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July 19, 2021

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

RE: Docket No. FDA-2008-D-0406 for "Frequently Asked Questions—Statement of Investigator (Form FDA 1572) (Revision 1)"

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is pleased to submit these comments on the Food and Drug Administration's (FDA's or the Agency's) Federal Register notice and request for comments entitled "*Frequently Asked Questions—Statement of Investigator (Form FDA 1572) (Revision 1)*."[1] PhRMA appreciates the effort to provide clarity on when a Form FDA 1572 waiver is needed and detail steps for sponsors to request a waiver of the Form FDA 1572 signature requirements for foreign investigators. PhRMA believes sponsors would benefit from complete and clear guidance relating to use of the waiver.

PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested nearly $1 trillion in the search for new treatments and cures, including an estimated $83 billion in 2019 alone.

I. GENERAL COMMENTS

PhRMA appreciates FDA's efforts to update the 2010 guidance,[2] *Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs; Frequently Asked Questions (FAQ) - Statement of Investigator (Form FDA 1572*) and provide additional information in the current draft guidance. PhRMA members conduct high-quality clinical research including trials and observational studies to rigorously test scientific hypotheses and gather scientific data in accordance with applicable laws and regulations globally, as well as locally recognized good clinical practices. Principles for the conduct of clinical research are set forth in internationally recognized documents such as the Declaration of Helsinki and the Guideline for Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH). When conducting multinational,

[1] 86 FR 27449; Frequently Asked Questions—Statement of Investigator (Form FDA 1572) (Revision 1) (May 20, 2021). Available at https://www.federalregister.gov/d/2021-10612.

[2] FDA, Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs – Frequently Asked Questions - Statement of Investigator (Form FDA 1572) (May 2010). Available at https://www.regulations.gov/document/FDA-2008-D-0406-0038.

multi-site trials, sponsors follow these international standards, local laws, and regulations as applicable.

PhRMA understands the general purpose behind FDA's issuance of the draft guidance is to respond to queries related to the use of Form FDA 1572, specifically when foreign investigators are unwilling or unable to sign the form. However, the current draft guidance lacks clarity regarding the rationale for the process FDA has put in place for the submission, review, and approval of Form FDA 1572 signature waiver requests ("waiver requests"). PhRMA encourages FDA to consolidate and streamline the 2010 guidance and current draft guidance to provide clear and explicit guidance to sponsors on this process. For example, PhRMA suggests that FDA revise the guidance to address timelines for communicating waiver decisions, under what circumstances waivers would not be granted, and how sponsors may proceed when waivers are not granted.

II. SPECIFIC COMMENTS

A. *PhRMA urges the Agency to align the Form FDA 1572 waiver request process with IND protocol amendment process to ensure timely initiation of clinical studies and patient access to important medicines*

Newly added *FAQ 43*[3] articulates FDA's recommendation that sponsors "*wait for the waiver request to be granted before initiating the study at the site*." FDA proceeds to note that the "*sponsor should not assume that no response or a delayed response from the Agency means that the request for waiver has been granted*." PhRMA believes that this approach may unnecessarily delay patient enrollment and clinical trials without clear benefit in many circumstances, as FDA would generally evaluate the same information sponsors would derive as part of their due diligence efforts to qualify sites and/or investigators. Ultimately, a recommendation to wait for FDA approval of the waiver request – with no clear timeline for FDA response - may lead to delays in drug development and patient access to important medicines. Accordingly, we recommend FDA amend the FAQ to recommend that sponsors may initiate clinical studies at sites where a Form FDA 1572 has not been signed *at the time the sponsor has submitted a request for waiver under 21 CFR 312.10*. This would align with the IND protocol amendment process for adding a new investigator, which does not require FDA pre-approval of the new investigator.[4] PhRMA believes this suggested approach would allow sponsors to obtain and submit all pertinent documentation, but with an understanding that site initiation will proceed. For example, waiver requests submitted at the start of IND filing could be evaluated by the Agency during the 30-day IND review period with waivers granted by default if no action is taken by the Agency.

[3] 86 FR 27449; Frequently Asked Questions—Statement of Investigator (Form FDA 1572) (Revision 1) (May 20, 2021). Available at https://www.federalregister.gov/d/2021-10612. Page 6, FAQ 43.

[4] 21 CFR 312.30(c) requires that sponsors "notify FDA of the new investigator within 30 days of the investigator being added."

To the extent FDA retains its recommendation that sponsors wait for FDA approval of waivers of the Form 1572 requirement before initiation of studies, PhRMA suggests FDA include an anticipated timeline by which FDA will respond to such waivers. Specifically, we recommend FDA strive to respond to such waiver requests within a pre-specified time-period. PhRMA believes that in most circumstances the information to be reviewed will be relatively streamlined and may be reviewed in a relatively short amount of time (e.g., within 30 days similar to IND).

