

Unit 3: USA

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3.1 Introduction: the FDA and the device amendments

United States device regulation is administered by the FDA, principally through the **Center for Devices and Radiological Health (CDRH)**, under the device provisions the Medical Device Amendments of 1976 built into the Federal Food, Drug, and Cosmetic Act. The architecture erected then still stands: every device is classified; every device, whatever its class, is subject to **general controls**, the baseline duties of establishment registration and device listing, labelling rules, the Quality System Regulation and adverse event reporting; higher classes attract **special controls** and premarket review in proportion to risk; and clinical study of a significant risk device runs under an investigational device exemption. Devices lawfully marketed before the 1976 amendments, **preamendments devices**, and devices found substantially equivalent to them form the reference population on which the 510(k) system of section 3.3 rests. Around the statute sit the user fee and modernisation acts, under which industry fees fund review performance goals, and the later statutory additions this unit meets: the De Novo pathway for novel low to moderate risk devices, the humanitarian device provisions for rare conditions, and the UDI rule.

3.2 Classification in the United States

FDA classification is by **device type**, set out in the classification regulations of 21 CFR Parts 862 to 892, organised by medical specialty panels, each type assigned to one of three classes according to the controls needed to assure safety and effectiveness. **Class I** devices present the lowest risk and are controlled by general controls alone; many are **exempt** from premarket notification, though not from registration, listing, labelling and the quality system (a small number are exempt even from parts of the quality system). **Class II** devices are those for which general controls alone are insufficient but for which special controls, performance standards, post market surveillance, patient registries or guidance, can provide the needed assurance; most reach the market through the 510(k) notification. **Class III** devices are those that support or sustain life, are implanted with significant risk, or present a potentially unreasonable risk of illness or injury, and for which the lesser controls cannot assure safety and effectiveness; they require premarket approval, the full evidentiary route of section 3.4. The class follows the generic type, not the individual brand, and a manufacturer who believes a device is misclassified, or whose device fits no existing type, uses the classification request and De Novo machinery of section 3.5. The examination contrast with Unit 1's model should be kept: the US three classes map onto the GHTF four by splitting the middle, Class II spanning what the model separates as B and C, which is why the 510(k) population is so wide.

Point	510(k) premarket notification	Premarket approval (PMA)
Legal basis	FD&C Act section 510(k)	FD&C Act section 515
Typical class	Class II, some Class I and a residue of Class III	Class III
Question asked	Substantially equivalent to a predicate device	Reasonable assurance of safety and effectiveness
Evidence	Comparison to the predicate, bench and performance data, clinical data only where needed	Full valid scientific evidence, usually including clinical investigation

Point	510(k) premarket notification	Premarket approval (PMA)
FDA act	Clearance: the device may be marketed	Approval: the application is approved
Change discipline	New 510(k) where a change could significantly affect safety or effectiveness	PMA supplements graded by the change, panel track to annual report

3.3 Premarket notification: the 510(k)

The **510(k)** is a notification, not an application, and its logic is comparative from first to last. The submitter must show that the device is **substantially equivalent** to a legally marketed **predicate device**, a preamendments device or a device itself cleared through the process: same intended use, and either the same technological characteristics or different characteristics that do not raise new questions of safety and effectiveness, with performance data demonstrating that the device is as safe and effective as the predicate. Intended use is the anchor: a new intended use defeats equivalence however similar the hardware. The submission assembles the device description, the predicate comparison, the labelling, the sterility, biocompatibility, software and electrical safety evidence as applicable, and the performance testing, with clinical data required only for the minority of cases where bench evidence cannot settle the comparison. FDA's decision is a **clearance**, expressed in an order finding substantial equivalence, after which the device may be marketed subject to general and any special controls; a finding of not substantially equivalent pushes the device toward De Novo classification or PMA. Variants exist for efficiency, the special 510(k) for a manufacturer's change to its own cleared device and the abbreviated 510(k) relying on standards and guidance, but the equivalence logic is constant. The professional caution is symmetrical to MRA202T's biosimilar lesson: equivalence is to a named predicate on a defined intended use, and marketing language that widens the use beyond the clearance is misbranding.

