

5.1 Reading the Code of Federal Regulations

The unit opens the American rulebook itself. Title 21 of the **Code of Federal Regulations** (CFR) collects the Food and Drug Administration's binding regulations, and the syllabus names the seven parts that govern clinical research and its downstream duties. The parts are read as a system: Parts 50 and 54 protect the participant and the integrity of the data at the level of the investigator; Part 312 governs the investigational stage; Part 314 the approval stage; Part 320 the equivalence evidence; and Parts 812 and 822 carry the same logic into devices and the postmarket period. A regulatory writer cites these parts the way a lawyer cites sections of an Act: the part number is the address of the duty.

21 CFR: The Parts That Govern Clinical Research



Title 21 of the Code of Federal Regulations: the FDA rulebook for clinical research

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Figure: The 21 CFR map: the seven parts of the FDA rulebook that this unit reads in detail (Unit 5, section 5.1).

5.2 21 CFR Part 50: protection of human subjects

Part 50 is the American consent code. It requires that informed consent be obtained from the participant or a legally authorised representative under circumstances that give sufficient opportunity to consider participation and minimise coercion, and it lists the **basic elements of consent** every consent process must convey, in substance: that the study is research, its purpose, duration and procedures and which are experimental; the reasonably foreseeable risks; the benefits reasonably expected; the appropriate alternatives; the extent of confidentiality and who may inspect records, including FDA; the treatment and compensation position if injury occurs in research offering more than minimal risk; whom to contact about the research, about rights and about injury; and that participation is voluntary and may be discontinued without penalty. The part then governs consent in emergency research exceptions, the additional safeguards for children (Subpart D, parental permission and assent, echoing section 2.10), and the **documentation** of consent by a signed form, with short form and waiver provisions for defined cases. Part 50 is read with its institutional twin, Part 56 on IRBs, which this subject met in Unit 2: the form states the information, the board polices the process.

5.3 21 CFR Part 54: financial disclosure by clinical investigators

Part 54 attacks a quieter corruption. A clinical investigator with a financial interest in the outcome (equity in the sponsor, a proprietary interest in the product, significant payments beyond trial costs) has an incentive that can bias design, conduct and reporting, and the part requires the applicant to disclose the investigators' financial arrangements and interests, on the certification and disclosure forms the agency prescribes, covering the period of the study and one year after its completion, so that FDA can assess the data with the interest in view and require remedies, from disclosing the interest in the application to redesigning or repeating a study, where reliability is compromised. The part's lesson generalises: in clinical research, undisclosed interest is treated as a data integrity defect, not as a private matter.

5.4 21 CFR Part 312: the IND regulations

Part 312 is the operating system of American drug investigation. Its matter: when an IND is required and its content (the application form, the protocol, the chemistry, manufacturing and controls information, the pharmacology and toxicology, previous human experience and the investigator's brochure); the **phases of investigation** the part recognises (Unit 1's phases in regulatory dress); the sponsor's duties to select qualified investigators, keep them informed, monitor the investigation, control the product and records, and review safety information from all sources; the **investigator's duties** under the signed statement of investigator, Form FDA 1572; the grounds on which FDA may impose a **clinical hold**, suspending all or part of an investigation for unreasonable risk or defective design; the treatment use provisions for expanding access outside trials; and the **IND safety reporting** duty of section 5.9, which sits in this part at section 312.32. An IND is, in form, a notice that becomes effective by the passage of the review period unless the agency acts; in substance it is the licence under which every American drug trial runs.

5.5 21 CFR Part 314: applications for approval to market

Part 314 governs the destination document, the application for FDA approval to market a new drug, the NDA of Unit 3's pathways. Its clinical research content is the evidentiary standard the trials must satisfy: the application must contain full reports of the investigations, and approval requires **substantial evidence of effectiveness** from adequate and well controlled investigations (the statutory phrase of section 3.4, given regulatory flesh here, including the characteristics of a well controlled study), together with evidence of safety, and manufacturing and controls adequate to preserve the product's identity, strength, quality and purity. The part also houses the machinery trials feed after approval: postmarketing reporting of adverse drug experiences (section 314.80), annual reports, supplements for changes, and the withdrawal provisions. Part 314 is where Unit 1's staircase ends: every phase exists so that this part's questions can be answered yes.

