA

There is still time to influence the recommendations contained in these guidances. Comments for both are being accepted until July 17. More information on both guidances is available from Rosemary Addy of the FDA's CDER at 301-796-2200, or send email to pedsdrugs@fda.gov.

We begin with the following excerpt from the second guidance listed above (see "IV-A. Considerations Regarding Data in Pediatric Populations," subsection "4. Safety Information."

Safety Data Needed from Pediatric Studies

"Safety information from adult human studies and animal models may provide preliminary information regarding the expected safety profile of a drug in pediatric populations, but safety information from administration of the drug to children is almost always needed to establish safety in the pediatric population.

Adverse effects of a drug in pediatric populations may not be predictable based on the adult experience, particularly adverse effects related to behavior, cognition, or growth. Nonetheless, pediatric safety information that is available from different formulations of a drug, or from other closely related drugs within the same class, as appropriate, should be reviewed" (guidance, May, revision 1, p. 12; on the Web at https://www.fda.gov/media/168202/download).

The more legalistic approach of the first guidance described above sets the regulatory stage with its definition of the human subject group affected by the new recommendations, as follows.

Regulatory Definition Sets Study Parameters

"For purposes of pediatric drug development, FDA generally considers the pediatric population to include those patients from birth to younger than 17 years (i.e., birth through 16 years of age), and to include the subpopulation age groups of neonates, infants, children, and adolescents.

Consistent with International Council for Harmonisation (ICH) guidelines, FDA considers these subpopulation age groups to be divided as follows:

- Neonates: birth through 27 days (corrected gestational age)
- Infants: 28 days to 23 months
- Children: 2 years to 11 years
- Adolescents: 12 years to younger than 17 years

The BPCA defines pediatric studies to mean at least one clinical investigation in 'pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary [of Health and Human Services] may include preclinical studies.'

For purposes of satisfying the requirements of PREA, assessments of safety and effectiveness [or 'efficacy'] must be performed in all relevant pediatric age groups, unless the assessments are waived or deferred.

The BPCA and PREA are designed to work together to encourage the development of data to inform the safe and effective use of drugs in pediatric populations. Under PREA, pediatric assessments are required for drug products with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless the drug is for an indication for which orphan designation has been granted" (guidance, May, Revision 1, p. 3 of 39; on the Web at https://www.fda.gov/media/168201/download). © **{TBC}**