

Unit 1: USA and Canada

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Regulatory Aspects of Drugs and Cosmetics, subject code MRA201T, is the first core subject of M.Pharm Regulatory Affairs, Semester 2. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Semester 1 built the home ground: MRA101T taught the good practices, MRA102T the documents and submissions craft, MRA103T the regulation of clinical research, and MRA104T the Indian statute book and intellectual property rights. This subject turns outward. Its question is the one every Indian manufacturer who exports must answer: how do the other regulatory systems of the world decide what may be sold as a drug or a cosmetic, and what must a dossier prove to each of them? The course is designed to impart fundamental knowledge on the drug development process and the regulatory requirements for approval of new drugs, drug products and cosmetics in regulated and semi-regulated countries, and its objectives are to know the process of drug discovery, development and generic product development, the approval process and registration procedures for active substances and drug products in the United States and the European Union, the cosmetics regulations of regulated and semi-regulated countries, and to make a comparative study of India against the other global regulated markets. The units are arranged as a journey outward from the most demanding markets to the widest world. Unit 1 studies the United States and Canada: the FDA, the Federal Food, Drug, and Cosmetic Act, the Hatch-Waxman settlement that created the modern generic industry, the application family of IND, NDA, ANDA and supplements, and cosmetics law in the USA and Canada including the MoCRA reform of 2022. Unit 2 studies the European Union and Australia: the networked EMA system, the four marketing authorization procedures, the ASMF and the Certificate of Suitability, variations and the Qualified Person, and the European cosmetics Regulation with its notification model, with Australia's ingredient based scheme beside it. Unit 3 studies Japan: the PMDA, the Pharmaceuticals and Medical Devices Act, the Master File system and Japan's distinctive post marketing re-examination machinery. Unit 4 steps back to the emerging markets and the World Health Organization: the regional harmonization committees, WHO GMP, the prequalification programme and the Certificate of Pharmaceutical Product. Unit 5 works through the Asian countries in detail, the ASEAN Common Technical Document, China and South Korea, the ASEAN five named in the syllabus, the CIS states and the GCC states, closing with cosmetics legislation across Brazil, ASEAN, CIS and GCC. Two habits pay off throughout. First, read every system as an answer to the same five questions: who authorizes, on what evidence, in what dossier, with what post approval duties, and how are cosmetics handled differently from drugs? Second, keep India in view: the comparisons the objectives demand are drawn at each stage, because the student who can set CDSCO beside FDA, EMA and PMDA understands all four better.

1.1 Historical perspectives: how the American system was built by disaster and reform

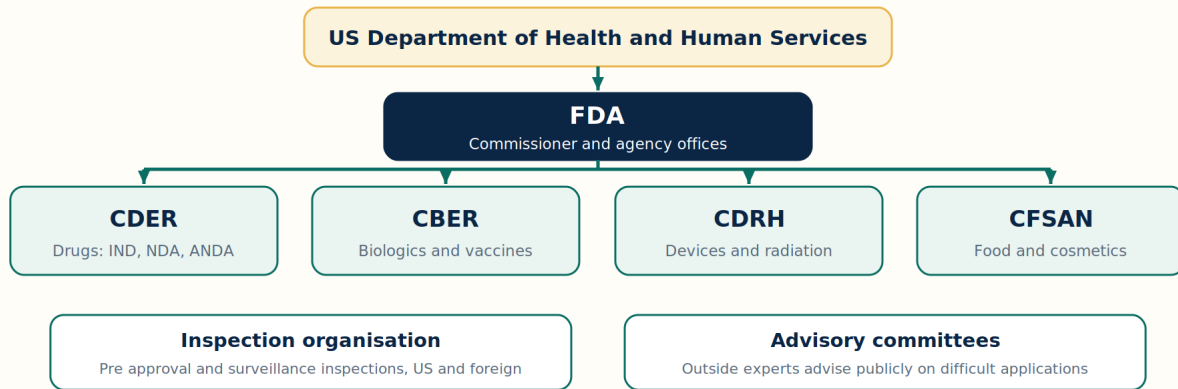
United States drug regulation is the oldest of the modern systems and the most openly shaped by catastrophe. The **Pure Food and Drugs Act 1906** created federal control over adulterated and misbranded products in interstate commerce, but it required the government to prove fraud and it said nothing about safety testing before sale. The gap was exposed in 1937, when a sulfanilamide preparation dissolved in diethylene glycol killed more than a hundred people, many of them children; because the elixir had never been tested for safety, no law had been broken by selling it. Congress answered with the **Federal Food, Drug, and Cosmetic Act 1938**, the statute that still governs: it required premarket notification of new drugs on safety grounds, created factory inspection powers and extended control to cosmetics and devices. A

