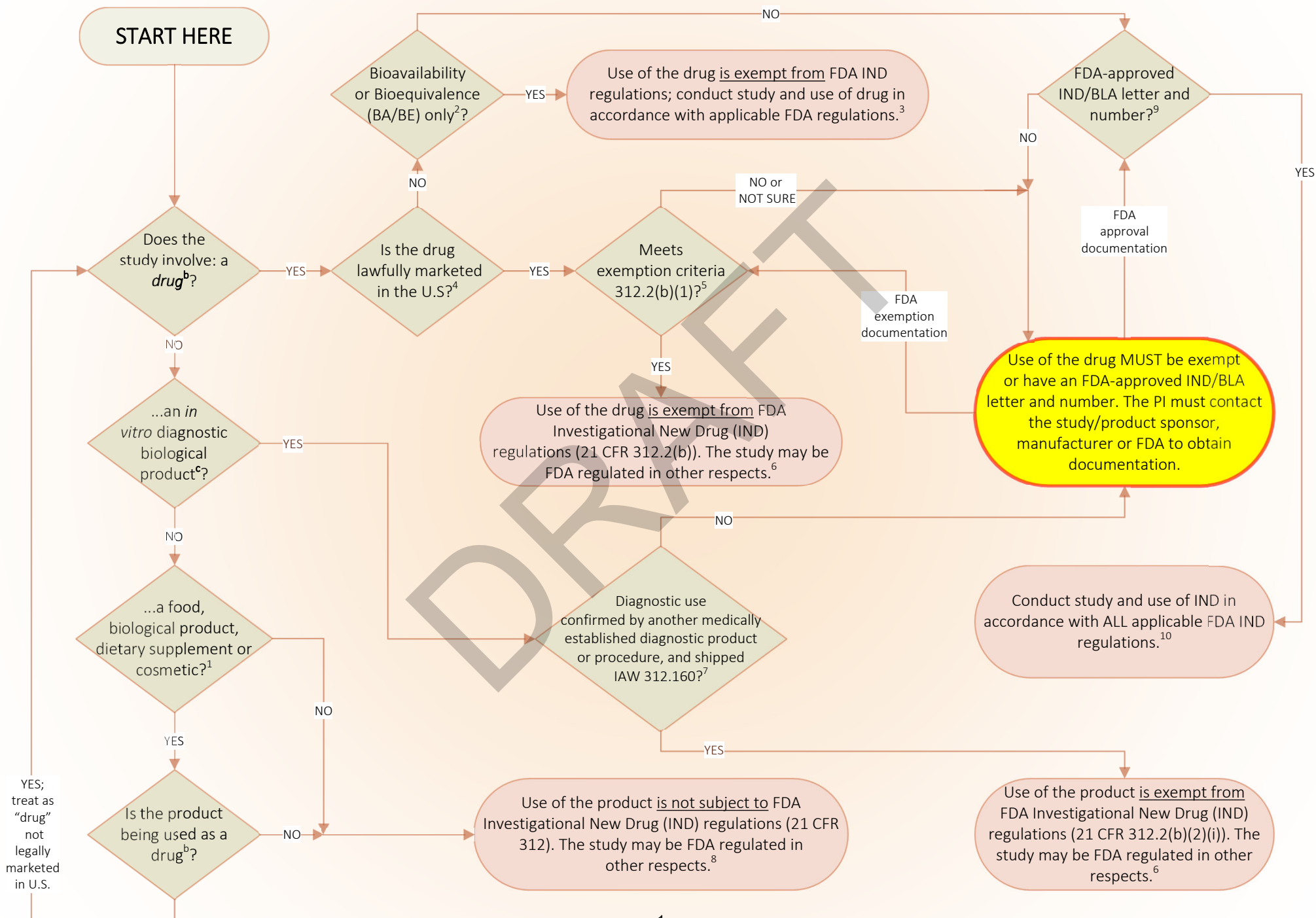


# DRUGS: Applicable FDA Investigational New Drug (IND) Regulations<sup>a</sup> (Revised May 27, 2022)



## NOTES (May 27, 2022)

<sup>a</sup>This algorithm applies to a *clinical investigation* that may involve U.S. Food and Drug Administration (FDA)-regulated drug products. A *clinical investigation* is defined as any experiment that involves a *test article* and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study (such as used in this algorithm), and clinical investigation are deemed to be synonymous. The term *test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation or the Public Health Service Act (21 United States Code of Federal Regulations (CFR) sections 56.102(c), (l)).

<sup>b</sup>**Drug:** defined by law as “(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food<sup>1</sup>) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)” (21 United States Code (USC) section 321(g)).

<sup>c</sup>**In vitro diagnostic products:** defined by law as “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FDC Act), and may also be *biological products* subject to section 351 of the Public Health Service Act” (21 United States Code of Federal Regulations (CFR) section 809.3(a)).

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*Generally, before any drug<sup>b</sup> may legally be marketed in the U.S., federal laws require that the drug be determined safe and effective for the drug’s intended use, in accordance with applicable FDA review requirements; these requirements also apply to any proposed changes in a drug’s intended use ( 21 U.S.C section 355); FDA regulations impose a wide range of requirements that span the spectrum from drug development to manufacturing, distribution, quality control, marketing and post-marketing activities. Exceptions to some of these requirements may be made for drugs that will be used and investigated in certain studies; these may be referred to as investigational new drugs or INDs.*

