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2 May 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 03D-0001 (Federal Register; February 3, 2003, Volume 68, Number 22, Pages 5301-5302) "Draft Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products"

Dear Sir/Madam:

On behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA), I would like to thank the Food and Drug Administration (FDA) for seeking comment on its draft "Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products" (the draft Guidance). PhRMA is a trade association representing the research-based pharmaceutical industry in the United States. PhRMA member companies invested an estimated $32 billion in 2002 in discovering and developing new medicines, and have more than 1000 drugs and biologics in development.

PhRMA is pleased to provide comment on the draft Guidance. In particular, PhRMA values the flexibility inherent in this draft Guidance permitting Sponsors to exercise scientific judgment in the application and design of nonclinical studies to support pediatric drugs. FDA properly recognizes that hazard identification and characterization for pediatric patients may derive from varied sources of data. These include adult human patients, existing pediatric data, standard toxicity tests, juvenile toxicity tests, or combinations thereof. Further, PhRMA recognizes that it may be ethically or logistically problematic to collect important safety information from pediatric clinical trials; under some of these circumstances, juvenile studies could provide important information. Considered together, PhRMA encourages FDA to engage in dialogue with Sponsors to determine, for specific products, whether nonclinical juvenile toxicity testing is needed. PhRMA also emphasizes that the decision to conduct these tests should be made case-by-case, after evaluation of available data.

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Overall impressions relate to several topics (A through H, below). Specific comments follow.

A) The stated objective of this document is "to provide guidance on the role and timing of animal studies in the safety evaluation of therapeutics" intended for pediatric patients. While the document appears to have raised all relevant "points to consider," it is difficult to foresee situations in which drugs for pediatric indications will *not* require nonclinical juvenile toxicity testing. PhRMA encourages FDA to expand the discussion found in Section III D2 ("Use of Available Data") to describe circumstances when a juvenile animal study would not be needed. The draft Guidance is less clear in providing specific information on FDA's expectations for designs of juvenile animal studies.

Moreover, PhRMA infers from the draft Guidance that FDA envisions nonclinical studies whenever target organ toxicity affects systems undergoing postnatal maturation (although whether this target organ information is derived from clinical information in adults, or standard toxicity test batteries, is not specified). PhRMA opinions regarding the role of toxicity data derived from peri- and postnatal development studies, to drive or rule out further nonclinical testing, are recounted below (E).

Finally, PhRMA encourages inclusion of references to the International Conference on Harmonisation (ICH) Guidances M3[1] and E11[2]. These guidances explicitly state that the most relevant data for pediatric use will generally be derived from clinical experience in adult humans (assuming that repeat-dose toxicity tests, reproductive toxicology studies and genetic toxicity studies have been completed).

B) PhRMA infers from this draft Guidance that FDA presumes that studies from juvenile animals may be more predictive of the pediatric clinical experience than the current battery of nonclinical testing, adult clinical experience, or limited (e.g. off-label) pediatric use. There are currently few data to support this hypothesis. It will be important to validate prospectively the utility of nonclinical juvenile data, and to compare their predictivity with those of adult human and nonclinical data from mature animals. PhRMA encourages FDA's efforts in this regard. Particularly, periodic publication of FDA statistics concerning concordance, false positive and false negative signals will represent an important scientific contribution. Also, PhRMA is interested in FDA's experience with the predictivity of nonclinical studies designed as general screens.

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[1] Guidance for Industry, M3: Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals. International Conference on Harmonization, 1997.

[2] Guidance for Industry, E11: Clinical investigation of medicinal products in the pediatric population. International Conference on Harmonization, 2000.

In the interim, the decision to conduct nonclinical juvenile studies should be made on a case-by-case basis, following significant dialogue between FDA and Sponsors regarding the need for and design of such studies. Further, as with all safety evaluations, risk management decisions should be based on weight of evidence, after consideration of all relevant data.