5.6 21 CFR Part 320: bioavailability and bioequivalence requirements

Part 320 defines the evidence by which sameness is proved: the definitions of **bioavailability** (the rate and extent to which the active ingredient reaches the systemic circulation) and **bioequivalence** (the absence of a significant difference in that rate and extent between pharmaceutically equivalent products), the requirement of in vivo evidence for defined categories, the study designs acceptable (fasting and fed, replicate designs for highly variable drugs), the analytical and statistical standards, and the **waivers** of in vivo testing where the evidence permits them, notably for solutions and under the biopharmaceutics classification logic. The part is the rulebook behind the ANDA of section 505(j) and behind India's own BA/BE discipline under the NDCT Rules, and its requirements for the expedited reporting of adverse experiences from BA/BE studies are expressly named again in the syllabus's safety reporting item below.

5.7 21 CFR Part 812: investigational device exemptions

Part 812 is Part 312 translated for devices. An **investigational device exemption** permits a device that has not been cleared or approved to be shipped for clinical investigation. Its machinery mirrors the drug system with device differences: the sponsor's application and duties, the investigator's agreement and duties, the labelling of investigational devices, and above all the fork between **significant risk** investigations, which require FDA approval of the IDE plus IRB approval, and **non significant risk** investigations, which proceed under IRB approval through the abbreviated requirements unless FDA rules otherwise. The part gives content to Unit 1's device sections: the investigation plan, the risk classification and the committee approval are the three legs on which every lawful device study stands.

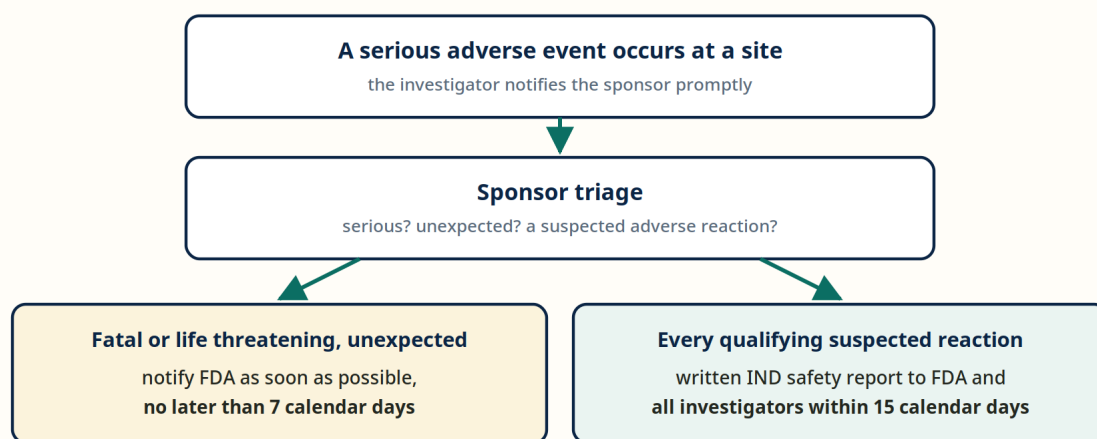
5.8 21 CFR Part 822: postmarket surveillance

Part 822 implements the agency's power (section 522 of the Act) to order **postmarket surveillance** of defined class II and class III devices: those whose failure would be reasonably likely to have serious adverse health consequences, devices intended for implantation for more than one year, and life sustaining or life supporting devices used outside a facility, among the statutory categories. The sponsor of such an order must submit a surveillance plan for approval within the period the order states, conduct the surveillance (for up to 36 months unless a longer period is agreed or ordered), and report interim and final results. The part closes the device lifecycle of this subject: premarket evidence under Parts 812 and the approval system, postmarket watchfulness under 822, the exact device parallel of the drug arc from Part 312 to Part 314's reporting duties.

5.9 FDA safety reporting for INDs and BA/BE studies

The syllabus singles out the reporting clocks, and the governing text is **21 CFR 312.32**, the IND safety reporting rule, which the BA/BE framework applies to bioavailability and bioequivalence studies as the syllabus states. Its architecture: the sponsor must review all safety information and notify FDA and all participating investigators of potential serious risks; an **expedited report** is required for each adverse experience that is **serious, unexpected and a suspected adverse reaction**, in writing within **15 calendar days** of the sponsor's initial determination, and, for an unexpected fatal or life threatening suspected adverse reaction, an initial notification as soon as possible and in no case later than **7 calendar days** after the sponsor first learns of it, with the complete report following within the 15 day frame; follow up information travels on the same 15 day clock. Findings from animal, epidemiological, pooled or clinical sources that suggest a significant risk are reported in the same expedited manner. These figures are quoted here because they are printed in the regulation itself; the general discipline they teach is comparative, since the NDCT Rules run their own clocks for serious adverse events, and the competent professional states each jurisdiction's rule from its own text rather than by analogy.