B. *PhRMA recommends that the Agency modernize the waiver request process by adopting a trial- or protocol-based waiver process for Form FDA 1572*

PhRMA recommends that FDA include guidance and establishment of a process for certain common types of waiver requests from the Form 1572 requirement. Specifically, PhRMA encourages FDA to adopt a trial- or protocol-based waiver process. Under such a process:

- new or changed information about investigators or sites could be provided as amendments or updates to the initial waiver rather than submitting waiver requests on individual investigators that need to be qualified, and
- individual investigator amendments/updates could proceed unless FDA responds to sponsors within a pre-specified timeframe (such as within 30 days similar to IND).

Given FDA's acknowledgement that regional, national, and/or local laws may prevent investigators from signing Form 1572, FDA could provide a streamlined waiver review for trials or protocols that will include sites where the form cannot be signed, internationally recognized GCP standards are followed (e.g., GCP-related ICH guidelines) and comply with applicable regional, national, and/or local requirements.

PhRMA also suggests that the FDA permit a study- or country-level waiver under 21 CFR 312.10; this would streamline the process further by allowing sponsors to provide documentation to the FDA as each site is added by referencing the country-level waiver. Additionally, PhRMA recommends that the Agency allow waivers to be applied across all studies included under the IND in countries that do not allow investigators to sign the Form FDA 1572 to ensure timely study initiation.[5] Finally, to the extent that individual Form FDA 1572 waivers are required, FDA should allow batch submission requests to minimize delays in enrollment, simplifying the submission process for sponsors and review process for FDA.

In addition to the comments provided above, PhRMA provides comments pertaining to lines or sections of the current draft guidance (See Appendix I).

[5] EFPIA, EFPIA CDEG position paper on the use of Form 1572 for clinical trials performed outside the USA (July 14, 2020). Available at https://www.efpia.eu/media/413440/efpia-cdeg-position-paper-on-the-use-of-form-fda-1572-for-clinical-trials-performed-outside-the-usa.pdf.

III. CONCLUSION

PhRMA appreciates the Agency providing revised guidance to sponsors regarding Form FDA 1572. PhRMA continues to support regulations and guidance documents that promote human subject protection and efficient and timely drug development.

Respectfully submitted,

/S/	/S/
Kristin Dolinski Deputy Vice President, Science and Regulatory Advocacy	Sarah K Spaulding (Martin), MS, PhD Director, Science and Regulatory Advocacy

APPENDIX I.

Line/Section	Text & Comment	Proposed Solution
Lines 98 - 100	The draft guidance states that a "sponsor can request that FDA provide a specific waiver from the part 56 institutional review board (IRB) requirements, allowing an IEC that complies with good clinical practice to substitute for the IRB."	PhRMA recommends FDA provide clarity on if the waiver will be applied across the study.
Lines 102 – 107	The draft guidance states that "[t]he second exception is that the requirements for informed consent under 21 CFR part 50 for particular clinical trials (e.g., emergency research under 21 CFR 50.24, clinical investigations involving pediatric subjects under subpart D) are more extensive than ICH E6 with respect to IRB responsibilities. Our experience has not revealed that this difference has caused a conflict, but in the event of one, we would be willing to discuss a resolution with the sponsor on a case by-case basis."	PhRMA recommends that FDA address whether a waiver would be needed in this circumstance.
Lines 117	New Section IV provides updated FAQs that respond to queries received by FDA.	PhRMA encourages FDA to consider other practical issues that arise during clinical research that are not already addressed in the FAQ. While the updated FAQ included in Section IV are helpful to sponsors, PhRMA encourages FDA to consider adding additional detail on specific instances that may arise during clinical research that impact the status of a submitted Form FDA 1572 (e.g., when a site changes an investigator, when an investigator moves to a different site that is also part of the clinical program, considerations for patients enrolled at a site that experiences one of the above situations).
Line 151	FDA states that the inclusion of "other information justifying a waiver" is one option for the submission of a waiver request.	PhRMA requests that FDA provide examples of "other information."

Line/Section	Text & Comment	Proposed Solution
Lines 195-211	This section notes when a sponsor should submit a waiver request, including the addition of new investigators. However, it does not clarify whether a sponsor needs to seek a new or updated waiver if an investigator has an updated Form FDA 1572 during the trial.	PhRMA recommends that the waiver apply to the investigator through the course of the study.
Lines 205-208	The draft guidance states that "if after a waiver request is granted, new investigators are added to this IND protocol who refuse or cannot sign the Form FDA 1572 and the sponsor wants to request a waiver of the Form FDA 1572 signature requirement, they will need to submit a new waiver request applicable to these new investigators (21 CFR 312.53(c)(1); 21 CFR 312.10))."	PhRMA recommends that there be an option to amend the initial waiver request.