C) PhRMA infers from the draft Guidance that FDA presumes that the entire interval of postnatal maturation for an organ system constitutes a "critical developmental period." At present, available literature documents age-related intervals of postnatal maturation in several species, including human. However, there are currently no data to document that these intervals represent "critical" periods, with their connotations of enhanced susceptibility to toxic response. Prospective identification of true "critical" developmental periods in animal models, accompanied by the validation of the predictivity of this information for the pediatric clinical experience, will be important.

PhRMA encourages FDA to state clearly and consistently that animal experimental model selection must be based on the pharmacology and toxicology of target organs, with precise consideration of their postnatal development in the context of intended ages of pediatric use. This can only be accomplished when the need for and design of nonclinical juvenile studies is determined case-by-case. Secondarily, PhRMA supports dialogue between FDA and Sponsors concerning the relative merits of adult human and nonclinical data to identify target organs for evaluation in juvenile animals. Finally, PhRMA suggests that the tables in Section VI be revised for clarity; and augmented with information from available reviews representing more extensive literature evaluations. One example is the series of articles commissioned by International Life Sciences Institute (ILSI)- Health and Environmental Sciences Institute (HESI) summarizing the literature of comparative postnatal maturations for the respiratory, renal, and male and female reproductive systems; these will be published in the journal *Birth Defects Research* before the draft Guidance is finalized. Additional articles in this series, describing comparative postnatal maturations of the central nervous and cardiovascular systems, are underway. Alternatively, PhRMA would be pleased to support FDA by identifying scientific experts that could assist in this endeavor.

D) PhRMA infers from the draft Guidance that FDA presumes that periods of "rapid growth and development" represent intervals of enhanced susceptibility to toxic response. At present, data documenting the validity of this assumption are lacking. It is equally plausible that periods of rapid growth afford enhanced resilience, or that catch-up growth may be observed during subsequent periods. Prospective validation of this hypothesis will be important.

E) PhRMA further encourages FDA to provide specific guidance regarding the use of existing toxicology data in assessing the need for nonclinical juvenile toxicity testing. For example, with documentation of pup exposure and evaluation of existing endpoints, it may be possible to determine whether direct neonatal dosing is necessary; and/or whether to conduct further studies in juvenile animals. Thus, in the case of a drug with a long half-life that is placentally-transferred and secreted into milk, it is plausible that existing pre- and -postnatal data found in other safety studies would support clinical studies in term neonates and infants.

F) When juvenile studies are conducted, and given the pivotal role of toxicokinetic data in study design and interpretation, PhRMA would like to see additional emphasis placed on careful assessment of juvenile exposure to parent drug and active metabolites. Particularly, kinetic differences may account for important age-related toxicities. Toxicokinetic information will be critical for pediatric risk assessment.

G) The issue of labeling is one of regulation, and is probably best deleted from a document intended to give guidance.

That said, the discussion dealing with the application of nonclinical data to human risk management is reminiscent of earlier discussions surrounding drug use in pregnancy. PhRMA trusts that lessons learned from exchanges on pregnancy labeling, particularly the desirability of integrating clinical and nonclinical data, will be applied to the pediatric setting. Specifically, PhRMA advocates that, where appropriate, clinical safety data supercede nonclinical findings. The inclusion of adverse events from nonclinical juvenile studies in product labeling, when not replicated in clinical trials of comparable length, is discouraged. Until the predictive utility of juvenile studies has been validated, this information could discourage medically-justified pediatric treatment. Further, the section regarding the use of nonclinical information to preclude product approval should be amended to indicate that this decision must be driven by thorough risk-benefit considerations.

H) Additional clarification regarding excipient testing is sought, consistent with levels defined in ICH Q3B.[3] Animal studies are often conducted with formulations other than the clinical formulation, provided that excipients in the clinical formulation were previously characterized. PhRMA anticipates that excipient testing would be informative only when such substances are novel.

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[1] Guidance for Industry, Q3B: Impurities in new drug products. International Conference on Harmonization, 1997

Finally, the draft Guidance does not address testing of active metabolites or enantiomers.

Specific Comments

Quotations from the draft Guidance are underlined.