*Use this algorithm to see if the use or investigation of a drug is subject to U.S. Food and Drug Administration (FDA) regulations that require submission of an application to the FDA for approval before such use or investigation involving the drug is permitted. Whether or not such drug-related application may be required, a study may still be subject to many other FDA regulations (e.g., Institutional Review Board (IRB) review; Investigational Device Exemption (IND) Application; Good Clinical Practice training; serious adverse event reporting; data and safety monitoring; ClinicalTrials.gov registration; etc.).*

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<sup>1</sup> A *food* is defined as “(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article” (21 USC 321(f)); a biological product is defined as The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings (42 USC section 262(i)); a *dietary supplement* is defined as “(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. . . . Except when deemed a *drug* . . . a dietary supplement shall be deemed to be a food” (21 USC 321(ff)); a *cosmetic* is defined as means (1) articles

intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap (21 USC section 321(i)).

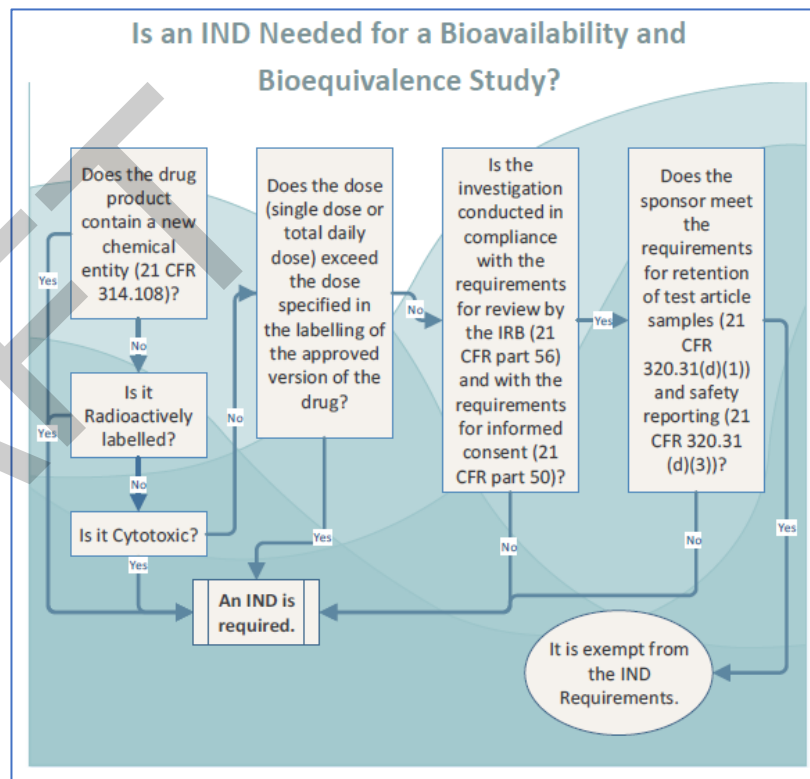
To locate any United States Code (USC) citation included in these Notes, see <https://www.govinfo.gov/>, browse for the United States Code, 1994-Present, and then search for the referenced Title and sections. To locate any United States Code of Federal Regulations (CFR) citation included in these Notes, see <https://www.ecfr.gov/> and search for the referenced Title and sections. The eCFR is not an official edition of the U.S. Code of Federal Regulations, but as a U.S. government online resource the eCFR provides more timely versions and ease of use.

