This document summarizes changes in *Policy 500 Research Involving Drugs, Biological, and Nutritional Products* (referred to as Policy 500 in this document) that NIH investigators should be aware of, from the SOP mentioned below.

The policy describes the responsibilities of NIH investigators, non-NIH investigators, NIH sponsors, and the NIH Institutional Review Board (IRB) when conducting or reviewing human subjects research (HSR) that involves the use of drugs, biological products, or nutritional products (e.g., dietary supplements or foods) that are under the oversight of the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS).

This table is a high-level summary. It is not an in-depth review, and not all points raised in the policy will be included here. Therefore, NIH investigators are responsible for reviewing Policy 500 and complying with the requirements of the policy.

Note: Text from the policy and other policy titles are italicized.

Policy 500 Research Involving Drugs, Biological, and Nutritional Products	**SOP Superseded by Policies:**
Policy 500 partially supersedes	***SOP 15 Research Regulated by the Food and Drugs Administration (FDA): General Procedures for Both IND and IDE Applications*** When inactivated, this SOP will be archived in the Policy Archive.
Policy 500 fully supersedes	***SOP 15A Research Regulated by the Food and Drugs Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)*** When inactivated, this SOP will be archived in the Policy Archive.

Applicability of Policy 500 - This policy applies to:

- **NIH investigators when conducting FDA-regulated research involving drugs, biological products, or nutritional products (referred to in this policy as "test articles"), whether or not the research is conducted under an Investigational New Drug application (IND).**
  - **Information regarding treatment use and expanded access to investigational drugs, biological products or nutritional products is addressed in NIH *Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices.***
- **Non-NIH investigators when conducting FDA-regulated research involving the use of drugs, biological products, or nutritional products, when the NIH IRB is the Reviewing IRB.**
- **NIH IRB as the Reviewing IRB.**

Policy Requirement	SOP Requirement
Section C.1. – *NIH investigators and non-NIH investigators conducting human subjects research involving drugs, biological products, or nutritional products, must comply with all applicable FDA regulations including, but not limited to, 21 CFR parts 50, 56, 312 and 600 as well as those set forth in HHS regulations at 45 CFR 46.* *AND* **Section C.2.** – *When reviewing and approving research that involves drugs, biological products, or nutritional products, the NIH IRB must apply the applicable FDA regulations including, but not limited to, 21 CFR parts 50, 56, 312 and 600 as well as those set forth in HHS regulations 45 CFR 46.* Policy 500 is largely regulatory and reflects FDA and Common Rule requirements of which investigators and the IRB should already be aware.	**SOP 15, Section 15.2.** – *NIH researchers will conduct research that involves test articles* and human subjects* (i.e., clinical investigations*, in accordance with relevant FDA and Department of Health and Human Services (DHHS) regulatory requirements.* AND **SOP 15, Section 15.4.2.A.** – *The IRB will review the research protocol in accordance with applicable DHHS regulations (see SOP 8 – Procedures and Required Documentation for Initial Review of Protocols by a Convened NIH Institutional Review Board.), and FDA regulations (see 21 CFR part 56, References, for FDA regulations related to IRBs).*
Section C.3. – *By NIH policy, NIH investigators may not be Sponsors, effective January 15, 2018. However, investigators may have sponsor responsibilities when required by regulation.* *AND* **Section E.3.** – *a. By NIH policy, INDs shall be held by the IC, rather than by the NIH PI on the clinical protocol.* *b. Investigators may serve as the sponsor for expanded access protocols. (See Policy 502 Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles).)* Except in the case of expanded access protocols, the ICs hold all INDS rather than the NIH PI.	NA (Not applicable) SOP 15A was published prior to the January 15, 2018 NIH policy on who may be a sponsor in the IRP.