3.4 Premarket approval: the PMA

Premarket approval is the scientific review route for Class III devices, and it asks the drug style question in device language: whether there is **reasonable assurance of safety and effectiveness** for the device under the conditions of use in its labelling, judged on valid scientific evidence. The application is a full dossier: device description and principles of operation; the manufacturing section, audited by a preapproval inspection of the plant against the Quality System Regulation, so that a PMA can fail on manufacturing as well as on data; the nonclinical laboratory studies; the clinical investigations, conducted under an IDE; the labelling; and the benefit risk analysis that draws them together. Review is by CDRH with, for many original PMAs, an advisory panel meeting in public, and the outcomes are approval, an approvable letter identifying what remains, or a not approvable letter. Approval is then defended for the product's life by the **PMA supplement** ladder: panel track supplements for changes affecting safety or effectiveness, reviewed before implementation; prior notice and 30 day supplements for defined manufacturing changes; and annual reports for the changes that need only be recorded, the ladder MRA102T taught in the drug lifecycle now in its device form. Post approval studies may be imposed as conditions of approval, and the annual report carries the running account of changes, complaints and literature. The PMA population is small beside the 510(k) population, but it holds the devices whose failure is least forgivable, and its discipline is correspondingly the closest in this subject to the drug world's.

3.5 The De Novo route and humanitarian devices

Two smaller routes complete the approval map, both standard and both useful in examinations for placing a device that fits neither great gate. The **De Novo** classification request serves the novel device of low to moderate risk for which no predicate exists: without it, novelty would default the device to Class III and PMA however gentle its risk. The applicant asks FDA to classify the device into Class I or Class II on the strength

of its risk profile and proposed special controls; a granted De Novo creates a new device type, authorises marketing, and, in the system's neat recursion, makes the device itself a predicate for later 510(k)s. The **humanitarian device exemption** serves devices intended for conditions affecting only a small population each year: it requires that the device be designated a humanitarian use device, and it then exempts the applicant from the PMA requirement to demonstrate effectiveness, while still requiring safety and a showing that no comparable device is available and that the probable benefit outweighs the risk, with institutional review board approval governing its clinical use. Both routes teach the same lesson as their existence: the American system's classes are the risk judgment, and the routes are engineered to keep the evidence demanded proportionate to that judgment.

