Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

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)

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ICH

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Preamble:

This addendum should be read in close conjunction with the original ICH S6 guidance (ICH S6). In general the addendum is complementary to the guidance, and where the addendum differs from ICH S6, the guidance in the addendum prevails.

I. INTRODUCTION (1)[2]

A. Purpose of the Addendum (1.1)

The purpose of the addendum is to complement, provide clarification on, and update the following topics discussed in ICH S6: species selection, study design, immunogenicity, reproductive and developmental toxicity, and assessment of carcinogenic potential. Scientific advances and experience gained since publication of ICH S6 call for this addendum. This harmonized addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3Rs (reduce/refine/replace) principles and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to the use of appropriate in vitro alternative methods for safety evaluation. These methods, if accepted by all ICH regulatory authorities, can be used to replace current standard methods.

[1] This guidance was developed within the Safety Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, June 2011. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, June 2011.

This guidance promotes safe and ethical development and availability of new pharmaceuticals.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

B. Background (1.2)

The recommendations of this addendum further harmonize the nonclinical safety studies to support the various stages of clinical development among the regions of European Union (EU), Japan, and the United States. The present addendum represents the consensus that exists regarding the safety evaluation of biotechnology-derived pharmaceuticals.

C. Scope of the Guidance (1.3)

This addendum does not alter the scope of the original ICH S6 guidance. For biotechnology-derived products intended to be used in oncology the guidance *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (ICH S9) should be consulted.

II. SPECIES SELECTION (2)

A. General Principles (2.1)

A number of factors should be taken into account when determining species relevancy. Comparisons of target sequence homology between species can be an appropriate starting point, followed by in vitro assays to make qualitative and quantitative cross-species comparisons of relative target binding affinities and receptor/ligand occupancy and kinetics.

Assessments of functional activity are also recommended. Functional activity can be demonstrated in species-specific cell-based systems and/or in vivo pharmacology or toxicology studies. Modulation of a known biologic response or of a pharmacodynamic (PD) marker can provide evidence for functional activity to support species relevance.

Consideration of species differences in target binding and functional activity in the context of the intended dosing regime should provide confidence that a model is capable of demonstrating potentially adverse consequences of target modulation. When the target is expressed at very low levels in typical healthy preclinical species (e.g., inflammatory cytokines or tumor antigens), binding affinity and activity in cell-based systems can be sufficient to guide species selection.

Assessment of tissue cross reactivity (see Note 1) in animal tissues is of limited value for species selection. However, in specific cases (i.e., where the approaches described above cannot be used to demonstrate a pharmacologically relevant species) tissue cross-reactivity (TCR) studies can be

used to guide selection of toxicology species by comparison of tissue binding profiles between those human and animal tissues where target binding is expected.

As described in ICH S6, when no relevant species can be identified because the biopharmaceutical does not interact with the orthologous target in any species, use of homologous molecules or transgenic models can be considered.

For monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term safety study (see ICH S6) in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate. Alternatively, when animal models of disease are used to evaluate proof of principle, a safety assessment can be included to provide information on potential target-associated safety aspects. Where this is not feasible, appropriate risk mitigation strategies should be adopted for clinical trials.

Species selection for an antibody-drug/toxin conjugate (ADC) incorporating a novel toxin/toxicant should follow the same general principles as an unconjugated antibody (see above). (See Note 2.)

B. One or Two Species (2.2)

If there are two pharmacologically relevant species for the clinical candidate (one rodent and one nonrodent), then both species should be used for short-term (up to 1 month duration) general toxicology studies. If the toxicological findings from these studies are similar *or* the findings are understood from the mechanism of action of the product, then longer term general toxicity studies in one species are usually considered sufficient. The rodent species should be considered unless there is a scientific rationale for using nonrodents. Studies in two nonrodent species are not appropriate.

The use of one species for all general toxicity studies is justified when the clinical candidate is pharmacologically active in only one species. Studies in a second species with a homologous product are not considered to add further value for risk assessment and are not recommended.

C. Use of Homologous Proteins (2.3)

Use of homologous proteins is one of the alternative approaches described in ICH S6, section III.C (3.3). Studies with homologous proteins can be used for hazard detection and understanding the potential for adverse effects due to exaggerated pharmacology, but are generally not useful for quantitative risk assessment. Therefore, for the purposes of hazard identification, it can be possible to conduct safety evaluation studies using a control group and one treatment group provided there is a scientific justification for the study design and dose selected (e.g., maximum pharmacological dose).