Section II.A.

Lines 58-85. Some therapeutics used in pediatric patients have shown different safety profiles when used in adult patients ... While some age-dependent effects can be largely predicted by knowledge of the changes in drug metabolic pathways during development, others cannot be predicted.

PhRMA recommends that this section be deleted. It is unclear from the examples that nonclinical juvenile toxicity tests would have predicted the differences between pediatric and adult clinical toxicities. Alternatively, FDA is encouraged to share examples of adverse clinical events that were predicted *a priori* by juvenile animal studies.

Section II.B.

Lines 91-92. Standard toxicology studies using adult animals, or safety information from adult humans, cannot adequately predict drug effects in immature systems.

There are presently insufficient data to evaluate the validity of this statement. Prospective validation of the predictivity of all three approaches (standard toxicology tests, adult human experience and nonclinical juvenile toxicity tests) will be important (cf. Section B, above).

Lines 94-103. The structural and functional characteristics of many organ systems differ significantly between children and adults as a result of the growth and development that take place during maturation. Examples of these organ systems include (1) the brain ... and (5) the reproductive system, where maturation is not completed until adolescence.

Gastrointestinal-hepatobiliary function should be incorporated in the list of organ systems that undergo significant postnatal maturation. These systems have direct consequences for bioavailability and clearance, including biotransformation (cf. Section C, above, regarding appended Tables).

Lines 103-4. It is thought that pediatric organ systems at highest risk for drug toxicity are those that undergo significant postnatal development.

This statement is intuitively appealing, albeit without rigorous underlying support. Presently, anecdotal evidence supports both increased and reduced risk. It may be that immaturity of function at *any* stage of development better predicts a novel pediatric experience than the dynamics of maturation, *per se*. It will be important to determine both factors that increase *and* decrease risk (cf. section D, above).

Lines 107-10. Because some juvenile animals (e.g., rodents, rabbits, dogs, nonhuman primates) in general exhibit developmental characteristics similar to those of pediatric patients, these animals are considered appropriate models for assessing drug effects in the pediatric population.

Some qualification of this observation is required, based on important exceptions (e.g. some endocrine phenomena in rodents have no human correlates).

Lines 112-23. There is evidence that studies in juvenile animals can be useful in the prediction of age-related toxicity in children. Following are examples of such studies:...

The existence of animal models that replicate the pediatric experience provides an important means for examining mechanisms of toxicity. However, the ultimate goal of juvenile toxicity testing for pediatric risk assessment should be the identification of potential safety concerns using predictive models. Three of four of the cited examples represent post-hoc analyses: i.e., developmentally unique toxicities were identified in pediatric populations prior to the development of animal models. While these examples support the significant potential of animal models for specific hypothesis testing, it would be helpful to have examples of the converse (i.e., nonclinical studies that did not replicate the pediatric experience). Thus, while PhRMA acknowledges theoretical advantages to nonclinical juvenile toxicity testing, the predictive value of these efforts is presently uncertain.

Lines 125-37. Other examples of drug-induced, postnatal developmental toxicity in animals include ... Although the significance of these findings for humans is uncertain ...

PhRMA recommends that this section be deleted. The relevance of the examples cited for pediatric safety evaluations is unproven. There are many examples of nonclinical toxicities in adult species that are not predictive of the human adult clinical response; this is also likely to be true for juvenile animals.[4]

[4] There is no consensus on the clinical implications of nonclinical fluoroquinolone chondrotoxicity for pediatric use.

Section III.A.

Lines 145-7. The nonclinical safety evaluation of pediatric therapeutics in juvenile animals should primarily address the potential effects on growth and development that have not been studied or identified in previous nonclinical and clinical studies.

This statement is ambiguous, and can be interpreted as a recommendation to study a myriad of endpoints in all juvenile populations. PhRMA encourages the Guidance authors to clarify their intent. Additionally, to reiterate, PhRMA encourages FDA to engage in dialogue with Sponsors to determine whether nonclinical juvenile toxicity testing is needed, and to emphasize that the decision to conduct these tests should be made case-by-case after evaluation of available data.