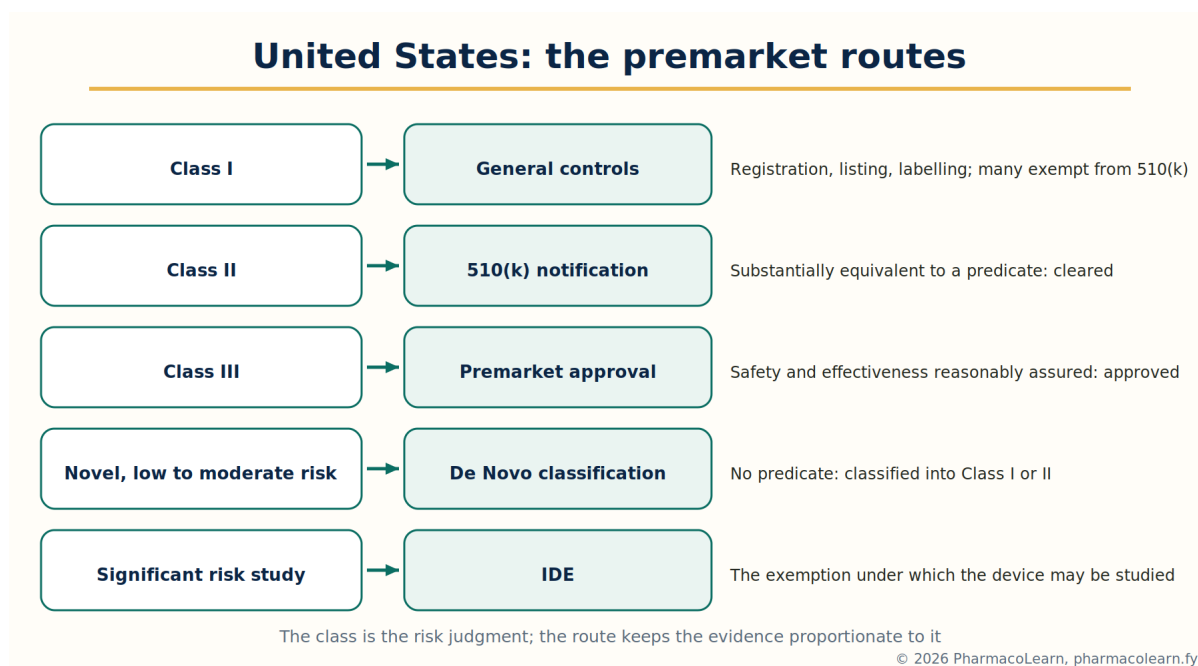


Figure: The American premarket map of sections 3.2 to 3.5: Class I under general controls, Class II to the 510(k) comparison against a predicate, Class III to the PMA's own proof of safety and effectiveness, the novel low to moderate risk device diverted to De Novo, and clinical study of the significant risk device held under the IDE until its route is run (Unit 3, section 3.5).

3.6 Investigational Device Exemption: the IDE

The **Investigational Device Exemption**, 21 CFR Part 812, is the permission under which an unapproved device may be shipped and studied clinically, the device counterpart of the drug IND of MRA103T. Its hinge is the distinction between **significant risk** and **nonsignificant risk** studies. A significant risk device is one that is implanted, life supporting or life sustaining, of substantial importance in diagnosis or treatment, or otherwise presenting a potential for serious risk to the subject; its study requires an FDA approved IDE application, assembling the device description, the prior investigations and bench data, the investigational plan and protocol, the risk analysis, the investigator agreements and the informed consent documents, with institutional review board approval at each site, and FDA may disapprove or condition the study. A nonsignificant risk study is treated as having an abbreviated IDE: the sponsor documents the risk judgment, and the study proceeds with IRB approval and the abbreviated duties of labelling, monitoring and record keeping, though FDA can overrule the judgment. Under either, the recurring duties are sponsor monitoring, investigator compliance, device accountability, adverse device effect reporting to FDA and the IRBs, and the prohibition of promotion or commercial distribution of the investigational device. The IDE is also the gatekeeper of evidence quality for the PMA: the clinical investigations a PMA relies on are expected to have been conducted under it, in compliance with the informed consent and IRB parts of the CFR.

3.7 Quality system requirements: 21 CFR Part 820

The **Quality System Regulation**, 21 CFR Part 820, is the American legal form of the device quality system, the counterpart in force of law to ISO 13485's standard, and FDA inspections test a plant against it directly. Its subparts run the familiar architecture with American accents: quality system and management responsibility, with the management review and quality audit duties; design controls, the QSR's most examined element, requiring design and development planning, design input and output, review, **verification, validation**, transfer and change control, all accumulated in the **design history file**; document and record controls, including the **device master record**, the complete recipe of specifications and procedures from which a device is made, and the **device history record**, the production history of each batch or unit, the device world's answer to the batch record family of MRA102T; purchasing controls over suppliers and components; production and process controls, with process validation where results cannot be fully verified; acceptance activities, labelling and packaging control, handling, storage, distribution and installation; and the closing subparts on nonconforming product, **corrective and preventive action**, complaints and servicing, with statistical techniques where appropriate. The comparison with ISO 13485 is a set question, and its answer is alignment with different instruments: the two systems cover substantially the same ground, the QSR as a regulation enforced by FDA inspection and the ISO standard as a certifiable standard, a convergence the single audit programme of Unit 5 exploits, and which FDA has moved to complete by harmonising Part 820 with ISO 13485. The student should state the position exactly: Part 820 as the syllabus prints it is the operative text for this course, with the harmonisation named as the direction of travel.