III. STUDY DESIGN (3)

A. Dose Selection and Application of PK/PD Principles (3.1)

The toxicity of most biopharmaceuticals is related to their targeted mechanism of action; therefore, relatively high doses can elicit adverse effects, which are apparent as exaggerated pharmacology.

A rationale should be provided for dose selection taking into account the characteristics of the dose-response relationship. Pharmacokinetic-pharmacodynamic (PK-PD) approaches (e.g., simple exposure-response relationships or more complex modeling and simulation approaches) can assist in high dose selection by identifying (1) a dose that provides the maximum intended pharmacological effect in the preclinical species and (2) a dose that provides an approximately 10-fold exposure multiple over the maximum exposure to be achieved in the clinic. The higher of these two doses should be chosen for the high dose group in preclinical toxicity studies unless there is a justification for using a lower dose (e.g., maximum feasible dose).

Where in vivo/ex vivo PD endpoints are not available, the high dose selection can be based on PK data and available in vitro binding and/or pharmacology data. Corrections for differences in target binding and in vitro pharmacological activity between the nonclinical species and humans should be taken into account to adjust the exposure margin over the highest anticipated clinical exposure. For example, a large relative difference in binding affinity and/or in vitro potency might suggest that testing higher doses in the nonclinical studies is appropriate. In the event that toxicity cannot be demonstrated at the doses selected using this approach, then additional toxicity studies at higher multiples of human dosing are unlikely to provide additional useful information.

B. Duration of Studies (3.2)

For chronic use products, repeat dose toxicity studies of 6 months' duration in rodents or nonrodents are considered sufficient, providing the high dose is selected in accordance with the principles above in section 3.1. Studies of longer duration have not generally provided useful information that changed the clinical course of development.

For chronic use of biopharmaceutical products developed for patients with advanced cancer, the principles for duration of toxicology studies are outlined in ICH S9.

C. Recovery (3.3)

Recovery from pharmacological and toxicological effects with potential adverse clinical impact should be understood when they occur at clinically relevant exposures. This information can be obtained by an understanding that the particular effect observed is generally reversible/nonreversible or by including a nondosing period in at least one study, with at least one dose level, to be justified by the sponsor. The purpose of the nondosing period is to examine reversibility of these effects, not to assess delayed toxicity. The demonstration of complete recovery is not considered essential. The addition of a recovery period just to assess potential for immunogenicity is not required.

D. Exploratory Clinical Trials (3.4)

The flexible approaches to support exploratory clinical trials as outlined in the guidance *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (ICH M3(R2)) can be applicable to biopharmaceuticals. It is recommended that these approaches be discussed and agreed upon with the appropriate regulatory authority.

IV. IMMUNOGENICITY (4)

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies. Such analyses in nonclinical animal studies are not relevant in terms of predicting potential immunogenicity of human or humanized proteins in humans.

Measurement of anti-drug antibodies (ADA) in nonclinical studies should be evaluated when there is:

(1) evidence of altered PD activity;
(2) unexpected changes in exposure in the absence of a PD marker; or
(3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.).

Since it is difficult to predict whether such analysis will be called for prior to completion of the in-life phase of the study, it is often useful to obtain appropriate samples during the course of the study, which can subsequently be analyzed when warranted to aid in interpretation of the study results. When ADAs are detected, their impact on the interpretation of the study results should be assessed (see also section III.F (3.6), paragraph 2 in ICH S6 for further guidance on the impact of immunogenicity).

Characterization of neutralizing potential is warranted when ADAs are detected and there is no PD marker to demonstrate sustained activity in the in vivo toxicology studies. Neutralizing antibody activity can be assessed indirectly with *ex-vivo* bioactivity assay or an appropriate combination of assay formats for PK-PD, or directly in a specific neutralizing antibody assay.

V. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY (5)

A. General Comments (5.1)

Reproductive toxicity studies should be conducted in accordance with the principles outlined in the guidance *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility* (ICH S5); however, the specific study design and dosing schedule can be modified based on an understanding of species specificity, the nature of the product and mechanism of action, immunogenicity and/or pharmacokinetic behavior, and embryo-fetal exposure.

An assessment of reproductive toxicity with the clinical candidate in a relevant species is generally preferred. The evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species. When the clinical candidate is pharmacologically active in rodents and rabbits, both species should be used for embryo-fetal development (EFD) studies, unless embryo-fetal lethality or teratogenicity has been identified in one species.

Developmental toxicity studies should only be conducted in nonhuman primates (NHPs) when they are the only relevant species.