Lines 147-50. In limited circumstances, it can be important to include the pediatric clinical formulation's inactive ingredients in testing, particularly in cases where the drug's pharmacodynamics or distribution is altered by the inactive ingredients.

The Guidance authors should consider citing examples whereby the magnitudes of pharmacodynamic or pharmacokinetic changes are considered "altered," because this statement appears inconsistent with Section IV.C.1, lines 362-4 (Because the primary purpose of these studies is to identify potential hazards, small changes in exposure and distribution by route generally are not considered important). Further, note that formulation of compounds for animal dosing to mimic pediatric formulations may not be practical, when consideration is given to dose levels and volumes (cf. section H above).

Lines 150-1. The scope of this document does not encompass testing of excipients for use in pediatric populations.

Excipients are historically problematic in pediatrics; the Guidance should discuss the evaluation of novel (i.e., previously uncharacterized) substances, with reference to levels in ICH Q3B. Notwithstanding this, it may be more important to understand excipient clearance in adult humans, and to determine whether clearance mechanisms are functional in pediatric patients, than to conduct specific nonclinical studies of excipients in juvenile animals (cf. Section H, above).

Lines 156-8. Juvenile animal studies are of special interest when an identified target organ toxicity in adults is also an organ with significant postnatal development.

Cf. Sections B and C above and comments for lines 103-4.

Section III.B.1

Lines 168-73. Juvenile animal studies are primarily conducted to address safety issues associated with long-term exposure during critical developmental periods. Where pediatric clinical studies involve long-term exposure, juvenile animal studies should be conducted before initiation of the long-term clinical studies. Where the indication is for long-term use, but the clinical trials are short-term, the juvenile animal studies should be available before submission of the marketing application.

PhRMA requests that FDA define the duration of "long-term" exposure. Additionally, this text implies that juvenile animal studies will be conducted by default whenever clinical experience is likely to be "long-term," without regard to scientific justification.

Section III.B.2.

Lines 179-85. Where pediatric clinical studies do not involve long-term exposure, it is not necessary to complete juvenile animal studies before initiation of pediatric clinical studies...However...it may be more efficient to complete juvenile animal studies early so that clinical studies can be designed to evaluate potential long-term hazards.

The recommendations in this section seem contradictory. Further, clarification regarding the phrase "in conjunction with" is needed – should these be underway, or complete prior to initiation of pediatric trials?

Lines 191-3. Where there is not sufficient clinical data or experience because of minimal prior adult and pediatric experience, juvenile animal studies should be completed before initiation of pediatric clinical trials, regardless of whether the clinical trials involve long-term exposures.

The question arises how the determination of "sufficiency" of clinical data or experience is made, and whether there will be Sponsor-FDA interaction in arriving at this decision. Moreover, there are further, concrete considerations posed by the use of short-term juvenile studies to support short-term pediatric use that may confound the utility of nonclinical testing. Accelerated maturation of animal organ systems (particularly rodent) implies that a 30-day course of treatment may have different consequences for animal and human. Thus, treatment for 30 days in the life of a weanling rodent represents treatment for half the period to maturity; it is not difficult to foresee that toxicities may be more severe under this circumstance than treatment for 30 days in the life of a human toddler. Conversely, unless the specifics of organ system maturation have been well-documented in the animal species, reducing the interval of exposure in the animal model relative to the intended clinical use is likewise associated with potential for suboptimal testing protocols. In summary, further consideration

should be given to the value of juvenile studies when the anticipated clinical experience will be brief.

Lines 193-6. Similarly, where there have been reports of adverse effects with off-label use in pediatric patients, and there are not adequate data to evaluate the relationship between the drug and the adverse effects, juvenile animal studies should be completed before initiation of pediatric clinical studies.