second disaster, thalidomide, which reached the United States only in investigational quantities because a single FDA reviewer, Frances Kelsey, held the application back, produced the **Kefauver-Harris Amendments 1962**, which added the requirement that a new drug be shown **effective** as well as safe, on the basis of adequate and well controlled investigations, and brought advertising and informed consent under federal discipline. The later landmarks are about money and speed rather than safety: the **Drug Price Competition and Patent Term Restoration Act 1984**, known universally as **Hatch-Waxman**, created the abbreviated generic pathway and the patent term restoration bargain examined at section 1.5; the **Prescription Drug User Fee Act 1992 (PDUFA)** let FDA charge sponsors for review and commit to performance goals in return, and it has been reauthorized roughly every five years since; the **FDA Amendments Act 2007** added risk evaluation and mitigation strategies and mandatory post marketing powers; the **Food and Drug Administration Safety and Innovation Act 2012** added the breakthrough therapy designation and the generic and biosimilar user fee programmes; and the **21st Century Cures Act 2016** adjusted evidence standards, including the place of real world evidence in defined settings. The pattern matters for the whole subject: American regulation is one statute, repeatedly amended after failure or political pressure, administered by an agency whose review the applicant industries largely fund through user fees.

1.2 Organization structure and functions of the FDA

The Food and Drug Administration is an agency of the Department of Health and Human Services, headed by a Commissioner appointed by the President. Its regulatory work is done through product centres. The **Center for Drug Evaluation and Research (CDER)** regulates prescription and over the counter human drugs and runs the IND, NDA and ANDA programmes of this unit. The **Center for Biologics Evaluation and Research (CBER)** regulates vaccines, blood products and most therapeutic biologics, which MRA202T treats in full. The **Center for Devices and Radiological Health (CDRH)** runs the device programmes of MRA203T. The **Center for Food Safety and Applied Nutrition (CFSAN)** is the home of cosmetics regulation, a placement that itself explains much about the American approach to cosmetics in section 1.16. Around the centres sit the inspection organisation, which conducts pre approval and surveillance inspections of domestic and foreign plants, and the advisory committee machinery through which outside experts publicly advise on difficult applications. Three functions define FDA for the regulatory professional. It is a **premarket gatekeeper**: no new drug may be sold until FDA approves its application. It is a **standards setter**: through regulations, guidance documents and the compendial system it writes the technical rules of manufacture and testing. And it is an **enforcement body** with its own administrative ladder, from inspection observations and warning letters to import alerts, seizure and injunction, the ladder MRA102T meets in the inspection units.

The US FDA: centres and what each one regulates



Centres review the dossiers; the inspection force verifies on site

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Figure: The FDA inside the Department of Health and Human Services: the Commissioner, the product centres that hold the drug, biologics, device and cosmetics programmes, and the inspection organisation (Unit 1, section 1.2).