When the clinical candidate is pharmacologically active only in NHPs, there is still a preference to test the clinical candidate. However, an alternative model can be used in place of NHPs if appropriate scientific justification is provided.

When no relevant animal species exists for testing the clinical candidate, the use of transgenic mice expressing the human target or homologous protein in a species expressing an ortholog of the human target can be considered, assuming that sufficient background knowledge exists for the model (e.g., historical background data) (see Note 1 of ICH S6). For products that are directed at a foreign target such as bacteria and viruses, in general, no reproductive toxicity studies would be expected (See section II.A (2.1)).

When the weight of evidence (e.g., mechanism of action, phenotypic data from genetically modified animals, class effects) suggests that there will be an adverse effect on fertility or pregnancy outcome, these data can provide adequate information to communicate risk to reproduction, and under appropriate circumstances, additional nonclinical studies might not be warranted.

B. Fertility (5.2)

For products where mice and rats are pharmacologically relevant species, an assessment of fertility can be made in one of these rodent species (see ICH S5). ICH S5 study designs can be adapted for other species provided they are pharmacologically relevant; in addition, the design of the study should be amended as appropriate, for example to address the nature of the product and potential for immunogenicity.

It is recognized that mating studies are not practical for NHPs. However, when the NHP is the only relevant species, the potential for effects on male and female fertility can be assessed by evaluation of the reproductive tract (organ weights and histopathological evaluation) in repeat dose toxicity studies of at least 3 months' duration using sexually mature NHPs. If there is a specific cause for concern based on pharmacological activity or previous findings, specialized assessments such as menstrual cyclicity, sperm count, sperm morphology/motility, and male or female reproductive hormone levels can be evaluated in a repeat dose toxicity study.

If there is a specific concern from the pharmacological activity about potential effects on conception/implantation and the NHP is the only relevant species, the concern should be addressed experimentally. A homologous product or transgenic model could be the only practical

means to assess potential effects on conception or implantation when those are of specific concern. However, it is not recommended to produce a homologous product or transgenic model solely to conduct mating studies in rodents. In absence of nonclinical information, the risk to patients should be mitigated through clinical trial management procedures, informed consent, and appropriate product labeling.

C. Embryo-Fetal (EFD) and Pre/Postnatal Development (PPND) (5.3)

Potential differences in placental transfer of biopharmaceuticals should be considered in the design and interpretation of developmental toxicity studies (see Note 3).

For products pharmacologically active only in NHPs, several study designs can be considered based on intended clinical use and expected pharmacology. Separate EFD and/or PPND studies, or other study designs (justified by the sponsor) can be appropriate, particularly when there is some concern that the mechanism of action might lead to an adverse effect on embryo-fetal development or pregnancy loss. However, one well-designed study in NHPs that includes dosing from day 20 of gestation to birth (enhanced PPND; ePPND) can be considered, rather than separate EFD and/or PPND studies.

For the single ePPND study design described above, no Caesarian section group is warranted, but assessment of pregnancy outcome at natural delivery should be performed. This study should also evaluate offspring viability, external malformations, skeletal effects (e.g., by X-ray) and, ultimately, visceral morphology at necropsy. Ultrasound is useful to track maintenance of pregnancy but is not appropriate for detecting malformations. These latter data are derived from postpartum observations. Because of confounding effects on maternal care of offspring, dosing of the mother postpartum is generally not recommended. Other endpoints in the offspring can also be evaluated if relevant for the pharmacological activity. The duration of the postnatal phase will be dependent on which additional endpoints are considered relevant based on mechanism of action (see Note 4).

Developmental toxicity studies in NHPs can only provide hazard identification. The number of animals per group should be sufficient to allow meaningful interpretation of the data (see Note 5).

The sponsor should justify the study design if other NHP species are used. The developmental toxicity studies in NHP as outlined above are just hazard identification studies; therefore, it might be possible to conduct these studies using a control group and one dose group, provided there is a scientific justification for the dose level selected. An example of an appropriate scientific justification would be a monoclonal antibody that binds a soluble target with a clinical dosing regimen intended to saturate target binding. If such a saturation of target binding can be demonstrated in the animal species selected and there is an up to 10-fold exposure multiple over therapeutic drug levels, a single dose level and control group would provide adequate evidence of hazard to embryo-fetal development.

D. Timing of Studies (5.4)

If women of child-bearing potential are included in clinical trials prior to acquiring information on effects on embryo-fetal development, appropriate clinical risk management is appropriate, such as use of highly effective methods of contraception (see ICH M3(R2)).