Juvenile studies should not be mandated by off-label adverse events. (It is possible that the toxicity correlates with excessive plasma concentrations, such that a pediatric pharmacokinetic study might be more informative. Alternatively, if the toxicity were idiosyncratic, juvenile studies would be uninformative.) Rather, the decision to conduct juvenile animal studies should be made only after consideration of all available information, and after dialogue between FDA and the Sponsor.

Section III.C.

Lines 200-3. The appropriateness and design of juvenile animal studies should consider (1) the intended or likely use of the drug in children, (2) the timing of dosing in relation to phases of growth and development in pediatric populations and juvenile animals, and (3) the potential differences in pharmacological and toxicological profiles between mature and immature systems.

PhRMA recommends the addition of a fourth consideration relating to study design: that of known species differences between animal models and the intended pediatric population, such that only appropriate animal models are considered. Relatedly, it will be important to further develop the appended tables (cf. Section C, above).

Lines 212-4. Taking this into consideration, whenever feasible, an initial study designed to address end points of concern for multiple potential pediatric populations should be considered.

PhRMA suggests the deletion of this statement. Nonclinical juvenile studies should be designed only after consideration of pediatric age groups for the intended indication, after rational assessment of animal models that will parallel the clinical population. For example, asthma is not diagnosed in newborns or infants; it is not rational to test potential asthma therapeutics in neonatal animals.

Lines 214-6. In all cases, studies using juvenile animals should be considered when adequate information could not be generated using standard nonclinical studies or from conducting clinical trials.

To reiterate, whether standard nonclinical studies generate adequate information is unlikely to be known until there is pediatric experience; in the case of drugs

used during childhood for chronic conditions, sufficient clinical experience may encompass a decade or more of use.

Section III.D.

Lines 230-2. The end points to be assessed in the nonclinical studies should be tailored to address concerns for a particular pediatric population.

PhRMA recommends inclusion of previously-referenced definitions from FDA of pediatric subpopulations; as well as information which permits extrapolation from the appended tables to these populations.

Lines 236-7. Available data should be carefully evaluated when considering the importance of studies in juvenile animals.

An important aspect of this evaluation will be interactions among developmental scientists and pediatric clinical trial specialists to evaluate the relevance or advisability of juvenile animal study conduct, after careful assessment of available data.

Lines 246-55. Toxicology assessment can include studies of general toxicity, reproductive toxicity, genetic toxicity, carcinogenicity, and other special toxicities. Studies in juvenile animals are occasionally available. Target organs of drug toxicity of the drug both in humans and animals should have been identified in these studies. A thorough evaluation of these data should enable scientists to (1) judge the adequacy of the nonclinical information, (2) identify potential safety concerns for the intended population, and (3) identify any gaps in the data that might be addressed by testing in juvenile animals. Based on this evaluation, in some circumstances it can be concluded that studies in juvenile animals would not be informative and are not necessary.

In many circumstances, it is simple to formulate theoretical safety concerns for pediatric patients from both the nonclinical battery and the adult human data; whether these concerns are predictive of the pediatric experience cannot be known without said experience. Further, it is widely acknowledged that there are gaps in the age ranges of rodent and non-rodent species used in standard toxicity testing; this circumstance is likely to exist for every drug in development. PhRMA recommends that this section of draft Guidance be edited to suggest that relevant decisions be made after consultations between FDA and Sponsor.

Additionally, in the interest of clarity, PhRMA encourages the Guidance authors to cite examples of drugs indicated for pediatric use for which juvenile studies were deemed uninformative and unnecessary. PhRMA can envision specific circumstances under which juvenile studies might not yield important insights. These would include drugs for which safety margins between NOAELs of nonclinical studies and anticipated human therapeutic exposures are high; as

well as drugs for which the intended pediatric course of therapy is brief, when serious toxicities are only apparent upon protracted administration.

Lines 259-60. The toxic effects of drugs on postnatal development are believed most likely to occur in those organs and tissues that undergo significant postnatal development.

Cf. Section C, above, and lines 103-4.

Lines 260-2. Organ systems identified to undergo considerable postnatal growth and development include the nervous, reproductive, pulmonary, renal, skeletal, and immune systems.