3.8 Labeling requirements: 21 CFR Part 801

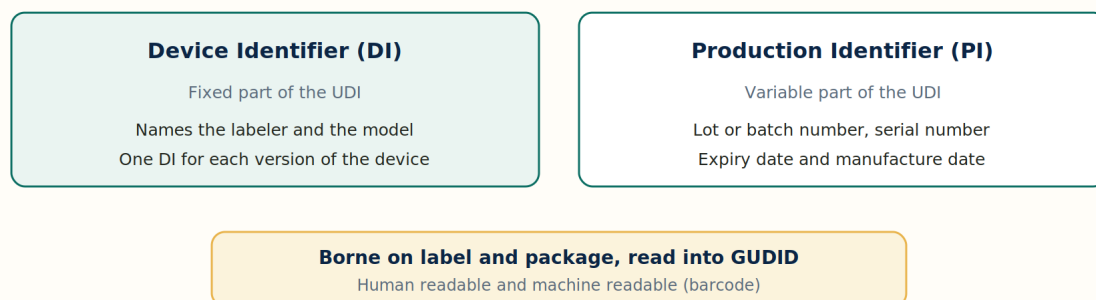
21 CFR Part 801 governs device labelling, and in the American scheme labelling is a control, not a courtesy: a device whose labelling is false or misleading, or lacks required information, is misbranded and unlawful whatever its engineering merit. The general duties require the name and address of the manufacturer or distributor, an adequate statement of the intended use and directions for use sufficiently detailed for the intended user, prescription or over the counter as the case may be, and the warnings, precautions and contraindications that safe use requires, with prominence rules so that the safety matter is not buried. Prescription devices carry the federal prescription legend and are exempt from the adequate directions requirement only on conditions, including that they are labelled with the information a practitioner needs and confined to professional channels. Subparts address particular families, in vitro diagnostic products among them, whose labelling must state the intended use, the performance characteristics and the limitations of the test, since a diagnostic's labelling is where its truth is told. Two Unit 3 themes meet here: the intended use stated in labelling is the same intended use that anchors classification and 510(k) equivalence, so labelling discipline is market access discipline; and labelling is an IDE and UDI carrier, investigational devices bearing their caution legend, and marketed devices bearing the unique identifier of the next section.

3.9 Post marketing surveillance and Unique Device Identification

The American post market system has three instruments, and the syllabus names the third expressly. The first is **medical device reporting**, 21 CFR Part 803: manufacturers, importers and device user facilities must report device related deaths, serious injuries and reportable malfunctions to FDA, the reports populating the public database from which signals are read. The second is **postmarket surveillance** in its strict sense, the authority under section 522 of the Act for FDA to order prospective surveillance studies of specified Class II and Class III devices, life sustaining devices, implants and devices with significant paediatric use among them, so that questions visible only in wide use are answered by design rather than by accumulation of reports; corrections, removals and recalls, reported under Part 806, complete the enforcement side. The third is the **Unique Device Identification system**: the UDI rule requires most

devices to bear a **unique device identifier** on their label and packaging, in human readable and machine readable form, composed of a **device identifier**, the fixed part naming the model and labeler, and a **production identifier**, the variable part carrying lot or batch, serial number, expiry and manufacture date as applicable, with the device's record lodged in FDA's public GUDID database. The UDI is what converts the reporting of section 2.7 from narrative to data: a malfunction report, a recall and an implant registry entry can all be tied to the exact device configuration, and traceability, the virtue MRA202T praised for biologics by brand and batch, is here built into every label by rule.

The UDI: what the identifier carries



Identification is vigilance machinery: reports and recalls tied to the exact device

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Figure: The two parts of the unique device identifier of section 3.9: the device identifier, fixed, naming labeler and model, and the production identifier, variable, carrying lot, serial number and dates, read together from the label into the GUDID record (Unit 3, section 3.9).

3.10 IVDs in the United States: basics, classification and approval

An American IVD is a device, classified like any other by risk into Classes I, II and III under the panels for chemistry, haematology, immunology, microbiology and the rest, and routed by the same gates of this unit: most routine assays reach the market by 510(k) clearance against a predicate assay, high risk tests, companion diagnostics and blood screening assays among them, by PMA, and novel moderate risk tests by De Novo. What distinguishes IVD review is the performance language: an assay is judged on **analytical performance**, accuracy, precision, analytical sensitivity and specificity, interfering substances and stability, and on **clinical performance**, the diagnostic sensitivity and specificity of its results against the true condition in the intended population, with its labelling under Part 801's IVD subpart stating intended use, performance characteristics and limitations. Two boundary topics are standard teaching. **Laboratory developed tests**, assays designed and used within a single clinical laboratory, lived for decades under enforcement discretion; the regulatory position on them has been contested and has shifted with rulemaking and litigation, and the careful statement for the student is that the area is in transition and the laboratory's own quality obligations under the clinical laboratory rules apply throughout. And the **companion diagnostic**, an IVD essential to the safe and effective use of a corresponding drug, is reviewed in coordination with the drug, so that test and therapy reach the market together with matched labelling.

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