For biopharmaceuticals pharmacologically active only in NHPs, where there are sufficient precautions to prevent pregnancy (see ICH M3(R2), section XI.C (11.3), paragraph 2), an EFD or ePPND study can be conducted during Phase III, and the report submitted at the time of marketing application. When a sponsor cannot take sufficient precaution to prevent pregnancy in clinical trials, either a complete report of an EFD study or an interim report of an ePPND study (see note 6) should be submitted before initiation of Phase III. Where the product is pharmacologically active only in NHPs and its mechanism of action raises serious concern for embryo-fetal development, the label should reflect the concern without warranting a developmental toxicity study in NHPs and therefore administration to women of child-bearing potential should be avoided.

If the rodent or rabbit is a relevant species, see ICH M3(R2) for timing of reproductive toxicity studies. ICH M3(R2) should also be followed for the timing of data on fertility for products where rodents are relevant species.

For oncology products which fall within the scope of ICH S9, see that guidance for aspects relating to timing of study conduct.

VI. CARCINOGENICITY (6)

The need for a product-specific assessment of the carcinogenic potential for biopharmaceutical should be determined with regard to the intended clinical population and treatment duration (see the guidance *S1A The Need for Carcinogenicity Studies of Pharmaceuticals*). When an assessment is warranted, the sponsor should design a strategy to address the potential hazard.

This strategy could be based on a weight of evidence approach, including a review of relevant data from a variety of sources. The data sources can include published data (e.g., information from transgenic, knock-out or animal disease models, human genetic diseases), information on class effects, detailed information on target biology and mechanism of action, in vitro data, data from chronic toxicity studies and clinical data. In some cases, the available information can be sufficient to address carcinogenic potential and inform clinical risk without additional nonclinical studies.

The mechanism of action of some biopharmaceuticals might raise concern regarding potential for carcinogenicity (e.g., immunosuppressives and growth factors). If the weight of evidence (see above) supports the concern regarding carcinogenic potential, rodent bioassays are not warranted. In this case potential hazard can be best addressed by product labeling and risk management practices. However, when the weight of evidence is unclear, the sponsor can

propose additional studies that could mitigate the mechanism-based concern (see ICH S6, section IV.H (4.8)).

For products where there is insufficient knowledge about specific product characteristics and mode of action in relation to carcinogenic potential, a more extensive assessment might be appropriate (e.g., understanding of target biology related to potential carcinogenic concern, inclusion of additional endpoints in toxicity studies).

If the weight of evidence from this more extensive assessment does not suggest carcinogenic potential, no additional nonclinical testing is recommended. Alternatively, if the weight of evidence suggests a concern about carcinogenic potential, then the sponsor can propose additional nonclinical studies that could mitigate the concern, or the label should reflect the concern.

The product-specific assessment of carcinogenic potential is used to communicate risk and provide input to the risk management plan along with labeling proposals, clinical monitoring, postmarketing surveillance, or a combination of these approaches.

Rodent bioassays (or short-term carcinogenicity studies) with homologous products are generally of limited value to assess carcinogenic potential of the clinical candidate.

Alternative approaches can be considered as new strategies/assays are developed.

ENDNOTES

Note 1

Tissue cross-reactivity (TCR) studies are in vitro tissue-binding assays employing immunohistochemical (IHC) techniques conducted to characterize binding of monoclonal antibodies and related antibody-like products to antigenic determinants in tissues. Other technologies can be employed in place of IHC techniques to demonstrate target /binding site distribution.

A TCR study with a panel of human tissues is a recommended component of the safety assessment package supporting initial clinical dosing of these products. However, in some cases, the clinical candidate is not a good IHC reagent and a TCR study might not be technically feasible.

TCR studies can provide useful information to supplement knowledge of target distribution and can provide information on potential unexpected binding. Tissue binding per se does not indicate biological activity in vivo. In addition, binding to areas not typically accessible to the antibody in vivo (i.e., cytoplasm) is generally not relevant. Findings should be evaluated and interpreted in the context of the overall pharmacology and safety assessment data package.

When there is unexpected binding in human tissues, an evaluation of selected animal tissues can provide supplemental information regarding potential correlations or lack thereof with preclinical toxicity. TCR using a full panel of animal tissues is not recommended.

Since a bi-specific antibody product will be evaluated in a TCR study using a panel of human tissues, there is no need to study the individual binding components.

Evaluating the tissue binding of homologous products does not provide additional value when TCR studies have been conducted with the clinical candidate in a human tissue panel and is not recommended.