As indicated previously, the authors should consider addition of hepatobiliary and gastrointestinal systems.

Lines 263-5 ... a reasonable approach is to assure that exposure to the drug takes place during periods of rapid growth and development.

The meaning of this statement is ambiguous; PhRMA encourages the Guidance authors to define these periods for each species, including human; and to cite specific rationales for their concern about developmental toxicities during these intervals (e.g., previous drug experiences that demonstrated same).

Lines 273-6. We recommend that the timing of the intended use of the drug be considered as it relates to periods of rapid postnatal growth and development. If the drug is intended for use in children undergoing phases of rapid overall growth and development, efforts should be made to use an animal model undergoing a corresponding growth phase.

See above, lines 200-3; and lines 263-5. Further, PhRMA requests guidance for circumstances in which these periods of rapid overall growth and development do not coincide with intervals of target organ maturation.

Lines 290-2. We suggest that toxicological and pharmacological effects be studied even when the primary postnatal developmental period in humans does not coincide with the intended treatment phase.

This suggestion could engender screening tests that encompass all endpoints throughout all development. Is it intended to apply only to those cases where target organs in adults undergo significant postnatal development? Notwithstanding, the suggestion conflicts with statements elsewhere that treatment periods should be based on human-to-animal comparisons of developmental periods for specific organ systems. Further, testing in populations whose primary postnatal developmental period is not coincident with the intended pediatric population could create animal models with uncertain clinical relevance.

Alternatively, PhRMA would ask the authors to be specific about circumstances they envision that warrant the stated comprehensive approach to juvenile toxicity testing.

Lines 292-3. This suggestion is based on the observation that development is generally a continuous event.

Notwithstanding, there are important aspects of growth and development that are literally discontinuous (growth spurts, sexual maturation and puberty).

Section IV.A.

Lines 301-6. Studies conducted in juvenile animals to support the safety of therapeutics intended for use in pediatric patients can be protocols specifically designed for juvenile animals or modified protocols of traditional toxicity testing. Dedicated juvenile animal protocols can be most aptly designed to address concerns based on known properties of the drug, product class, or other information. Modified repeat-dose toxicity studies can provide a more general screen for potential hazards.

N.B. prior to selection of study design, the impact of dosing and handling on immature animals should be systematically assessed.

Lines 315-6. Assessment of developmental end points not usually included in standard repeat-dose toxicity studies may also be important.

Examples of such endpoints should be cited, particularly in non-rodent species.

Section IV.B.1.

Lines 324-337. The species of juvenile animal tested should be appropriate for evaluating toxicity end points important for the intended pediatric population. Traditionally, rats and dogs have been the rodent and nonrodent species of choice. However, other species may be more appropriate in some circumstances ...

There are drugs, including biologics, for which neither rodent nor dog is an appropriate toxicology model; and for which non-human primates are employed in parts of the standard toxicology battery. However, juvenile animal studies in non-human primates should be conducted only in cases where no alternate species is suitable.

Section IV.B.3.

Lines 347-9. An adequate number of animals should be used to clearly demonstrate the presence or absence of effects of the test substance.

The authors should consider clarifying their expectations for a minimum number of animals for each species.

Section IV.C.

Lines 358-62. Assessment of toxic effects by more than one route can be appropriate if the drug is intended for clinical use by more than one route of administration. It may be helpful to test by multiple routes where different routes are anticipated to result in different systemic and local exposure of such magnitude that it could be expected to have an impact on the occurrence of postnatal toxicity.

Testing by the most feasible clinical route offering the greatest exposure should be the default paradigm; evaluation of secondary routes can be accomplished by bridging studies.[5]

Lines 366-9. Under most circumstances, determination of drug metabolism in juvenile animals would not be needed. However, if adverse effects that could be related to metabolic differences between adult and juvenile animals are observed, toxicokinetic studies can provide useful information for assisting in study interpretation.

