Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2023
Pharmacology/Toxicology

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the nonclinical evaluation of the immunotoxic potential of pharmaceuticals. *Immunotoxicity* is, for the purposes of this guidance, defined as unintended immunosuppression or stimulation (including hypersensitivity), which can include adverse effects of exaggerated pharmacology of pharmaceuticals that are intended to act as immunomodulators.[2] This guidance applies to drug products, including small molecule drugs and oligonucleotides, as well as certain biological products such as biotechnology-derived therapeutic proteins (referred to herein as *biopharmaceuticals*). For the purposes of this guidance, the term *pharmaceutical* will be used as a general term that encompasses all of these product types. Cell and gene therapies, adjuvanted vaccines, and blood products are not within the scope of this guidance.

In general, FDA's guidance documents 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.

II. BACKGROUND

The immune system is a complex and tightly regulated system that involves multiple biological components (e.g., circulating peptides, proteins and cells, tissue-resident cells, as well as

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, an *immunomodulator* is a pharmaceutical that is intended to alter the performance of a discrete component of the immune system to either stimulate or suppress specific immune system activities.

specific tissues and organs distributed throughout the body) and mediates complex physiological responses, with the primary purpose of protecting the body from infections, tumors, and foreign substances. Perturbations of the function of the immune system have the potential to result in adverse consequences—immunotoxicity—which can in some cases be severe. Therefore, an assessment of the ability of pharmaceuticals to adversely affect the activity of the immune system is an essential component of evaluating the safety of pharmaceuticals.

There are internationally harmonized guidances that provide recommendations related to the assessment of immunotoxicity risk. The primary guidances concerning immunotoxicity assessment of small molecule drugs and biopharmaceuticals are the ICH guidances for industry *S8 Immunotoxicity Studies for Human Pharmaceuticals* (April 2006)[3] and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012). The guiding principle of both guidances is that the assessment of immunotoxic potential relies primarily upon integration of the findings of the general toxicity studies in combination with other data, such as (1) pharmacological properties of the pharmaceutical, (2) intended patient population, (3) structural similarities to compounds known to affect the immune system, (4) pharmaceutical disposition, (5) and findings in clinical studies. For immunomodulators, the role of the intended target in immune function should also be considered. When this first-tier assessment identifies a potential immunotoxicity hazard, more specific assessments of immune function may be warranted to further characterize the risk to human subjects and patients.

In addition to these aforementioned ICH guidances, FDA maintained guidance for investigational new drugs that was published as final guidance in 2002.[4] The guidance provided immunotoxicity guidance that was outside of the scope of ICH S8 (e.g., hypersenstitivity, adverse immunostimulation). This present guidance expands upon the previously withdrawn 2002 guidance by broadening the scope to also include pharmaceuticals intended to affect the immune system, biopharmaceuticals, and oligonucleotides. Expanded guidance is also provided for assessing the carcinogenicity risk of immunomodulators, methods to assess the risk for adverse immunostimulation (e.g., cytokine release assays), nonanimal methods for assessing dermal sensitization, approaches for assessing the effects of immunotoxicants on pregnancy, and developmental immunotoxicity.

This guidance finalizes the draft guidance for industry *Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics* (February 2020).[5]

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[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See the guidance for industry *Immunotoxicology Evaluation of Investigational New Drugs* (October 2002)—withdrawn.

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

For product-specific recommendations related to this guidance, FDA recommends that sponsors contact the appropriate review division.[6]

III. ASSESSING THE POTENTIAL TO SUPPRESS IMMUNE SYSTEM ACTIVITY

A. General Immunosuppression Assessment

As noted above, internationally harmonized guidance regarding nonclinical immunotoxicity assessment of small molecule drugs and biopharmaceuticals is provided by ICH S8 and ICH S6(R1), respectively. The following concepts for the assessment of immunosuppression risk should be considered in conjunction with these guidances.

For pharmaceuticals (including biopharmaceuticals) that are intended to act via a suppressive immunomodulatory mechanism of action (MoA), sponsors should fully assess the known immunobiology of the intended mode of action as it relates to the potential for adverse consequences of exaggerated pharmacology. For less well-characterized immune targets, this assessment may warrant one or more dedicated nonclinical studies[7] to better inform the risk of exaggerated target engagement. In addition, dedicated assays may be warranted to characterize the effects of the pharmaceutical on other related immune functions. The specifics of on- and off-target assay selection should be dictated by the intended MoA of the pharmaceutical along with scientific evaluation of how the intended immune suppression may affect related activities of the immune system.

