Major FDA Applications for Drugs and Biologics

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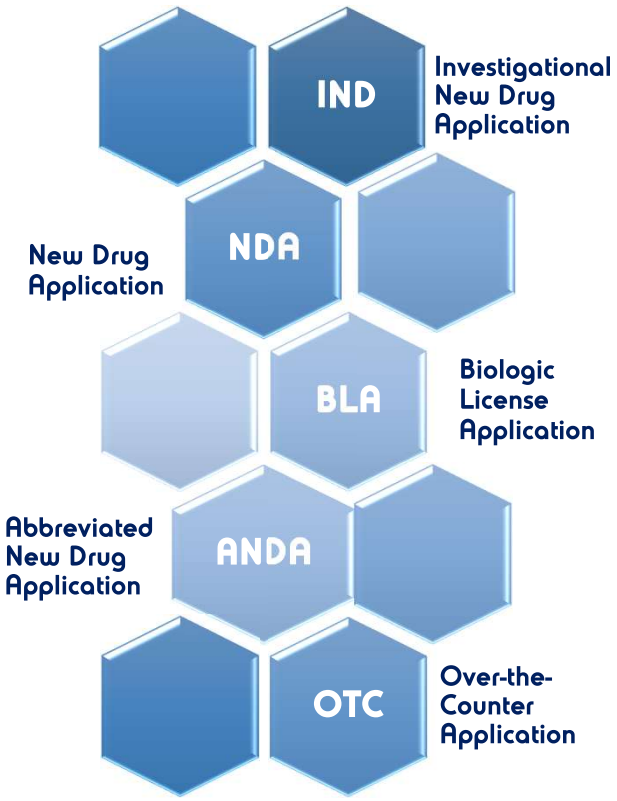
There are 2 broad application types for drugs & biologics regulated by FDA:
❑requests for authorization for clinical investigations. i.e. IND
❑requests for marketing approval, i.e. NDA, ANDA, BLA



Investigational New Drug Application (IND)

- ❑ IND is the launching point for clinical investigations in the US and its primary purpose is to ensure the safety and rights of clinical trial participants.
- ❑ Provides a legal framework that allows Sponsors to transport their investigational products to clinical sites. Once submitted, the Sponsor has to wait 30 days before initiating the trial.
- ❑ INDs may be commercial or research:
  - Commercial INDs allow for the development of a drug or biologic with the goal of ultimately submitting a marketing application.
  - Research INDs are for research purposes
- ❑ Emergency INDs may be submitted by physicians for the treatment of immediately life-threatening conditions when there is no standard acceptable treatment and no time to receive an Investigational Review Board (IRB) approval.
- ❑ All IND applications must include animal pharmacology and toxicology studies, manufacturing information, clinical protocol and Investigator's information.

New Drug Application (NDA)

- ❑ NDA is a formal request made by a Sponsor to market a new drug in the US and are typically regulated by Center for Drug Evaluation and Research (CDER).
- ❑ A NDA aims to provide sufficient evidence
  - to support the safety and effectiveness of a drug and
  - to show that the benefits of its use outweigh the risks.
- ❑ On top of the above, FDA reviews the drug's proposed labeling and determines the compliance of manufacturing methods.
- ❑ A NDA is expected to include:
  - primary data
  - summaries of the results of non-clinical and clinical studies,
  - Pharmacokinetic and pharmacodynamics analyses,
  - characterization of the drug's ingredients
  - toxicological evaluation
  - description of all manufacturing processes and quality control parameters.

Over-the-Counter (OTC) Application

- ❑ OTC drugs are regulated by the Office of Non-prescription Drugs (ONPD).
- ❑ There are two pathways by which marketing of OTC products may be achieved:
  - Compliance with an OTC drug monograph, i.e. a set of regulatory standards for different therapeutic drug classes that includes acceptable ingredients, doses, formulations, and labeling requirements
  - Approval under an NDA or ANDA
- ❑ If the standards of an applicable OTC monograph are met, marketing pre-clearance is not required by the FDA. If the OTC drug deviates from the final monograph, a formal marketing application (e.g., NDA) may be required.

Biological License application (BLA)

- ❑ BLA is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce and is regulated by Center for Drug Evaluation and Research (CDER).
- ❑ In correspondence to NDA, a BLA is expected to include data on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of the biological product.