<sup>2</sup> *Bioavailability* (BA) is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. *Bioequivalence* (BE) is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 314.3). BA/BE studies are generally conducted to explore less expensive but safe and equally efficacious generic analogs to other drug products (Shein-Chung Chow, 2014, available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157693/>).

<sup>3</sup> Provided certain FDA regulatory criteria are satisfied, a BA/BE-only study is exempt from FDA IND requirements (21 CFR 320.31(d)). Refer to the chart; for related guidance, visit the FDA's Guidance documents page (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents>) and search for "Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND" guidance document. Regardless of IND regulatory outcome, Institutional Review Board (IRB) review is always required IAW applicable federal laws and FSU policies.

<sup>4</sup> Drug products that may be lawfully marketed in the U.S. are those drugs that for which there is unequivocal FDA documentation (i.e., a letter to an applicant of a New Drug Application (NDA) or a Biologics License Application (BLA) from FDA approving the NDA or licensing the BLA, or an abbreviated application for marketing a drug product in the United States, together with the drug product's approved labeling—final approved text and graphics of the drug product's prescribing information, generally limited to prescribing information and medication guide for prescription products; for non-prescription drug products, the approved labeling will consist of the carton and immediate container labels).

Authoritative information about FDA drug product approvals may be found at these FDA web sites: <https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases> and <https://www.accessdata.fda.gov/scripts/cder/daf/>. Drug study sponsors/manufacturers/distributors should provide study teams with documentation for any FDA approved drugs that will be used in a study, and study teams should maintain this documentation; the documentation may be required by the FSU IRB. For purpose of this algorithm, any drug product for which the use or investigation in a study does not strictly conform to the drug product's FDA approval for its intended or indications for use is NOT considered "lawfully marketed in the U.S".



<sup>5</sup> The use in a study of a drug that is lawfully marketed in the United States may be exempt from FDA IND requirements IF ALL THE FOLLOWING SECTIONS APPLY: (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and (v) The investigation is conducted in compliance with the requirements of § 312.7 (e.g., no promotion or commercial distribution of the IND) (21 CFR 312.2(b)(1)).

<sup>6</sup> Note that even if the use in a study of a drug is exempt from FDA IND requirements, other FDA regulations may still apply to the use of the drug and otherwise to the study as well, including regulations pertaining to clinical investigations, IRB and other drug-related requirements (e.g. FDA approval of the drug; drug label and labelling; post-marketing studies; adverse event reporting; use medical devices or other FDA-regulated test articles; etc.). See <https://www.fda.gov/drugs/guidance-compliance-regulatory-information> and <https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate>. Regardless of IND regulatory outcome, Institutional Review Board (IRB) review is always required IAW applicable federal laws and FSU policies.