These statements do not provide guidance on the advisability of toxicokinetic studies. Adverse effects are frequently related to drug exposure, and drug exposure is often related to drug metabolism. Thus, in reality it will often be necessary to examine the relationship between adverse outcome and drug metabolism.

Section IV.D.

Lines 399-410. The selection of toxicological end points to be monitored in a juvenile animal study is critical for assessing the effects of a drug on development and growth ... Studies should include, at a minimum, measurements of growth (e.g., serial measurements of crown-rump length, tibia length, growth velocity per unit time, or other appropriate parameters), body weight, clinical observations, organ weights, and gross and microscopic examinations ... For developmental neurotoxicity assessments, well-established methods should be used to monitor key functional domains of the central nervous

[5] A possible exception is the intravenous route, when a less-invasive route offers adequate exposure.

system, including assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, and learning and memory.

Whether existing toxicology study designs are modified, or juvenile studies are designed *de novo*, serial capture of these endpoints will be labor-intensive, and will require many animals. Moreover, whether these suggested parameters are sufficiently sensitive to detect toxic responses that are *not* reflected in conventional body weight or external appearance data is unknown; increased sensitivity should be manifested by a reduced NOAEL. Finally, it is vital that endpoints be validated as predictors of pediatric risk; e.g. if reversible growth retardation is reported, the significance of these measurements for risk assessment is unclear.

Lines 400-2. Studies should be designed to determine drug effects on overall growth of organ systems that develop postnatally (e.g., skeletal, renal, lung, neurological, immunologic, and reproductive systems).

One interpretation of this recommendation is that all systems should be routinely assessed, although this may be neither practical nor scientifically justified. Instead, organ systems should be selected for assessment on a case-by-case basis, after application of rational criteria.

Lines 412-5. It can be helpful to determine the relationship between toxicologic end points and drug exposure (e.g., predosing, immediate postdosing, time of peak plasma concentration). To differentiate long-term effects on development from acute effects, it may be appropriate to measure certain end points immediately before daily administration of the drug.

The distinction between acute and chronic effects based on C_{min} should not be generalized. In some cases, the distinction cited is real. Conversely, even in the presence of immeasurable plasma drug concentrations at T_{24}, it is possible that "acute" effects may persist, due to drug residence in peripheral compartments.

Section V.A.

Lines 437-44. In some cases where toxicities of significant concern are observed, studies in juvenile animals might indicate that pediatric trials could not be conducted that would provide for an adequate margin of safety compared to apparent efficacious doses. It may not be possible to safely conduct pediatric clinical trials if toxicities identified in juvenile animal studies (1) are likely to occur in pediatric patients, (2) cannot be monitored clinically, and (3) would not be considered acceptable potential consequences of treatment. Demonstration of irreversible adverse effects in juvenile animal studies could preclude clinical studies in pediatric subjects.

In our estimation, only item (3) should contribute to determining whether results of nonclinical juvenile toxicity testing preclude use in pediatric populations; i.e., a risk-benefit analysis should supercede all other considerations.

Section V.B.

Lines 448-68. Nonclinical toxicology studies in juvenile animal models could demonstrate adverse effects that the Sponsor should consider (1) in seeking postmarketing commitments, (2) in labeling a product for pediatric use, or (3) in determining the approvability of a drug for pediatric use ... Finally, it is possible that nonclinical findings could result in a product label that specifically warns against use in pediatric patients.

As indicated previously, PhRMA recommends deletion of references to product labeling, which are not properly discussed in Guidance format (cf. Section G, above).

Section VI.

PhRMA encourages the authors to update these tables with more rigorous literature evaluations, such as those conducted on behalf of ILSI-HESI (cf. Section C, above). That said, some questions arise as to the means whereby FDA will confirm or validate that developmental stages and endpoints studied in animals correlate with meaningful developmental parameters in the pediatric population. Further, if FDA considers that certain species are particularly appropriate for toxicity testing of specific organ systems, this should be indicated.

PhRMA is pleased to submit these comments to the FDA. If you require further information, please do not hesitate to contact me.

Sincerely,

Sara Radcliffe

Sara Radcliffe