1.3 The Federal Register and the Code of Federal Regulations

American regulatory law reaches the practitioner through two publications, and the syllabus names them because confusing them is a working error. The **Federal Register** is the daily journal of the federal government: where FDA publishes proposed rules for public comment, final rules, and notices including approval and withdrawal actions. It is chronological, a record of what the government did and when. The **Code of Federal Regulations (CFR)** is the codified, subject arranged body of the rules currently in force, revised annually; Title 21 is the food and drugs title. The working instruments of this branch live in Title 21: Part 210 and Part 211 (cGMP, from MRA101T), Part 201 (drug labeling), Part 312 (investigational new drugs), Part 314 (applications to market a new drug, including the ANDA provisions), Part 320 (bioavailability and bioequivalence) and Part 11 (electronic records and signatures). The discipline the pair teaches is chronological literacy: the CFR tells you what the law is today, while the Federal Register preamble tells you why FDA adopted it, what comments it rejected, and how it intends to enforce it, which is often what a regulatory argument turns on. Guidance documents bind neither party formally; they state the agency's current thinking, and the professional treats them as the safe route, not the only route.

1.4 The Federal Food, Drug, and Cosmetic Act: the operative ideas

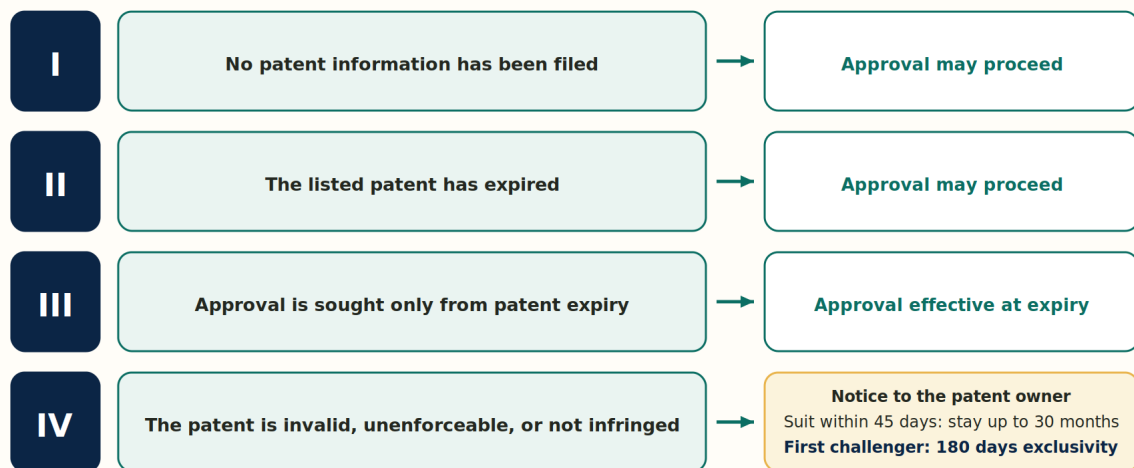
Beneath the history of section 1.1, the Act works through a handful of operative ideas that every later topic in this unit uses. A **new drug** is defined functionally: a drug not generally recognised as safe and effective for its labelled conditions, and such a drug may not be introduced into interstate commerce unless an approved application is in effect for it; that single prohibition is the legal engine of the NDA system. The Act prohibits **adulterated** drugs, a concept that expressly includes failure to manufacture under current good manufacturing practice, so a GMP failure is not merely an inspection finding but a statutory offence against the product itself; and it prohibits **misbranded** drugs, whose labelling is false or misleading or lacks the required statements. The 1962 effectiveness standard is implemented through the substantial evidence test described above. Enforcement runs through the courts (seizure, injunction, criminal prosecution) and through administrative instruments the agency controls directly, above all **refusal of admission of imports** and import alerts, which is the power an Indian exporter feels most directly. Two structural features deserve note. The Act gives FDA no general premarket approval power over **cosmetics**, which is why section 1.16 is a story of exception and of the MoCRA reform. And the Act is the parent statute of the orphan, combination and generic regimes of this unit, each an amendment era grafted onto the 1938 frame.

