AstraZeneca

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Date: MAY 0 1 2003

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

Re: Docket Number 03D-0001
Response to FDA Call for Comments
Draft Guidance for Industry on Nonclinical Safety Evaluation
of Pediatric Drug Products

Dear Sir or Madam:

Reference is made to the February 3, 2003 Federal Register notice announcing the request for comments on a draft guidance for industry entitled "Nonclinical Safety Evaluation of Pediatric Drug Products."

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to George A. Kummeth, Associate Director, at (302) 885-8415.

Sincerely,

Gary P. Horowitz

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Enclosure

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Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products

General Comments

- 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. In fact, the document frequently offers "points to consider" - allowing the Sponsor to apply the use of scientific judgment to determine, when, if, and how best to evaluate the potential juvenile toxicity of new compounds.

- However, the Guidance provided is at times vague, lacking sufficient information to provide clear direction and some parts of the document seem to be contradictory to other parts. For example, the scope of the document (Section I) is stated to be "limited to safety effects that cannot be adequately, ethically, and safely assessed in pediatric clinical trials." This statement implies that juvenile animal testing is to be done on a case-by-case basis, as necessary. In contrast, in another section (III) it is stated "Standard toxicology studies using adult animals, or safety information from adult humans, cannot adequately predict drug effects in immature systems." This sentence implies that testing would be required on all drugs and not merely on a case-by-case basis. There are other such examples (e.g., should the active moiety or the final formulation be tested?, should the design of the study address concerns for a *particular* or *multiple* pediatric population(s)?). A more internally-consistent approach would be helpful to avoid confusion.

- As the Guidance is currently written, it is difficult to envision situations in which drugs for pediatric indications will *not* require nonclinical juvenile toxicity testing. The document, as it stands now, can be interpreted as recommending conduct of juvenile studies in almost all cases. Such a misinterpretation could lead to delays in development and marketing of medicines for children, this being in contradiction with the intent of the whole regulation on pediatrics. Examples that document specific instances in which juvenile toxicity tests provide important information, as well as instances in which they are not necessary, would be helpful.

- Exposure is an essential element in risk assessment. A suggestion is that there should be a clear recommendation that drug, and significant active metabolite concentrations be measured in any of the juvenile toxicology studies conducted. This would be accomplished using standard (ICH S3 Guideline) toxicokinetic study designs that would allow for the estimation of C_{max} and AUC for parent and significant metabolites in all dose groups.

- The Agency should consider eliminating Section V (Application of Juvenile Animal Data in Risk Management Considerations), as it does not seem in line with the stated objective of the Guidance. Additionally, other available Pharmacology and Toxicology FDA Guidances do not contain such information. We would suggest that the Agency consider placing this information in a separate

guidance related to the use of nonclinical juvenile animal safety data in clinical risk management, similar to the Reviewer Guidance on the integration of study results to assess concerns about human reproductive and developmental toxicities.

- Further, the Guidance often uses the phrase "critical periods of development," although the meaning of this phrase is not defined. It is unclear whether the authors intend the reader to interpret this as windows of susceptibility, as intervals encompassing the maturational period, or both. Provision of *clinical* data that define critical windows of susceptibility for developing organ systems would be useful in determining analogous timepoints in nonclinical species. Similarly, the Guidance frequently suggests that toxicity testing will be important when drugs are intended for administration during periods of "rapid growth and development." Definition of these periods during childhood will assist in the selection of analogous intervals for nonclinical testing.

- Finally, there are few data available to indicate whether specific juvenile toxicity tests will be more predictive of the pediatric clinical experience than the current battery of nonclinical testing or the adult clinical experience. It will be important to prospectively validate the utility of these juvenile data, and to compare their predictivity with those of adult human and nonclinical data. We encourage the Agency's efforts in this regard.

Specific Comments

Section II.B.

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.

It is thought that pediatric organ systems at highest risk for drug toxicity are those that undergo significant postnatal development. This statement is intuitively attractive, 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.

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 predictive models. Unfortunately, 3 of 4 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. Additionally, examples of the converse (i.e., nonclinical studies that did not replicate the pediatric experience) are not discussed. Thus, while we acknowledge theoretical advantages to nonclinical juvenile toxicity testing, the predictive value of these efforts is presently uncertain.

Other examples of drug-induced, postnatal developmental toxicity in animals include... Although the significance of these findings for humans is uncertain... There are many examples of nonclinical toxicities in adult species that are not predictive of the human adult clinical response. Whether this is also true for juvenile animals is presently uncertain, although likely.

Section III.A.
Under the Scope, it would be desirable to indicate that juvenile animal testing is not required routinely for all drugs, for example, those drugs that do not produce adverse effects in adult animals/humans and that do not have a target organ for toxicity that has significant postnatal development.

As stated, the Scope of this guidance is the toxicological assessment of the active moiety – it does not routinely encompass testing of excipients. Thus, statements elsewhere in the document about potential testing requirements for formulation excipients should be removed or clarified.