Abbreviated new Drug Application (ANDA)

- ❑ An ANDA is submitted to the FDA for the review and approval of a generic drug product and are regulated by the Office of Generic Drugs (OGD).
- ❑ They are called abbreviated because they are generally not required to include preclinical and clinical (human) data to establish safety and effectiveness.
- ❑ An ANDA needs to demonstrate bioequivalence, i.e. that the generic product performs in the same manner as the innovator drug (e.g. by measuring the time it takes the generic drug to reach the bloodstream in healthy volunteers).

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	IND	NDA	BLA	ANDA	OTC
Covered under	FDC Act 21 CFR part 312	Section 505 FDC Act 21 CFR part 314	PHS Act, Section 351 21 CFR 600-800	Section 505(j) FDC Act 21 CFR part 314 Waxman-Hatch Act BPCIA	FDC Act 21 CFR 330
Regulated by	CDER/CBER	CDER	CBER	CDER/OGD	ONPD
Type of Submission	Research purposes	Marketing purposes			
Types	▪ Commercial/Treatment (21CFR 312.34) ▪ Research ▪ Emergency/Physician initiated (CDF 312.23, 312.34)	505 (b)(1) 505 (b)(2) 505(j)	351(a)	▪ Generic: 505(j) ▪ Biosimilar: 351(k)	N/A
Data required	▪ Full-preclinical ▪ CMC ▪ Clinical protocol ▪ Investigator's information	▪ Full preclinical including PK/PD ▪ CMC/QM ▪ Clinical data ▪ Proposed labeling	▪ CMC/QM ▪ Clinical data, including medical effects of the biological product ▪ Proposed labeling	Demonstration of bioequivalence	▪ CMC focusing on safety studies for ingredients ▪ Proposed labeling
Listed in		Orange Book	Purple Book	Orange Book	OTC Monograph & federal Register
Timeline	The Sponsor shall wait 30 days (FDA Safety Review)to initiate the trial after IND submission	Date of filing begins the 180-day period of the review.	FDA deadline: 6 months of the 60 day filing date Day 74 letter: within 74 calendar days from the date of FDA's receipt of the original submission	Within 10 months of submission date; within 8 months for priority ANDAs	

CBER: Center for Biologics Evaluation and Research; CDER: Center for Drug Evaluation and Research; CMC: Chemistry, Manufacturing and Controls; OGD: Office of Generic Drugs; ONPD: Office of non-Prescription Drugs; OTC: Over-the-Counter; PD: pharmacodynamics; PK: pharmacokinetics; QM: Quality Management

Electronic Common Technical Document (eCTD): The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

Drug Master Files (DMFs): Submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products. According to the FDA, a DMF application is neither approved nor disapproved, but its information is used to review an INDs, NDA,s BLAs, ANDAs, or Export Applications.

There are 4 types of DMF Files:

- Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation; or Drug Product
- Type III Packaging Material
- Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V FDA-Accepted Reference Information

Major FDA Applications for Medical Devices

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- Medical devices are classified into 3 categories based on potential risk to patients and this ultimately determines the applicable ate FDA regulatory pathway.

- Devices are regulated by FDA's Center for Devices and Radiological Health (CDRH)

- There are 3 basic processes to obtain FDA marketing approval for medical devices, depending on the nature of the device and the circumstances under which approval is sought: 1) the PMA process; 2) the Premarket Notification (510(k) process; and 3) the humanitarian device exemption (HDE) process.

Class 1
- Low inherent risk
- No formal route to market
- Examples: band-aids drapes, hospital beds, reusable scalpels

Class 2
- Medium inherent risk
- Usually routed to market with a 510(k) clearance
- Examples: catheters, syringes, absorbable sutures, guidewires, hip implants

Class 3
- high inherent risk
- Routed to market via PMA
- Examples: heart valves, stents, spinal cord stimulators, defibrillators

Premarket Notification - 510(k)	Premarket Approval - PMA
Based on substantial equivalence	Based on safety and performance
For class 1 (if needed) and 2 (rarely class 3)	For class III medical devices
Comparison with predicate device is usually sufficient (10-15% of applications require clinical data)	Requires clinical evidence
Leads to clearance	Leads to approval
Timeline= 30-90 days	Timeline= 180 days
No pre-approval inspection	Pre-approval inspection
No requirement for PMS activities	Requirement for PMS activities
Rare requirement for advisory panel review	Advisory panel review may be required for some devices