For biopharmaceuticals that are 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 in principle to the weight-of-evidence (WoE) evaluation as described in ICH S8. Whether any additional studies are warranted would be guided by the findings of the integrated evaluation.

For small molecule drugs that act via an antiproliferative MoA, such as those used to treat cancer, follow-up assays such as those discussed in ICH S8 are generally not warranted.

B. Immunosuppression and Carcinogenicity

Immunosuppression has the potential to increase the risk of certain tumor types in humans, depending on which components of the immune system are suppressed and to what extent. Tumors arising from immunosuppression are primarily associated with loss of control of chronic/latent pathogen infections, although direct interference with tumor surveillance could

[6] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[7] FDA supports the principles of the 3Rs (replace/reduce/refine) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, and feasible. FDA will consider whether the alternative method is adequate to meet the nonclinical regulatory need.

also result in an increased risk for tumors. As such, sponsors should consider the effects of a drug on the immune system when assessing its carcinogenic potential.

Sponsors should follow the recommendations in the ICH guidances for industry *S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996), ICH S6(R1), *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010), and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals—Questions and Answers* (June 2018) regarding the need for a carcinogenicity assessment as well as which experimental approaches may be warranted. To date, animal models, including rodent carcinogenicity studies, have been shown to be of limited help in identifying an increased cancer risk that may arise in patients as a consequence of immunosuppression. This is particularly true when the increased tumor risk is caused by recrudescence of latent viral oncogenes, infectious agents, or chronic inflammatory states, for which significant species differences exist that make clinical translatability challenging. 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 also particularly relevant for pharmaceuticals that lack the intended pharmacological activity in rodents and/or when standard carcinogenicity studies in rodents are not technically feasible. A WoE-based risk assessment may also be adequate for most immunomodulatory biopharmaceuticals.

This WoE-based risk assessment should address relevant attributes of the drug and drug target(s), including an evaluation of the impact on immune cell subpopulations and the potential for a drug to increase tumor promotion, growth, and metastasis, with an emphasis on clinical translatability. The effects of the pharmaceutical on key immune components thought to be involved in tumor surveillance (e.g., natural killer cells, T cells, antigen-presenting cells), such as downregulation or functional impairment of key immune cell populations, should be considered. For small molecule drug products in particular, the WoE-based risk assessment should also address the carcinogenic relevance of any compound-specific toxicology findings not related to the product's 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.[8]

FDA recommends that sponsors discuss their proposed approach for assessing carcinogenic potential of their product with the appropriate review division.

C. Immunosuppression and Opportunistic Infections

Profound immunosuppression is known to increase the risk of opportunistic infections, which are typically associated with a wide range of bacteria, viruses, fungi, and parasites. The standard general toxicology studies are not designed to be able to reliably predict the risk of these

[8] See the ICH draft guidance for industry *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals* (November 2022). When final, this guidance will represent the FDA's current thinking on this topic.

infections occurring in humans. If the WoE review suggests a cause for concern, then an appropriately focused host resistance model, which may provide additional insight, could be considered. 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.

VI. ASSESSING THE POTENTIAL TO INCREASE IMMUNE SYSTEM ACTIVITY

A. Immunostimulation

Assessment of the risks associated with a heightened immune response normally requires a safety evaluation paradigm that differs from that of immunosuppression, and may use specific assays or alternative methodologies for translation to first-in-human trials.

Except where indicated, *immunostimulatory pharmaceuticals* are defined in this section as products that are intended to either directly stimulate signaling in an immune cell subtype or indirectly enhance the immune system response by blocking or activating an endogenous regulator of the immune system response.

Toxicities of these products are often the result of exaggerated pharmacological activity but may also be caused by expression of the target receptor in untargeted immune cell subpopulations or tissues. It is therefore important to understand the MoA of the pharmaceutical when determining which assays are most appropriate to evaluate the potential hazards. For example, assays used when evaluating the immunotoxicity of T cell-engaging (direct activation) molecules would be different from assays used when evaluating checkpoint inhibitors or receptor agonists. 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.

The following are examples of immunostimulatory effects:

- Excessive release of cytokines that can cause severe adverse reactions[9] as shown by the near-fatal clinical responses to the monoclonal antibody TGN1412 (Duff 2006). It should be noted that the intended MoA of TGN1412 was immunosuppression through activation of regulatory T cells, but its administration resulted in strong immunostimulation of effector memory T cells. There are now commonly used in vitro models available to evaluate the potential for this hazard (Bugelski et al. 2009; Finco et al. 2014; Grimaldi et al. 2016).