1.5 The Hatch-Waxman settlement and the Orange Book

The **Drug Price Competition and Patent Term Restoration Act 1984** was a negotiated settlement between two industries. The innovators received **patent term restoration**: up to five years of patent life lost during development and review may be restored, subject to caps, including the rule that the restored term cannot give more than 14 years of effective patent life after approval. The generic industry received the **Abbreviated New Drug Application**: a statutory route to approval on proof of sameness and bioequivalence to a listed drug, without repeating its clinical trials, sheltered in development by the regulatory review exemption that India copied as Section 107A (MRA104T). The settlement is administered through the **Orange Book**, formally the list of Approved Drug Products with Therapeutic Equivalence Evaluations, in which the innovator lists the patents it claims cover the approved drug. A generic applicant must certify against each listed patent, and the four certifications are the grammar of American generic litigation:

Certification	Meaning	Consequence
Paragraph I	No patent information has been filed	Approval may proceed
Paragraph II	The patent has expired	Approval may proceed
Paragraph III	Approval is sought only from patent expiry	Approval effective at expiry
Paragraph IV	The patent is invalid, unenforceable or not infringed	Notice to the patent owner; suit within 45 days triggers an automatic stay of approval for up to 30 months; the first successful challenger earns 180 days of generic marketing exclusivity

Orange Book Paragraph certifications I to IV



One certification is made against every patent listed in the Orange Book

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Figure: Paragraph I to IV: what the ANDA applicant asserts about each listed patent, and what each assertion sets in motion, including the 30 month stay and the 180 day exclusivity of the first Paragraph IV challenger (Unit 1, section 1.5).

The elegance of the scheme is that patent disputes are fought on a regulatory timetable: the stay holds approval while the court decides, and the 180 day prize pays the first challenger for clearing weak patents out of the way. Compare India (MRA104T): no linkage and no stay; the same conflict runs there as pure civil litigation after approval.

1.6 The Purple Book and the biologics settlement

Biologics arrived at the abbreviated pathway a generation later, through the **Biologics Price Competition and Innovation Act 2009**, enacted as part of the Affordable Care Act 2010. It created the 351(k) abbreviated licensure pathway for biosimilars and interchangeable products under the Public Health Service Act, with 12 years of reference product exclusivity. The **Purple Book** is the biologics counterpart of the Orange Book: the official lists of licensed biological products, including biosimilars and interchangeable products and their exclusivity information. The Purple Book is deliberately a list of licensure facts, not a patent register on the Orange Book model; patent disputes for biologics run through the statutory information exchange between biosimilar applicant and reference sponsor that practitioners call the patent dance, rather than through listed patent certifications.

1.7 The Drug Master File system in the United States

A **Drug Master File** is a confidential dossier lodged with FDA by the maker of an active substance, a component or a packaging material, which FDA reviews only in connection with an application that references it; the applicant who relies on it never sees its contents, and authorisation to reference it is given by a **Letter of Authorization**. The system protects the supplier's trade secrets while keeping one reviewed source of substance data on file. FDA recognises five types: Type I, manufacturing site, facilities and operating procedures; Type II, drug substance, its intermediates and the materials used in their preparation, the workhorse of the system; Type III, packaging material; Type IV, excipients, colourants, flavours and other additives; and Type V, FDA accepted reference information. One modern qualification, already met in MRA102T: FDA no longer accepts new Type I files, that facility information having moved into establishment registration and application level disclosure, though existing Type I files remain of record. A DMF is never approved or rejected on its own; it is reviewed when referenced, found adequate or deficient in that connection, and the deficiency is communicated to the holder, not to the applicant who referenced it. The CTD world files the same content in Module 3.2.S, and the European and Japanese counterparts of this section are the ASMF of section 2.4 and the Master File of section 3.4, compared in the table at section 2.4.

1.8 The IND: permission to test in humans

Clinical investigation in the United States runs under an **Investigational New Drug** application, Part 312. The IND is an exemption from the prohibition on shipping an unapproved drug: it assembles the preclinical pharmacology and toxicology, the chemistry and manufacturing information for the investigational product, and the protocol and investigator information, and the sponsor may begin the trial **30 days** after FDA receives the IND unless FDA imposes a clinical hold. The hold, and its lifting, is the live regulatory instrument of the trial era, used where human subjects would be exposed to unreasonable risk or the information is inadequate. FDA interaction is continuous from there: pre IND meetings, end of phase meetings, annual reports, protocol amendments and the expedited safety reports of 21 CFR 312.32 (the 7 and 15 calendar day reports met in MRA103T). The IND is not an approval of anything; it is the supervised space in which the evidence for an NDA is generated. India's NDCT Rules permission and the EU clinical trial authorisation are the same institutional idea in other legal clothes.