In limited circumstances it can be important to include the pediatric clinical formulation's inactive ingredients in testing... The use of "in limited circumstances" here appears to contradict the footnote on page 9 "Safety evaluations of inactive formulation components *should be conducted* to determine potential adverse effects in pediatric subjects."

Toxicological assessment should include analysis of effects on postnatal growth and development for systemic and local toxicity in relation to issues of concern to the expected pediatric population in consideration of their developmental status. Specific examples of endpoints *not routinely monitored* that describe effects on growth and development would be enlightening.

Juvenile animal studies are of special interest when an identified target organ toxicity in adults is also an organ with significant postnatal development. See above and below.

Section III.B. [Move paragraph below to III.D.?]

In Section III-B, Points 1-3, the requirements for juvenile animal testing, as stated, imply that such testing is required for all drugs, regardless of qualifying status. This is in contrast to the Scope, as stated in Section I.A., which is limited to safety effects that cannot be adequately, ethically, and safely assessed in pediatric clinical trials. Also, in Section III.A, the implication is that juvenile studies are of interest when the identified target organ in adults is also an organ with significant postnatal development.

Juvenile animal studies are primarily conducted to address safety issues associated with long-term exposure during critical developmental periods. If this is accurate, is it still necessary/relevant to conduct juvenile animal studies to support a drug only intended for short-term clinical use? See the related comments regarding the issues posed by short-term juvenile studies.

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. Such studies can be conducted in conjunction with the clinical trials. However, because juvenile animal studies may identify potential hazards, and it may be important to clinically evaluate the relevance of identified potential hazards to determine the extent of human risk, it may be more efficient to complete juvenile animal studies early so that clinical studies can be designed to evaluate potential long-term hazards. In the first sentence, it is not clear: 1) whether the recommendation is for the animal studies to be conducted - but that final, quality assured reports would not be required to support the clinical trials (as described in the Content and Format of INDs guidance); 2) whether shorter-term studies only should be conducted at this point; or 3) whether it is not necessary to initiate any studies before the trial begins. The last statement reflects an important concern, but seems to contradict the first statement, and perhaps should be focused on the need to address specific safety issues. For example, if very aggressive treatment will be given clinically, it may be preferable to conduct animal studies prior to initiation of the clinical trial.

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 issues posed by short-term juvenile studies to support short-term pediatric use 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 animals and humans. 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, consideration should be given to the value of juvenile studies when the anticipated clinical experience will be brief.

Section III.C.

Taking this into consideration, whenever feasible, an initial study designed to address end points of concern for multiple potential pediatric populations should be considered. The meaning of this statement is unclear. Does the Agency envision a single study comprising birth through maturity in a given species; or multiple studies examining developmental intervals analogous to those identified in the pediatric population? Perhaps an example could be provided for clarification?

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.

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 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. Unfortunately, consideration of each of these points does little to clarify when there is need for juvenile toxicity studies. As previously indicated, it will be difficult to judge the adequacy of the standard toxicology battery as a predictive tool in the absence of pediatric data. In many circumstances, it is simple to formulate theoretical safety concerns for pediatric patients from both the nonclinical battery and the adult human experience; 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. Considered together, it is unlikely that evaluation of existing data would predict novel toxicities in a developmental paradigm, a situation with which the Guidance authors are clearly concerned.[1] In the interest of clarity, the authors are encouraged to cite examples of drugs indicated for pediatric use for which juvenile studies were deemed uninformative and unnecessary; and discuss "lessons learned" in the process.

We can envision circumstances under which juvenile studies might not be informative or necessary. 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.

The toxic effects of drugs on postnatal development are believed most likely to occur in those organs and tissues that undergo significant postnatal development. See above.

[1] **Section V.A.** Nonclinical toxicology studies designed to support the safety of clinical trials in pediatric subjects should identify hazards specific to this population.

...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; the authors are encouraged to define these periods for each species, including humans.

Given the variable rate of postnatal development during different periods of childhood, the definition of *long-term* treatment can vary by pediatric population. For example, intended treatment of several weeks may not be considered long term in early adolescence, but it might be considered long term for the neonate, given the duration of some developmental windows. While we agree that the definition of long-term and short-term treatment can vary with developmental stage, the example given does not provide sufficient guidance. Providing more precise definitions for developmental windows for different age ranges, for example, premature infants, neonates, children, etc., would be helpful.

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. Guidance is also requested for circumstances in which these periods of rapid overall growth and development do not coincide with intervals of target organ maturation.

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. We invite the authors to be specific regarding circumstances that might warrant this sweeping approach.

Section IV.A.

In nonrodents, we recommend that studies be started with younger animals than is the usual practice... By definition, studies in juvenile animals would be initiated in animals younger than those used in adult animal studies. For dogs, the range of ages at dosing initiation to fulfill this recommendation could be from one week to 16 weeks of age, and for nonhuman primates the age range would be wider. We recommend either deleting the sentence or providing more specific guidance here regarding the choice of age based on the species to be used or the endpoints to be studied.

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.