- General immune activation of T cells, T regulatory cells, or antigen-presenting cells caused by checkpoint inhibitor engagement resulting in immune-mediated tissue damage in nontarget organs.

[9] See guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014).

- Rapid, generalized depletion of target cells via immune clearance mechanisms resulting in generalized immune activation (with or without cytokine release) as can be observed with rapid Fc receptor–based clearance.

- Activation of pathogen-associated molecular pattern receptors (e.g., toll-like receptors) and/or complement by oligonucleotides.

Below are examples of assays that may be considered for the evaluation of these types of hazards. This list is not intended to be all-inclusive, as new assays and technologies are constantly emerging and evolving. Sponsors should use the criteria defined above to determine which assays will best identify the hazards associated with their molecule and what dosing and monitoring will be most appropriate for the first-in-human clinical trial. All assays should include appropriate positive and negative controls and have clear, measurable outcomes. Information should be provided to support that the conducted assay(s) is fit-for-purpose (e.g., validation study results, literature citation).

- Cytokine release assay — Standard assays to date include use of soluble and immobilized formats using peripheral blood mononuclear cells, whole blood, and other matrices. Other formats that may be considered include endothelial cell/peripheral blood mononuclear cell co-culture assay, tumor and endothelial cell co-cultures, and use of patient-derived cells.

- Complement-dependent cytotoxicity/antibody-dependent cell-mediated cytotoxicity assays — Complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity assays evaluate cytolytic processes using either complement or antibody-dependent interactions for cell lysis to occur.

- Complement activation assays — Measurement of the levels in serum of activated complement fragments (C3a, C5a) and/or the Bb split product.

- Proliferation/activation assays — Many assays exist to assess proliferation, including carboxyfluorescein succinimidyl ester (CFSE) proliferation assay, 5-bromo-2'-deoxyuridine incorporation assay, flow cytometric assessment of activation markers, and the enzyme-linked immune absorbent spot (ELISpot) assay, among others. Such assays will evaluate the ability of T cells to activate and proliferate and in some cases assess innate immune activation of antigen-presenting cells.

- Other assays — Assays typically used to assess vaccine effectiveness or cellular proliferation such as MIMIC (minimal methylation classifier) and other new technologies can be considered depending on the molecule being evaluated. Novel methods, including microphysiological systems or immune-humanized mice, may also be options depending on the validation of these techniques.

If a product has already demonstrated a clear potential to directly cause cytokine release (e.g., a CD3 bispecific T cell redirector) or induce other forms of immune activation, then additional

assays may not be necessary, as the hazard has already been identified. Similarly, if one assay is positive, then an assay in another format may not be warranted.

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

For biopharmaceuticals intended to stimulate an immune response either directly or indirectly, a starting dose based on a minimal anticipated biologic effect level or a pharmacologically active dose may be more appropriate than a starting dose based on toxicology endpoints, such as the no-observed-adverse-effect level. The same approach may apply to drug products 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).

B. Dermal Sensitization

Topical pharmaceuticals should be assessed for their dermal sensitization potential. Dermal sensitization is an immune response to a previously encountered chemical or substance that results in an inflammatory dermal reaction upon reexposure. As an assessment of skin sensitization for individual chemicals, 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. Several in chemico and in vitro assays for skin sensitization and defined approaches for combining data are described in the Organisation for Economic Co-operation and Development (OECD) test guidelines.[10] Additionally, FDA also currently accepts the guinea pig maximization test using the clinical formulation to assess the sensitization potential of a topical drug product. FDA will also accept the murine local lymph node assay but no longer recommends this assay because of its technical limitations (Basketter and Kimber 2011).

[10] See OECD (2021), Test No. 442C: In Chemico Skin Sensitisation: Assays addressing the Adverse Outcome Pathway key event on covalent binding to proteins, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264229709-en; OECD (2018), Test No. 442D: In Vitro Skin Sensitisation: ARE-Nrf2 Luciferase Test Method, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264229822-en; OECD (2018), Test No. 442E: In Vitro Skin Sensitisation: In Vitro Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264359-en; OECD (2021), Guideline No. 497: Defined Approaches on Skin Sensitisation, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/b92879a4-en.

For topical pharmaceuticals, data from the dermal sensitization assessment should be submitted at the time of investigational new drug application submission.

