Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals: Guidance for Industry

David McMillan, Ph.D., DABT
Division of Pharmacology/Toxicology for Infectious Diseases (DPT-ID)
U.S. Food & Drug Administration
January 17th, 2024
Guidance Overview

• The Agency has recently published a new guidance on nonclinical immunotoxicity testing.

• Draft version was published in February 2020.
  – Originally intended as a joint CDER/CBER guidance.
  – Substantial feedback was received during the public comment period.

• Final version was published in June 2023.
  – Now a CDER-only guidance.
  – Final version is extensively revised from the draft version.
Introduction and Background

• The new guidance applies to small molecule drugs, oligonucleotides, biopharmaceuticals (collectively referred to as “pharmaceuticals”).
  – “Cell and gene therapies, adjuvanted vaccines, and blood products are not within the scope of this guidance”.

• Intended to supplement ICH S8 and S6(R1), and replaces the 2002 CDER guidance, “Immunotoxicology Evaluation of Investigational New Drugs”.
  – Includes expanded guidance for assessing the carcinogenicity risk of immunomodulators, methods to assess the risk for adverse immunostimulation, nonanimal methods for assessing dermal sensitization, approaches for assessing the effects of immunotoxicants on pregnancy, and developmental immunotoxicity.

• Sponsors are encouraged to contact the appropriate review division with questions about this guidance.
General Immunosuppression Assessment

• Guidance regarding nonclinical immunotoxicity assessment of small molecules and biopharmaceuticals is provided by ICH S8 and ICH S6(R1), respectively.

• For pharmaceuticals intended to induce immunosuppression, sponsors should fully assess the known immunobiology of the intended MoA as it relates to the potential for adverse consequences of exaggerated pharmacology.
  – For less well-characterized immune targets, one or more dedicated nonclinical studies may be needed.
  – Dedicated assays may be warranted to characterize the effects of the pharmaceutical on other related immune functions.
  – Assay design should be dictated by the intended MoA along with scientific evaluation of how the intended immune suppression may otherwise affect the immune system.

• For biopharmaceuticals not intended to affect the immune system, sponsors may consider performing an integrated evaluation of the potential for unintended immunosuppression.
  – This evaluation could be similar to the WoE evaluation described in ICH S8.
  – Additional studies could be warranted depending on the findings of this assessment.

• For small molecule drugs that act via an antiproliferative MoA (e.g., anti-cancer drugs), follow-up assays such as those discussed in ICH S8 are generally not warranted.
Immunosuppression and Carcinogenicity

- Immunosuppression may increase the risk of certain tumor types in humans, and sponsors are encouraged to consider the effects of a drug on the immune system when assessing its carcinogenic potential.

- Sponsors should follow the recommendations in ICH S1A, S6(R1), S9, and S9 Q&As regarding the need for a carcinogenicity assessment as well as which approaches may be warranted.
  - Animal models, including rodent carcinogenicity studies, are of limited help in identifying an increased cancer risk that may arise as a consequence of immunosuppression.

- For small molecule drugs for which an increased risk of carcinogenicity is anticipated as a result of profound drug-induced immunosuppression (e.g., antirejection pharmaceuticals), a written, WoE-based risk assessment may be adequate to assess carcinogenicity risk.
  - A WoE-based risk assessment is particularly relevant for pharmaceuticals that lack the intended pharmacological activity in rodents and/or when standard rodent carcinogenicity studies are not technically feasible.
  - A WoE-based risk assessment may also be adequate for most immunomodulatory biopharmaceuticals.
Immunosuppression and Carcinogenicity

• This WoE-based risk assessment should address relevant attributes of the drug and drug target(s), with an emphasis on clinical translatability.
  – Should include an evaluation of the impact on immune cell subpopulations, including those thought to be involved in tumor surveillance (e.g., natural killer cells, T cells, antigen-presenting cells).
  – Should also include the potential to increase tumor promotion, growth, and metastasis.
  – For small molecules in particular, should also address the carcinogenic relevance of any drug-specific toxicology findings not related to the intended effect on the immune system (e.g., off-target activity).