TCR studies cannot detect subtle changes in critical quality attributes. Therefore, TCR studies are not recommended for assessing comparability of the test article as a result of process changes over the course of a development program,

Note 2

If two species have been used to assess the safety of the ADC, an additional short-term study or arm in a short-term study should be conducted in at least one species with the unconjugated toxin. In these cases a rodent is preferred unless the toxin is not active in the rodent. If only one pharmacologically relevant species is available, then the ADC should be tested in this species. A novel toxicant calls for an approach to species selection similar to that used for a new chemical entity on a case-by case approach (e.g., for anticancer products in accordance with ICH S9). For toxins or toxicants that are not novel and for which there is a sufficient body of scientific

information available, separate evaluation of the unconjugated toxin is not warranted. Data should be provided to compare the metabolic stability of the ADC in animals with human.

Note 3

The species-specific profile of embryo-fetal exposure during gestation should be considered in interpreting studies. High molecular weight proteins (>5,000 D) do not cross the placenta by simple diffusion. For monoclonal antibodies with molecular weight as high as 150,000 D, there exists a specific transport mechanism, the neonatal Fc receptor (FcRn), which determines fetal exposure and varies across species.

In the NHP and human, IgG placental transfer is low in the period of organogenesis and begins to increase in early second trimester, reaching highest levels late in the third trimester (Pentsuk and Van der Laan, 2009). Therefore, standard embryo-fetal studies in NHPs, which are dosed from early pregnancy up to Gestation Day 50, might not be of value to assess direct embryo-fetal effects in the period of organogenesis, although effects on embryo-fetal development as an indirect result of maternal effects can be evaluated. Furthermore, maternal dosing in NHP after delivery is generally without relevance as IgG is only excreted in the milk initially (i.e., in the colostrum), and not later during the lactation and nursing phase.

Rodents differ from the NHPs and humans, as IgG crosses the yolk sac in rodents by FcRn transport mechanisms and exposure can occur relatively earlier in gestation than with NHPs and humans. In addition, delivery of rodents occurs at a stage of development when the pups are not as mature as the NHP or the human neonate. Therefore, rat/mouse dams should be dosed during lactation in order to expose pups via the milk up to at least day 9 of lactation when the offspring are at an equivalent stage of development as human neonates.

Note 4

The minimum duration of postnatal follow-up should be one month to cover early functional testing (e.g., growth and behavior).

In general, if there is evidence for adverse effects on the immune system (or immune function) in the general toxicology studies, immune function testing in the offspring during the postpartum phase of the enhanced pre/postnatal development (ePPND) study is warranted. When appropriate, immunophenotyping can be obtained as early as postnatal day 28. The duration of postnatal follow-up for assessment of immune function can be 3-6 months depending on the functional test used.

Neurobehavioral assessment can be limited to clinical behavioral observations. Instrumental learning calls for a training period, which would result in a postnatal duration of at least 9 months and is not recommended.

Note 5

A detailed discussion of the approach to determine group sizes in cynomolgus monkey ePPND studies can be found in Jarvis et al, 2010. Group sizes in ePPND studies should yield a sufficient number of infants (6-8 per group at postnatal day 7) in order to assess postnatal development and provide the opportunity for specialist evaluation if necessary (e.g., immune system).

Most ePPND studies accrue pregnant animals over weeks and months. Consideration should be given to terminating further accrual of pregnant animals into the study, and adapting the study design (e.g., by Caesarian section) when prenatal losses in a test item group indicate a treatment-related effect.

Reuse of vehicle-control treated maternal animals is encouraged.

If there is some cause for concern that the mechanism of action might lead to an effect on EFD or pregnancy loss, studies can be conducted in a limited number of animals in order to confirm the hazard.

Note 6

Endpoints to be included in an interim report of an ePPND study in NHPs:

- Dam data: survival, clinical observations, bodyweight, gestational exposure data (if available), any specific PD endpoints;
- Pregnancy data: number of pregnant animals started on study, pregnancy status at both the end of organogenesis (gestation day (GD) 50) and at GD100, occurrence of abortions and timing of abortions. There is no need for ultrasound determinations of fetal size in the interim report; these are not considered essential since actual birth weight will be available;
- Pregnancy outcome data: number of live births/still births, infant birth weight, infant survival and body weight at day 7 postpartum, qualitative external morphological assessment (i.e., confirming appearance is within normal limits), infant exposure data (if available), any specific PD endpoints in the infant if appropriate.

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