C. Systemic Hypersensitivity-Based Reactions

Systemic hypersensitivity reactions are significant potential pharmaceutical-induced adverse reactions. To date, however, there are no standard nonclinical assays to adequately evaluate the potential risks. Fit-for-purpose assays and/or a WoE assessment may be considered as long as they are appropriate and scientifically justified. For example, for drug-induced anaphylactoid reactions, in vitro assays such as complement activation or mast cell/basophil activation assays may have value in assessing risk. FDA recommends that sponsors discuss their proposed approaches for assessing systemic hypersensitivity risk, and whether such studies are warranted, with the appropriate review division.

V. ASSESSING ADVERSE EFFECTS ON IMPLANTATION AND PREGNANCY

Pharmaceuticals that affect the maternal immune system have the potential to adversely affect implantation of the embryo, fetal development, and the ability to maintain the pregnancy.

For pharmaceuticals that are not intended to affect the immune system, the risk for adverse effects on the maternal immune system that can affect implantation and gestation would typically be identified in the fertility and early embryonic development and/or embryo-fetal development studies conducted on most pharmaceuticals.[11] These studies would generally be considered adequate for assessing this risk.

Similarly, for pharmaceuticals that are intended to affect the immune system, fertility and early embryonic development and embryo-fetal development studies may have utility in characterizing the risk for adverse effects on the maternal immune system that can affect implantation and gestation. However, if the MoA of a pharmaceutical is known to be incompatible with fertility or maintenance of pregnancy, it may be appropriate to assess the risk based on a WoE approach.[12,13]

Fertility and early embryonic development studies are not generally warranted for pharmaceuticals intended to treat patients with advanced cancer.[14]

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[11] See the ICH guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021).

[12] Ibid.

[13] See the guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (May 2019).

[14] See ICH S9.

VI. ASSESSING DEVELOPMENTAL IMMUNOTOXICITY

Pharmaceuticals that have no appreciable adverse effect on the mature immune system nonetheless have the potential to adversely affect the developing immune system. Given the extended period over which the immune system develops, the immune system can be sensitive to adverse effects of pharmaceuticals throughout the fetal, neonatal, and juvenile stages of development.

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

If there is a concern that immune system development could be adversely affected by a pharmaceutical, and the existing data do not adequately characterize the risk to the exposed subject (pediatric patient or in utero or lactationally exposed infant), then sponsors should provide additional data to characterize this risk. As recommended in the ICH guidance for industry *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals* (May 2021), this can include the evaluation of immunotoxicology endpoints in the offspring of treated dams in otherwise warranted developmental toxicology studies (i.e., pre- and postnatal development (PPND) study or enhanced PPND (ePPND) study) if adequate exposure to the pharmaceutical is demonstrated in the offspring. A juvenile animal study in which juveniles are directly exposed to the pharmaceutical may be warranted if the PPND/ePPND study is unable to adequately characterize the risk. Juvenile and PPND/ePPND studies are generally not warranted for pharmaceuticals intended to treat patients with advanced cancer.

Should a study be warranted to assess the risk of developmental immunotoxicity, the test species should be appropriate for the endpoints being assessed. The endpoints to be included should be scientifically justified and appropriate for assessing the concern, and 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 system developmental landmarks across species (Skaggs et al. 2019), sponsors should ensure that the dosing interval covers the intended developmental period.

To avoid the potentially unwarranted use of animals, sponsors should consult with the appropriate review division before conducting ePPND or juvenile animal studies, particularly if the studies are being conducted solely for assessing developmental immunotoxicity risk.

VII. 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.

VIII. ADMINISTRATIVE CONSIDERATIONS

Sponsors should, to the extent practicable, follow existing guidance on placing immunotoxicology studies in the electronic common technical document (eCTD) format.[15] Stand-alone immunotoxicology studies should be included in the eCTD in section 4.2.3.7.2, with the exception of stand-alone assessments of antigenicity (allergenicity), which should be included in section 4.2.3.7.1. WoE assessments of immunotoxicology should be submitted to eCTD section 4.2.3.7.2. Data evaluating the immune system, which are part of a general repeat-dose toxicity study, including immunogenicity (antidrug antibody formation) data, should be included with the repeat-dose toxicity study in section 4.2.3.2. Please refer to the FDA eCTD technical specification *The Comprehensive Table of Contents Headings and Hierarchy*[16] for further details.

[15] See the ICH guidance for industry *M2 eCTD: Electronic Common Technical Document Specification* (April 2003).

[16] Accessible at https://www.fda.gov/downloads/drugs/ucm163175.pdf.

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