• For small molecule drugs that act through a more targeted modulation of the immune system, such that profound immunosuppression is unlikely, the conduct of one or more rodent carcinogenicity studies may be warranted.

• Sponsors are encouraged to contact the appropriate review division with questions.
Immunosuppression and Opportunistic Infections

• Profound immunosuppression is known to increase the risk of opportunistic infections.

• The standard general toxicology studies are not designed to be able to reliably predict the risk of these infections occurring in humans.

• If there is a cause for concern, then an appropriately focused host resistance model could be considered to address this risk.
  – The design of such a study, and whether it is warranted, should be discussed with the appropriate review division.

• Regardless, the risk of opportunistic infections in humans as a result of drug-induced immunosuppression should be evaluated clinically.
Immunostimulation

- The evaluation of immunostimulation differs from that of immunosuppression, and may necessitate use of specific assays or alternative methodologies to facilitate initiation of first-in-human trials.

- Sponsors should understand the MoA of the pharmaceutical when determining which assays are most appropriate to evaluate the potential hazards.
  - The MoA, cellular distribution of the molecule, and potential to induce direct immunostimulation in key cell types (e.g., T cells, dendritic cells) should guide the approach to assay selection.

- Examples of immunostimulatory effects:
  - Cytokine release syndrome and cytokine storm (e.g., TGN1412).
  - General immune activation of T cells, T regulatory cells, or antigen-presenting cells caused by checkpoint inhibitor engagement.
  - Rapid, generalized depletion of target cells via immune clearance mechanisms resulting in generalized immune activation (with or without cytokine release).
  - Activation of PAMPs (e.g., TLRs) and/or complement by oligonucleotides.
Immunostimulation

• Multiple assays may be considered for the evaluation of these types of hazards.
  – All should include appropriate positive and negative controls and have clear, measurable outcomes.
  – Justification (e.g., validation study results, literature citation) should be provided to ensure the selected assay(s) are appropriate.

• Examples of possible assays:
  – Cytokine release assay
  – CDC/ADCC assays
  – Complement activation assays
  – Proliferation/activation assays
  – Other assays, such as those used to assess vaccine effectiveness or cellular proliferation (e.g., MIMIC assay).
  – Novel methods, such as use of microphysiological systems or immune-humanized mice, may be considered as long as appropriate validation is provided.
Immunostimulation

• Additional assays may not be necessary if a product has already been shown to directly cause cytokine release (e.g., a CD3 bispecific T cell redirector) or induce other forms of immune activation.

• A positive response in a cytokine release assay may not preclude further development of a drug, but depending on the indication, magnitude/duration of the effect, and/or the number and functions of cytokines affected, it may impact starting dose selection and dose escalation, inform clinical monitoring, the need for potential interventions, and stopping criteria.

• For biopharmaceuticals intended to stimulate an immune response either directly or indirectly, a starting dose based on a MABEL or a pharmacologically active dose may be more appropriate than those based on toxicology endpoints (i.e., NOAEL).
  – The same approach may apply to drugs intended to stimulate specific immune system outcomes, depending on the relevance of available animal models.

• The above approaches may also be suitable for assessing the immunotoxicity risk of products whose intended pharmacology does not involve immune cell activation but nonetheless are expected to activate components of the immune system (e.g., oligonucleotides).
Dermal Sensitization

• Topical pharmaceuticals should be assessed for their dermal sensitization potential.

• FDA will consider a battery of studies (e.g., in silico, in chemico, in vitro) that have been shown to adequately predict human skin sensitization with an accuracy similar to existing in vivo methods (see OECD test guidelines).

• FDA also currently accepts the guinea pig maximization test using the clinical formulation.

• FDA will also accept the murine LLNA but no longer recommends this assay because of its technical limitations.

• For topical pharmaceuticals, data from the dermal sensitization assessment should be submitted at the time of IND submission.
Systemic Hypersensitivity-Based Reactions

- To date, there are no standard nonclinical assays to adequately evaluate the potential risks of systemic hypersensitivity reactions (e.g., anaphylaxis).