1.9 The NDA: the full application, and the PDUFA clock

The **New Drug Application**, filed under section 505(b)(1) of the Act, is the complete dossier: full reports of the investigations of safety and effectiveness, the chemistry, manufacturing and controls, the proposed labelling, and the patent information for Orange Book listing. Review is done by CDER against the performance goals FDA accepts under PDUFA: the standard widely published goals are review within **10**

months of the 60 day filing date for a standard application and within **6 months** for a priority application, priority being granted where the drug would significantly improve the treatment of a serious condition. Expedited programmes sit around the standard route: fast track, breakthrough therapy designation, and accelerated approval on a surrogate endpoint reasonably likely to predict clinical benefit. The review ends in an **approval letter** or a **complete response letter** setting out the deficiencies that prevent approval; the complete response is a normal working outcome, and resubmission classes and their clocks govern the second round. Obligations do not end at approval: supplements (section 1.12), annual reports, adverse event reporting under Part 314.80 and, where imposed, a REMS carry the file through its commercial life.

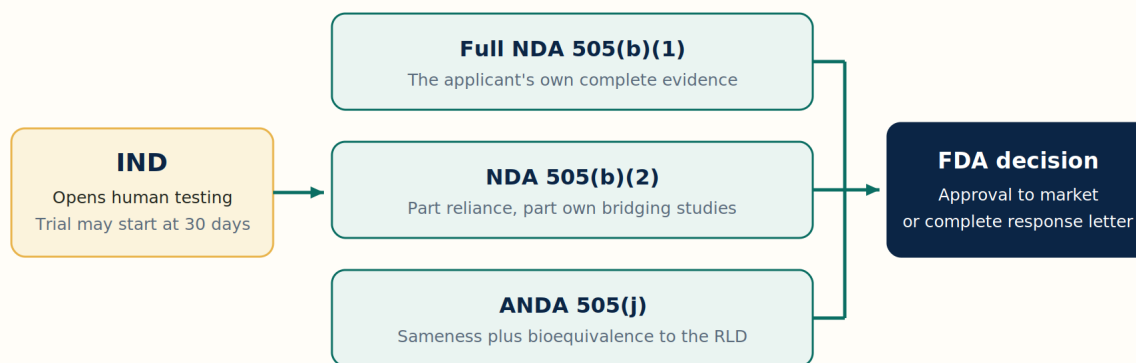
1.10 The 505(b)(2) route: the deliberate hybrid

Section **505(b)(2)** is the middle path the syllabus groups with the application family: an NDA that relies in part on data the applicant did not generate, published literature or FDA's previous finding of safety and effectiveness for an approved drug, bridged by the applicant's own studies. It serves the large class of rational product improvements that are neither new molecular entities nor copies: new dosage forms, new strengths, new combinations, new routes, changed active ingredients in defined ways, and switches from prescription to over the counter status. The applicant must still certify against Orange Book patents for the products it relies on, and may earn three years of exclusivity for new clinical investigations essential to approval. For the Indian formulator, 505(b)(2) is often the value added export strategy: the ANDA proves a copy, while the 505(b)(2) builds a differentiated product on an established safety base, at a fraction of a full NDA's cost.