IND Safety Reporting: The 7 and 15 Day Clocks



Follow up information: within 15 calendar days of receipt (21 CFR 312.32)

The ethics committee is informed in parallel; India runs its own NDCT clocks

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Figure: IND safety reporting under 21 CFR 312.32: from the site's first notice to the sponsor's 7 day and 15 day reports (Unit 5, section 5.9).

5.10 MedWatch and the pharmacovigilance guidance

MedWatch is FDA's safety information and adverse event reporting programme, the public face of the reporting system: healthcare professionals and consumers report voluntarily on the Form FDA 3500, manufacturers and other mandatory reporters file on Form FDA 3500A, and the programme returns the favour as a publisher, issuing safety alerts and labelling change notices by which the whole system learns. Beside it stands the guidance the syllabus names last among the American items, FDA's **Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment**, which states the agency's thinking on pharmacovigilance planning and on the use of pharmacoepidemiologic methods, observational data pressed into the service of safety questions trials cannot answer.

5.11 The European Union: the 2001 directives

The syllabus's European half opens with **EU directives 2001**, the shorthand for the legislative settlement of that year on which the Union's medicines system still visibly rests. Two directives carry the clinical weight. **Directive 2001/20/EC**, the Clinical Trials Directive, first approximated the member states' laws on trials: authorisation by competent authority and ethics committee, GCP compliance, licensing of investigational product manufacture and import, and safety reporting to the EudraVigilance system; it is the instrument the Clinical Trials Regulation of Unit 3 has now replaced in operation, and it is taught here because the syllabus names it and because a generation of dossiers speaks its language. **Directive 2001/83/EC**, the Community code for medicinal products for human use, is the consolidated marketing and manufacturing code behind the authorisation procedures of MRA201T. Directives bind member states as to the result to be achieved and are implemented through national law, which is why the older system produced national variants of one design, and why the shift to a directly applicable Regulation for trials was the natural correction.

5.12 EudraLex Volume 3: scientific guidelines

EudraLex is the Union's compendium of pharmaceutical legislation and guidance, and its volumes divide the world exactly as a regulatory writer shelves it. **Volume 3, Scientific guidelines for medicinal products for human use**, collects the EMA and ICH derived scientific and technical guidelines, quality,

nonclinical and clinical, by which dossiers are designed and judged: the guideline layer of Unit 4 in its European binding. Citing a Volume 3 guideline in a European submission shows the assessor that the programme was built to the published standard.

5.13 EudraLex Volume 9A: pharmacovigilance

Volume 9A, The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use, was for years the single statement of European pharmacovigilance obligation: the responsibilities of marketing authorisation holders and competent authorities, adverse reaction reporting, the PSUR system of Unit 1 in its European form, and risk management. The current position is that the 2010 pharmacovigilance legislation replaced the volume's operative content with the **Good Pharmacovigilance Practices (GVP) modules**, the living texts by which the European system now runs. Volume 9A is taught as the syllabus prints it, as the ancestor whose structure the GVP modules inherit.

5.14 The EU Annual Safety Report

The **EU Annual Safety Report** is the syllabus's name for the periodic safety accounting owed during development, the document by which a sponsor reported once a year per investigational product the safety experience of its trials to the member states concerned, so that the ethics committees and authorities of Unit 3 received a single considered account. Its content and rhythm were absorbed into the ICH **Development Safety Update Report (DSUR, ICH E2F)**, the harmonised annual safety report now used across the regions, tied to the product's development international birth date. The teaching holds both names, as the syllabus's literature does, and keeps the succession straight.

5.15 The EU Medical Device Regulation and ISO 14155

The unit closes where Unit 1 closed, with devices. With respect to clinical research, the **Medical Device Regulation (EU) 2017/745**, which replaced the Medical Devices Directive framework the older syllabus text names (see the verification record for the wording difference between the sources), imposes a clinical evaluation obligation across the device's life and requires **clinical investigations** for implantable and class III devices unless existing clinical data suffice, under member state authorisation, ethics review, a clinical investigation plan, and sponsor duties that parallel the drug system. The conduct standard for those investigations is **ISO 14155, Clinical investigation of medical devices for human subjects: Good clinical practice**, the device GCP: design, conduct, recording and reporting of investigations, the roles of sponsor, monitor, investigator and ethics committee, and the safety reporting of adverse events and device deficiencies. ISO 14155 stands to device research exactly as ICH E6 stands to drug research: one ethical root, two conduct standards, three regulatory doors, and a reporting duty that never sleeps.