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	Premarket Approval (PMA)	Premarket Notification - 510(k)
Overview	Novel or high-risk devices usually follow the PMA pathway, under section 515 of FDC Act Application methods: ❑ Traditional (CFR 814.20(b); inspection of manufacturing site; 180 days from submission to outcome ❑ Modular (submission in modular stages but same content with traditional) ❑ Streamline (used for well-established technologies; prerequisites 2-3 approved PMAs of the same type) ❑ Product Development Protocol (combination of IDE with PMA)	While the 510(k) pathway is faster, less expensive and requires less, if any, clinical evidence, this pathway depends on whether the device has a predicate, i.e. a similar device with similar intended purpose and indication of use, which is already FDA approved. substantially equivalent device: the new device has - the same intended use and same technological characteristics as the predicate, or - the same intended use as the predicate, different technological characteristics, but does not raise new questions of safety and effectiveness.
Process	Filing a PMA (21 CFR. 814.42) ⇒ In-depth review (21 CFR 814.44) ⇒ Panel Review (21 CFR 814.44) [if applicable] ⇒ Standard Conditions of Approval PMA Review Process ❑ Filing review ❑ Statistical review for filing ❑ Review of manufacturing information for compliance with the Quality System regulation (21 CFR 820) ❑ PMA filing decision ❑ Day-100 Meeting ❑ Quality System Inspection(s) ❑ Bioresearch Monitoring (BIMO) Audit (audit of clinical study data) ❑ Substantive review coordination and completion ❑ Approval or Non-approval letter	❑ Log-in and Acknowledgement Procedure ❑ Acceptance Review ❑ Substantive Review (including Substantive Interaction and Interactive Review) ❑ 510(k) Decision Letter ➢ The FDA goal to make a MDUFA Decision for a 510(k) is 90 FDA Days Did you know that 7 out of 10 510(k) submissions are rejected their first time!
Requirements	➢ Technical Sections ➢ Non-clinical Laboratory Studies Section ➢ Clinical Investigations Section To include in the submission: ❑ Manufacturer info ❑ Description of the device and function ❑ Practices & procedures ❑ Market history ❑ Manufacturing processes ❑ Discussion and Summary of clinical non-clinical studies ❑ Discussion of literature and all other published reports/information ❑ Conclusion on safety and effectiveness based on the above ❑ Reference to applicable performance standards ❑ Labeling and marketing documents ❑ Device samples if requested ❑ Financial certification and disclosure statement	➢ Device Classification ➢ Identification of Predicate device(s) ➢ Final draft labeling (statements for Indications of Use) ➢ Specifications including engineering drawings, photos, etc. ➢ Performance data such as bench, animal, or clinical testing (if applicable) ➢ Sterilization information (if applicable) ➢ Guidance document(s) specific to your device type, if it exists To include in the submission: Medical Device User Fee Cover Sheet (Form FDA 3601) CDRH Premarket Review Submission Cover Sheet ❑ Cover Letter ❑ 510(k) Acceptance Checklist ❑ Statement of Indications for Use ❑ 510(k) Summary or Statement ❑ 510(k) Summary + Statement ❑ Proposed Labelling ❑ Specifications (narrative + physical description) ❑ Substantial Equivalence Comparison (intended use, indications for use, target population, anatomical site, where used, energy used and/or delivered), human factors, design, performance, applicable standards, materials, biocompatibility, environmental compatibility, sterility, electrical/mechanical/chemical/thermal/radiation safety ❑ Performance data

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De Novo Application: for devices that do not have the high risks associated with class III, but for which no predicate device exists. Also used if FDA determines non-substantial equivalence for a device going through traditional 510(k) due to a new intended use or different technological characteristics that raise questions about safety and effectiveness.
Allows novel technologies to be classified as class II without undergoing a PMA application.

Humanitarian Device Exemption (HDE) is used for certain devices that treat rare diseases. Similar to the PMA pathway, it requires less clinical data or proof of effectiveness to enhance Manufacturers to develop devices. The devices must be approved by an IRB before an application is submitted.
Total review time by FDA is 75 days after the date of filing

Investigational Device Exemption (IDE): FDA requires that medical devices are granted an Investigational Device Exemption (IDE) prior to being tested in human subjects as part of a clinical trial to collect safety and efficacy data.
Usually obtained to support either a future 510(k) or PMA application.
Devices that are considered to have low or non-significant risks by an Internal Review Board (IRB) at the sponsoring or supporting institution do not require an IDE and can be used in the proposed study without FDA involvement.

Breakthrough Devices Program is a mechanism for expedited reviews for breakthrough devices defined as *"more effective treatment or diagnosis" of life-threatening or irreversibly debilitating diseases*
Benefits:

- ❑ earlier communication between the FDA and applicants; 60 days from submission to decision
- ❑ more flexibility in clinical study designs
- ❑ possibility of considering additional PMS data in lieu of premarket + expedited manufacturing inspections.