1.11 The ANDA: approval by sameness

The **Abbreviated New Drug Application**, section 505(j), inverts the NDA: instead of proving safety and effectiveness, the applicant proves **sameness** to a Reference Listed Drug: the same active ingredient, dosage form, strength, route and conditions of use, with differences argued to be without effect; pharmaceutical equivalence; labelling the same, subject to carving out protected indications; manufacture under cGMP; and **bioequivalence** to the reference product, shown ordinarily in a crossover study whose 90 percent confidence interval for the ratios of AUC and Cmax must fall within **80.00 to 125.00 percent** (MRA104T, Unit 4). FDA publishes product specific guidances that state, product by product, the study design it recommends, and the first cycle review goal under the generic user fee programme (GDUFA) is 10 months for a standard ANDA. The ANDA route is where Hatch-Waxman is executed: the paragraph certifications of section 1.5 are filed with the ANDA, and the 30 month stay and Paragraph IV litigation decide the launch date as surely as the review does.

US approval pathways: IND, NDA, 505(b)(2), ANDA



After approval, supplements (PAS, CBE-30, CBE-0, annual report) carry every change

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Figure: The American application family on one map: the IND opens human testing, the full NDA proves the new drug, the 505(b)(2) bridges to prior findings, and the ANDA proves sameness to the reference listed drug (Unit 1, section 1.11).

The ANDA journey (section 505(j))

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graph TD
    A[Reference Listed Drug identified in the Orange Book] --> B[Development under the regulatory review exemption]
    B --> C[Bioequivalence studies + CMC in CTD format]
    C --> D[ANDA filed with Paragraph I to IV certifications]
    D --> E[GDUFA review: completeness, BE, labelling, facility cGMP]
    E --> F[Tentative approval if a patent or exclusivity blocks final approval]
    F --> G[Final approval, Orange Book listing with equivalence code]
  
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The ANDA journey (section 505(j)) is a vertical flowchart showing the steps from identification to final approval. It begins with 'Reference Listed Drug identified in the Orange Book', followed by 'Development under the regulatory review exemption', 'Bioequivalence studies + CMC in CTD format', 'ANDA filed with Paragraph I to IV certifications', 'GDUFA review: completeness, BE, labelling, facility cGMP', 'Tentative approval if a patent or exclusivity blocks final approval', and finally 'Final approval, Orange Book listing with equivalence code'.

1.12 Supplements: changes to an approved NDA or ANDA

Approval is a state, not an event, and the supplement system grades post approval change by its potential effect on the product, in the framework MRA102T Unit 5 teaches from the documents side. A **Prior Approval Supplement (PAS)** is required for a major change, one with substantial potential to affect identity, strength, quality, purity or potency; it must be approved before distribution. **Changes Being Effectuated** supplements cover moderate changes: the CBE-30 is distributed 30 days after FDA receipt if FDA has not objected, and CBE-0 covers a defined set of changes that may be implemented on filing. Minor changes ride in the **Annual Report**. The SUPAC guidances give the ladder technical content for defined product classes, stating the tests and filings each level of change attracts. ANDA holders file the same categories of supplement against their approvals. The professional habit this unit builds is classification discipline: every post approval change is first a question of which rung of this ladder it stands on.

1.13 Orphan drugs

The **Orphan Drug Act 1983** addresses the market failure of rare diseases: where development costs cannot be recovered from a small patient population, the statute pays in regulatory currency instead. A

sponsor may obtain **orphan drug designation** for a drug intended for a condition affecting fewer than **200,000** persons in the United States (or more, where there is no reasonable expectation of cost recovery), and designation carries tax credits for clinical testing, a waiver of the PDUFA application fee, protocol assistance, and, on approval, **seven years of orphan exclusivity** during which FDA will not approve the same drug for the same use, subject to exceptions such as clinical superiority. Designation is not approval: the designated drug must still win an NDA, ANDA style evidence or BLA on the merits. The EU runs a parallel scheme (prevalence not more than 5 in 10,000, ten years of market exclusivity) which Unit 2 mentions in the centralised context, where orphan medicines are mandatory centralised products.