A study in juveniles from one animal species can be sufficient to evaluate toxicity end points for therapeutics that are well characterized in both adult humans and animals. It is anticipated that often this evaluation can be accomplished in the rodent using modified perinatal and postnatal developmental studies, although other approaches can be used. Examples of situations that cannot be addressed by the use of rodent or small laboratory

animal species should be cited. Also, please clarify whether this recommendation also applies to therapeutics of a new chemical class.

An adequate number of animals should be used to clearly demonstrate the presence or absence of effects of the test substance. Could references be provided for the appropriate approach to determining the "adequate number of animals?"

Section IV.C.

The expected clinical route of administration and formulation should be used when feasible, unless it has been demonstrated in nonclinical studies that an alternate route is more relevant to human clinical use. This statement appears to be contradictory to those in Section III.A. (Scope), where it states that evaluation should focus on the active moiety and does not encompass testing of excipients for use in pediatric populations.

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 main clinical route should be the primary testing strategy; evaluation of secondary routes should be accomplished by relevant bridging study(ies).

Under most circumstances, determination of drug metabolism in juvenile animals would not be needed. This statement appears to contradict the examples included in Section IIA that highlight metabolic differences as one of the primary reasons for differences in toxicity observed between juveniles and adults. Developmental differences that produce differences in drug disposition are clearly important, and highlight the need for the determination of drug metabolism and toxicokinetic information in juvenile systems (*in vivo* or *in vitro*).

Treatment-free periods designed to assess reversibility of possible adverse effects should also be considered. This statement should be strengthened to be consistent with the premise stated in the Introduction - that serious adverse effects that are irreversible are of particular concern. In addition, specific recommendations are requested regarding evaluation of delayed toxicity; for example, is it sufficient to assess toxicity at the time of organ maturation, at the point of sexual maturation, or in adult animals?

Dose selection should provide a clear dose-response relationship for adverse effects in juvenile animals, where possible. The purpose of the juvenile animal study should be to determine if there is a toxic effect in a target organ/system that is undergoing significant developmental change. Since, in most cases, it will be unknown if there is such an effect, it would be unreasonable to expect, or to require, the demonstration of such an exquisite dose-response relationship.

The high dose should produce frank toxicity, developmental or general. Can this be interpreted similarly to definitions used in repeat-dose and reproductive toxicity studies?

Clarification of the definition or inclusion of some specific examples would be helpful. For example, would body weight loss and/or decreased food consumption be considered sufficient evidence of frank toxicity, or would evidence of organ toxicity without body weight loss be considered sufficient?

We suggest that the following text be added to the Guidance as point 4.

C. Exposure
4. Toxicokinetic Assessment

> "The extent of systemic exposure to parent compound and significant metabolites should be determined in juvenile animal toxicology studies following guidelines previously established for the industry (1). To allow comparison of unbound plasma concentration data obtained from these studies to values observed in mature animals and humans, it may also be necessary to determine the extent of plasma protein binding of the parent compound and significant metabolites in juvenile animals.
>
> (1) ICH Harmonized Tripartite Guideline (S3A) Note for "Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies."

Section IV.D.

The selection of toxicological endpoints to be monitored in a juvenile animal study is critical . . . overall growth of organ systems that develop postnatally.... This paragraph seems to advocate more of a 'shotgun approach' to monitoring numerous developing organ system effects, rather than the more 'targeted approach' to particular pediatric populations that is advocated in other Sections of this document (e.g., III.D.1, IV.B.2). A clarification of this statement would be helpful.

For drugs affecting the reproductive system, as assessment of reproductive ability following treatment before sexual maturity may be necessary.

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. This section is overly detailed and focused on growth. The parameters listed are of value only for rodents, and are probably most important when treatment is started at a very early age. It is stated that these parameters represent a minimum. While these parameters are of value, their importance appears to be overemphasized.

For developmental neurotoxicity assessments, well-established methods should be used to monitor key functional domains of the central nervous system, including assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, and learning and memory. For these assessments, inclusion of recommendations for the timing of monitoring would be helpful. For example, should this assessment be conducted once or several times during treatment, or once during treatment and once during the recovery period if adverse effects are observed during the treatment period?

Section V.A.
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 supersede all other considerations.

Section V.B.
Finally, it is possible that nonclinical findings could result in a product label that specifically warns against use in pediatric patients. Again, in our estimation, the product label may be used to describe results of juvenile toxicity testing; however, the final decision on use in pediatric patients should follow a thorough risk-benefit analysis.

Section VI.
The authors are encouraged to update these tables. An alternative is that appended tables delineating endpoints for consideration in certain developing organ systems should be deleted as some, while factual, may be inadvertently misleading since they are not complete. In other cases, the data are no longer accurate. Instead, specific reference(s) should be given within the text of the guidance. Use of ILSI- HESI data is recommended.

Table B. Cynomolgus monkeys are more commonly used than Rhesus monkeys; therefore, information for Cynomolgus monkeys should be included either in addition to or in place of the Rhesus monkey information.

Table C. The precise meaning of the term "fusion" is unclear; growth or nonclosure could be considered as preferable terms.