- Fit-for-purpose assays and/or a WoE assessment may be considered if they are appropriately and scientifically justified.
  - Drug-induced anaphylactoid reactions, in vitro assays such as complement activation, or mast cell/basophil activation assays may have value in assessing risk.

- Sponsors should discuss their proposed approaches for assessing systemic hypersensitivity risk, and whether such studies are warranted, with the appropriate review division.
Assessing Adverse Effects on Implantation and Pregnancy

• Pharmaceuticals that affect the maternal immune system may adversely affect implantation, fetal development, and the ability to maintain pregnancy.

• For pharmaceuticals not intended to affect the immune system, the standard FEED and EFD studies are generally considered adequate for assessing this risk (see S5(R3)).

• For pharmaceuticals intended to affect the immune system, the standard FEED and EFD studies may help characterize these risks.
  – However, if the MoA of a pharmaceutical is known to be incompatible with fertility or maintenance of pregnancy, a WoE-based approach may be more appropriate.

• Fertility and early embryonic development studies are not generally warranted for pharmaceuticals intended to treat patients with advanced cancer (see S9).
Assessing Developmental Immunotoxicity

• Pharmaceuticals that have do not appreciably affect the mature immune system may nonetheless adversely affect the developing immune system.

• As described in ICH S8, an evaluation of the potential of a pharmaceutical to adversely affect the developing immune system relies on a WoE assessment of multiple factors.

• If there is a concern that a pharmaceutical may adversely affect immune development, and the existing data do not adequately characterize the risk to the subject (e.g., pediatric patient, or infant exposed in utero or via lactation), then sponsors should further characterize this risk.
  – As recommended in ICH S11, this can include the evaluation of immune endpoints in the offspring of treated dams in a PPND/ePPND study, if adequate exposure is demonstrated in the offspring.
  – A JAS in which juveniles are directly exposed to the pharmaceutical may be warranted if the PPND/ePPND study does not adequately characterize the risk.
  – JAS and PPND/ePPND studies are generally not warranted for pharmaceuticals intended to treat patients with advanced cancer.
Assessing Developmental Immunotoxicity

- Should a study be warranted to assess the risk of developmental immunotoxicity, the test species and endpoints should be appropriate and scientifically justified.
  - The endpoints could include enumeration of specific immune cell populations (immunophenotyping), the function of the immune system and its components, and/or the anatomical integrity of the immune system.
  - As there are differences in the timing of immune development, sponsors should ensure that the dosing interval covers the intended developmental period.

- Sponsors should consult the appropriate review division before conducting ePPND or JAS to avoid unnecessary use of animals.
Risk Assessment

• “There is limited understanding of the extent of reduced (or increased) immune function required to have a significant biological effect in humans (e.g., increased risk of infection, tumor development, or autoimmunity). A WoE approach where all immunotoxicity data are considered as a whole (e.g., consideration of the MoA of the drug, the translatability of nonclinical findings, the predicted extent and duration of human exposure, the clinical population, disease status, concomitant medication, etc.) is recommended when interpreting the findings of immunotoxicity assays and when considering the risk of clinically significant immunotoxicity occurring in humans.”
Administrative Considerations

• Sponsors should, to the extent practicable, follow existing guidance on placing immunotoxicology studies in the eCTD format.
  – Stand-alone immunotoxicology studies should be included in section 4.2.3.7.2
  – Stand-alone assessments of antigenicity (allergenicity) should be included in section 4.2.3.7.1.
  – WoE assessments of immunotoxicology should be included in section 4.2.3.7.2.
  – Data evaluating the immune system, which are part of a general repeat-dose toxicity study, including immunogenicity (ADA formation) data, should be included with the repeat-dose toxicity study in section 4.2.3.2.

• Sponsors should refer to the FDA eCTD technical specification *The Comprehensive Table of Contents Headings and Hierarchy* for further details.