<sup>7</sup> A study involving the following in vitro diagnostic biological product may be exempt from FDA IND requirements only if the in vitro diagnostic biological product meets the following criteria: the in vitro biological product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; shipped in compliance with §312.160 (labeling, in vitro use only, adequate records etc.); and in vitro biological products is limited to blood grouping serum, reagent red blood cells, and/or anti-human globulin (21 CFR 312.2(b)(2)).

<sup>8</sup> Note that while use of the product in the study may not be subject to FDA IND requirements, the study and/or use of a product that is (1) not a drug, (2) not a food, biological product, dietary supplement, or cosmetic, or (3) IS a food, biological product, dietary supplement, or cosmetic but is NOT being used as a drug, may still be subject to other FDA regulatory requirements. These include, for example, FDA regulations pertaining to clinical investigations, IRB requirements, FDA label and labelling requirements, and use of medical devices or other FDA-regulated test articles. See <https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate>. Regardless of IND regulatory outcome, Institutional Review Board (IRB) review is always required IAW applicable federal laws and FSU policies.

<sup>9</sup> Use of a drug in a study for which drug there is no FDA exemption, and/or to which drug the FDA IND regulations do apply, must have either a FDA-approved IND/IND number or FDA-approved BLA application/biologics license number, in accordance with FDA regulations (21 CFR 312.2(a); 21 CFR 600 et seq.). Approval is generally in the form of a letter issued by the FDA; a database of FDA-approved drugs or licensed biologics may be accessed here: <https://www.accessdata.fda.gov/scripts/cder/daf/> (drugs) or <https://purplebooksearch.fda.gov/> (biologics). The drug or biologics sponsor should provide the study team with a copy of the FDA approval letter and approved label information (i.e., final FDA-approved text and graphics of the drug product's prescribing information, generally limited to prescribing information and medication guide for prescription products; for non-prescription drug products, the approved labeling will consist of the carton and immediate container labels), with the approval letter and labeling uploaded with the IRB application). See label information below.

A *label* is defined as a display of written, printed, or graphic matter upon the immediate container of any article. *Labeling* is defined as all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such an article (Title 21 of the United States Code, section 321(k), (m)). Depending on the circumstances, labeling may include packaging, product inserts, Web sites, and other promotional materials. The term accompanying is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. 'Accompanying' also includes labeling that is brought together with the drug after shipment or delivery for shipment in interstate commerce (see FDA's Drug Labeling page at: <https://www.fda.gov/drugs/development-resources/labeling-information-drug-products>). When a drug that is planned for use in a study will include a use that does not strictly conform to the drug's label or labeling, then for purposes of this algorithm the use of the drug is NOT considered a use in accordance with the drug label.

For any drug that is the object of the study, a legible copy of the device label must be included in the IRB submission, and a clear statement in the protocol that the drug will bear a label with at least the following information:

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents, if appropriate; and
- the statement, "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions (21 CFR section 812.5).

See the sample FDA approved labels.

<sup>10</sup> Applicable FDA IND regulations are found at 21 CFR section 312; biologics applications are found at 21 CFR section 600. To locate these regulations, see <https://www.ecfr.gov/> and search for the Title 21, sections 312 or 600. The eCFR is not an official edition of the U.S. Code of Federal Regulations, but as a U.S. government online resource the eCFR provides more timely versions and ease of use. Study sponsor/PI/study team responsibilities for each drug include at least the following:

- Investigator's Brochure and packet insert for each unapproved drug;
- IND Documentation: FDA IND "study may proceed letter" (for investigator-initiated studies) or IND# on protocol (if sponsor is external to FSU), with start letter indicating reporting requirements;
- Data and safety monitoring plan;
- FDA forms 1571 and 1572;
- IRB review in accordance with 45 CFR Part 46 as well as 21 CFR sections 50, 56 and 312/600 as applicable; and,
- Completion of FSU CITI GCP training by the study's PI and all study team investigators.

Other responsibilities and FSU IRB requirements may apply.

(Revised May 27, 2022)