The serious adverse event clock (United States, 21 CFR 312.32)
Site learns of the event -> investigator notifies the sponsor promptly
-> Sponsor assesses: serious? unexpected? a suspected reaction?
-> Fatal or life threatening and unexpected:
 notify FDA as soon as possible, no later than 7 calendar days
-> Every serious, unexpected, suspected reaction:
 written IND safety report to FDA and all investigators
 within 15 calendar days
-> Follow up information: within 15 calendar days of receipt
Parallel duties run to the ethics committee and, in India, under the
NDCT Rules' own clocks: three systems, three texts, no borrowing

Frequently Asked Questions

Q: What is the difference between a 505(b)(2) application and an ANDA? Both rely on knowledge outside the applicant's own clinical programme, but at different depths. An ANDA under 505(j) claims sameness: the same active ingredient, dosage form, strength and route as a listed drug, proven by bioequivalence, with no new clinical efficacy trials. A 505(b)(2) application is a full NDA in form for a product that differs from the listed drug, a new formulation, indication or combination, which relies in part on published literature or FDA's earlier findings and bridges the difference with its own studies. See Unit 3, section 3.4.

Q: Does Schedule Y still govern clinical trials in India? Not as the operative code. Schedule Y of the Drugs and Cosmetics Rules was the governing text for three decades, and its vocabulary survives everywhere, but clinical trials, BA/BE studies, ethics committees and compensation are now governed by the New Drugs and Clinical Trials Rules 2019 under the same Act. Unit 3, sections 3.1 and 3.2 teach the syllabus's Schedule Y layer and the current NDCT position together.

Q: Why does Phase 0 use microdoses, and what can a Phase 0 study not show? A microdose, conventionally not more than 100 micrograms and a small fraction of the pharmacological dose, produces measurable pharmacokinetic information with negligible risk and a reduced preclinical package, letting a sponsor choose between candidate molecules cheaply. Because exposure is subtherapeutic and brief, the study cannot establish safety at real doses or any efficacy. See Unit 1, section 1.4.

Q: What is the difference between an IRB, an IEC and an Ethics Committee? Nothing of substance: they are the American (Institutional Review Board), ICH GCP (Independent Ethics Committee) and Indian (Ethics Committee) names for the same independent, multidisciplinary body that reviews, approves and continuously monitors a trial. The regulatory writer uses the term of the governing document's jurisdiction. Unit 2, section 2.11 covers composition and registration.

Q: When is a placebo control ethically acceptable? In the settled position of the Declaration of Helsinki and ICH E10: where no proven intervention exists, or where a proven intervention exists but compelling methodological reasons require placebo and participants face no additional risk of serious or irreversible harm. It is not acceptable where withholding treatment risks death or irreversible injury and another design could answer the question. Unit 2, section 2.9 and Unit 4, section 4.10.

Q: What must happen before a clinical trial can be registered and started in India? The sponsor needs the permission of the Central Licensing Authority (the DCGI at CDSCO) under the NDCT Rules 2019, the written approval of an ethics committee registered for the purpose, and registration of the trial with the Clinical Trials Registry of India before the first participant is enrolled. Unit 3, section 3.2.

Q: What does FDA require before it accepts a foreign clinical study it did not oversee? Under 21 CFR 312.120, in substance: the study was conducted to GCP including independent ethics committee review, the data can be validated by FDA including by on site inspection if necessary, and the population and conditions are applicable to United States patients and practice. Acceptability follows conduct, not geography. Unit 3, section 3.5 gives the full conditions.

Q: What is a data safety monitoring board, and why is it independent? A DSMB is a small expert group, appointed by the sponsor but firewalled from the trial team, that alone sees unblinded interim data and recommends whether a trial continues, changes or stops for benefit, harm or futility. Independence is the whole safeguard: the sponsor receives the recommendation, not the data, so commercial interest cannot argue with interim numbers. Unit 2, section 2.13.

Q: Which CFR part governs informed consent, and which governs the IND? Informed consent and the protection of human subjects sit in 21 CFR Part 50, with institutional review boards in Part 56 beside it; the investigational new drug framework, sponsor and investigator duties, clinical hold and IND safety reporting

at section 312.32, sits in 21 CFR Part 312. Unit 5, sections 5.2 and 5.4.

Q: ISO 14155 or ICH E6: which standard governs a device investigation? ISO 14155, the good clinical practice standard written for clinical investigations of medical devices, governs device investigations, standing to them as ICH E6 stands to drug trials; in the EU it operates within the Medical Device Regulation 2017/745, and in India within the Medical Devices Rules 2017. Unit 1, sections 1.10 to 1.12 and Unit 5, section 5.15.

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