1.14 Combination products

A **combination product**, defined in 21 CFR 3.2, combines drug, biologic and device constituents: physically or chemically combined (a prefilled syringe), packaged together (a kit), or separately supplied but labelled for use with each other. Regulation follows the **primary mode of action**: the constituent part providing the most important therapeutic action assigns the product to a lead centre, drug led to CDER, biologic led to CBER, device led to CDRH, with the Office of Combination Products as coordinator and the Request for Designation as the sponsor's formal remedy where assignment is disputed. One application ordinarily carries the whole product, and its manufacturing must satisfy a combined rule set: the drug cGMP of Parts 210 and 211 and the device quality system requirements, each applied to its constituents. For this branch the combination product is the boundary case that proves the centre map of section 1.2: the system is organised by product type only until a product refuses to be only one type.

1.15 Manufacturing, packaging and labeling considerations in the USA

Three standing disciplines apply to every approved product. **Manufacture** is under Parts 210 and 211 cGMP (MRA101T), policed by pre approval inspection for new applications and by surveillance inspection thereafter, with foreign establishments inside the same net and carrying facility fee obligations. **Packaging** is regulated as part of the product: container closure suitability is reviewed in the application, child resistant packaging is required under the Poison Prevention Packaging Act, tamper evident features apply to over the counter products, and the Drug Supply Chain Security Act 2013 adds unit level traceability. **Labeling** is reviewed and approved as part of the application: the structured prescribing information in the Physicians Labeling Rule format, carton and container labels under Part 201, Medication Guides and REMS materials where imposed, and for over the counter products the standardised Drug Facts panel. A label change is therefore a regulatory submission, supplement or annual report according to the ladder of section 1.12, and never a marketing decision alone.

1.16 Cosmetics in the United States: the exception, and MoCRA

American cosmetics law was, until very recently, the great exception among regulated products: the 1938 Act prohibited adulterated and misbranded cosmetics but gave FDA **no premarket approval** for cosmetics or their ingredients, the single exception being **colour additives**, which require premarket approval and, for many, batch certification. Voluntary registration of establishments and products through the Voluntary Cosmetic Registration Program was exactly that, voluntary. The **Modernization of Cosmetics Regulation Act 2022 (MoCRA)**, the most significant expansion of FDA cosmetics authority since 1938, changed the architecture without abolishing its exception: cosmetic **facilities must register** with FDA, cosmetic **products must be listed**, responsible persons must keep **safety substantiation** and report **serious adverse events** to FDA within 15 business days, FDA gained **mandatory recall** authority over cosmetics, records access, and a rule making programme for good manufacturing practice for cosmetics and for fragrance allergen labelling. Premarket approval was deliberately not introduced: the American model remains a post market system with notification and substantiation duties, which is the precise contrast the

EU section draws.

1.17 Cosmetics in Canada

Canada places cosmetics under its **Food and Drugs Act** and the **Cosmetic Regulations**, administered by Health Canada. The system is again notification based, without premarket approval: the manufacturer or importer must submit a **Cosmetic Notification Form** to Health Canada within **10 days** of first sale, identifying the product, its ingredients and their concentrations; notification is not approval, and Health Canada may act against products that present a risk. Ingredients are controlled through the **Cosmetic Ingredient Hotlist**, an administrative list of prohibited and restricted substances that functions as the practical boundary of lawful formulation, and labelling must follow the Consumer Chemicals and Containers Regulations and the labelling rules of the Cosmetic Regulations, with ingredient names in the **INCI** nomenclature, in English and French. Read against sections 1.16 and 2.15, the family resemblance is the teaching point: North America notifies cosmetics and polices them in the market, while the European Union notifies too, but wraps the notification in a responsible person, a product information file and a pre market safety assessment.

Applicati on	Statute	What must be proved	Full clinical programme
IND	FD&C Act, 21 CFR 312	Grounds for safe human testing	No: it opens testing
NDA 505(b)(1)	FD&C Act	Safety and effectiveness, full data	Yes, the applicant's own
NDA 505(b)(2)	FD&C Act	Safety and effectiveness, partly by reliance on literature or FDA's prior findings, bridged by own studies	Partial by design
ANDA 505(j)	FD&C Act	Sameness to the RLD plus bioequivalence	No, BE study instead
sNDA	FD&C Act, 21 CFR 314.70	The defined post approval change	As the change requires

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