Section E.1.a. – *When the research involves the clinical investigation of a test article, the PI will provide documentation in the protocol whether the test article(s) for use is under an IND or provide written justification for why the test article(s) is exempt from the requirement for an IND.* See section E.1.a. – E.1.a.V.ii. for specific obligations relating to either obtaining an IND or deeming the study to be exempt from IND requirements. It is worth noting for IND-exempt test articles, that the term "exempt" does not mean exempt from IRB oversight or from the entirety of FDA regulations. IND exempt means 'exempt from some of the requirements of 21 CFR 312.' All other FDA regulations still apply (e.g., 21 CFR 50, and 21 CFR 56).	**SOP 15A, Section 15.A.3.** – *Investigations involving investigational drugs* must be conducted in accordance with applicable FDA regulations, including the investigational new drug regulations at 21 CFR Part 312 (See References).* SOP 500 is reorganized for clarity. There are no changes in regulatory obligations.
Section E.1.b. through E.1.h. – This section of the policy describes the Principal Investigator's responsibilities under FDA regulation as they relate to: • conducting the investigation, • obtaining informed consent, • ensuring control of drugs under investigation, including documentation, maintenance, and tracking of the test article, • ensuring the protocol has a maintenance and tracking plan for the test article that includes receipt, storage, dispensing, and disposition of all investigational drugs, • safety reporting, including promptly reporting serious adverse events to sponsors and reporting AEs, AES, Deaths, UPs, protocol deviations, and noncompliance consistent with the sponsor reporting requirements, NIH	**SOP 15 and SOP 15A** included these same regulatory obligations. Policy 500 is reorganized for clarity.

IC policy, and *Policy 801 Reporting Research Events*, • submitting required reports, • recordkeeping, • and record retention. See Policy 500 for additional details.	
Section E.1.i. – *If the PI terminates or suspends a trial without prior agreement of the sponsor, the PI must inform the IRB and the sponsor promptly.* AND **Section E.1.j.** – *If the sponsor terminates or suspends a trial, the PI must promptly inform the IRB and provide the Board with a detailed written explanation of the termination or suspension.* AND **Section E.1.k. –** *If the Reviewing IRB terminates or suspends its approval of a trial, the PI will promptly inform the sponsor.* In addition, when a trial is terminated, the PI must work with the IRB to create a plan to promptly inform study subjects and to ensure appropriate therapy and follow-up for any enrolled or former study subjects, if applicable.	**SOP 15, section 15.3.12.** included these same obligations.
Section E.2. – lists sponsor responsibilities under relevant FDA regulations when the sponsor is the NIH or an NIH employee. See Policy 500 for additional details.	**SOP 15** and **SOP 15A** included these same regulatory obligations. Policy 500 is reorganized for clarity.
Section E.4. – outlines IRB responsibilities under relevant FDA regulations when the NIH IRB is the reviewing IRB. Under Policy 500, when the IRB cannot confirm that the test article is exempt from IND requirements, the IRB will either require the PI submit an IND application to the FDA or	**SOP 15** and **SOP 15A** included these same regulatory obligations. Policy 500 is reorganized for clarity

request a formal FDA determination as to whether an IND is needed. Such a determination by the FDA is considered to be final with regard to the need for an IND. The IRB will not fully process a submitted IRB application until a determination has been reached by the FDA, or until 30 days has elapsed since submission of the IND application. See Policy 500 for additional detail.	
Section E.5. – *Responsibilities related to FDA Inspections* **Section E.5.a.I. -** *NIH researchers who are informed of an FDA inspection must immediately notify their Clinical Director, Clinical Center (CC) CEO, ORSC, and OHSRP.* Policy 500 requires investigators, sponsors, IRBs, and other FDA regulated entities such as the NIH Radioactive Drug Research Committee, or the pharmacy, to make records available for FDA inspection. AND **Section E.5.c.** – *Any written responses to the FDA submitted by NIH researchers must first be approved by the Clinical Director, CC CEO, ORSC, and OHSRP.* (emphasis added) *The appropriate party must provide a draft response to the Clinical Director, CC CEO, ORSC, and OHSRP at least four business days before it must be submitted to the FDA.* See Policy 500 for additional details about this obligation.	**SOP 15, Section 15.3.6.C.** – FDA inspections: Investigators and IRBs must make records available for FDA inspection in accordance with 21 CFR 56.115(b), 312.68 and 812.145. NIH researchers and IRBs (see 15.4.3) who are informed of an FDA inspection or audit should immediately notify their Clinical Director(s) and the Director, OHSRP. AND **SOP 15, Section 15.3.6.C.2.** – Any written responses to the FDA submitted by NIH researchers must first be approved by the Clinical Director and the Director, OHSRP. Under Policy 500, the proposed response to the FDA inspection must also be approved by the CC CEO and ORSC.