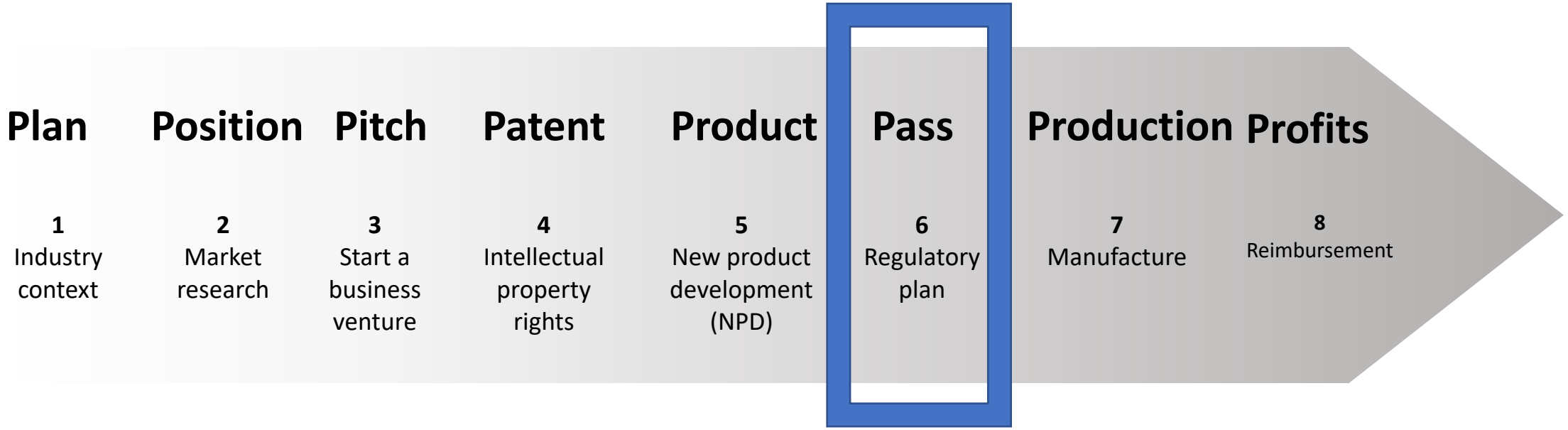
Commercializing Successful Biomedical Technologies 2nd Ed.

Shreefal Mehta



The regulated market: gateway through the FDA

Shreefal Mehta

Chapter 6

FDA role and significance for biomedical product development

1906 Food and Drugs Act.

- Establishing a national agency to put a stop to food adulteration and fake remedies
- This Act made it illegal to sell adulterated foods and make false claims about a food or drug and also carried these bans into interstate commerce.
- An existing Department of Chemistry was designated to carry out tests and enforce the law. The primary concern was to use scientific methods to analyze the risk to human health and safety

1936 Food and Drugs Act.

- required drug makers to show their products were safe before they went on the market.
- That gave rise to the regulatory pathway that drugs in development go through prior to approval, beginning with animal testing prior to human testing

The FDA

- ✓ Protecting consumer safety in the development and sale of food and medical products (drugs/
- ✓ devices/diagnostics).
- ✓ ensures that the claims made by a medical product accurately reflect its risks and benefits
- ✓ not only the gatekeeper to the market also specify the claims that the manufacturer can make

The approved label :

- *defines the patient population to whom the product can be sold.*
- *product development process has to be designed with the end label (indication) in mind*

FDA Focuses On Consumer Protection

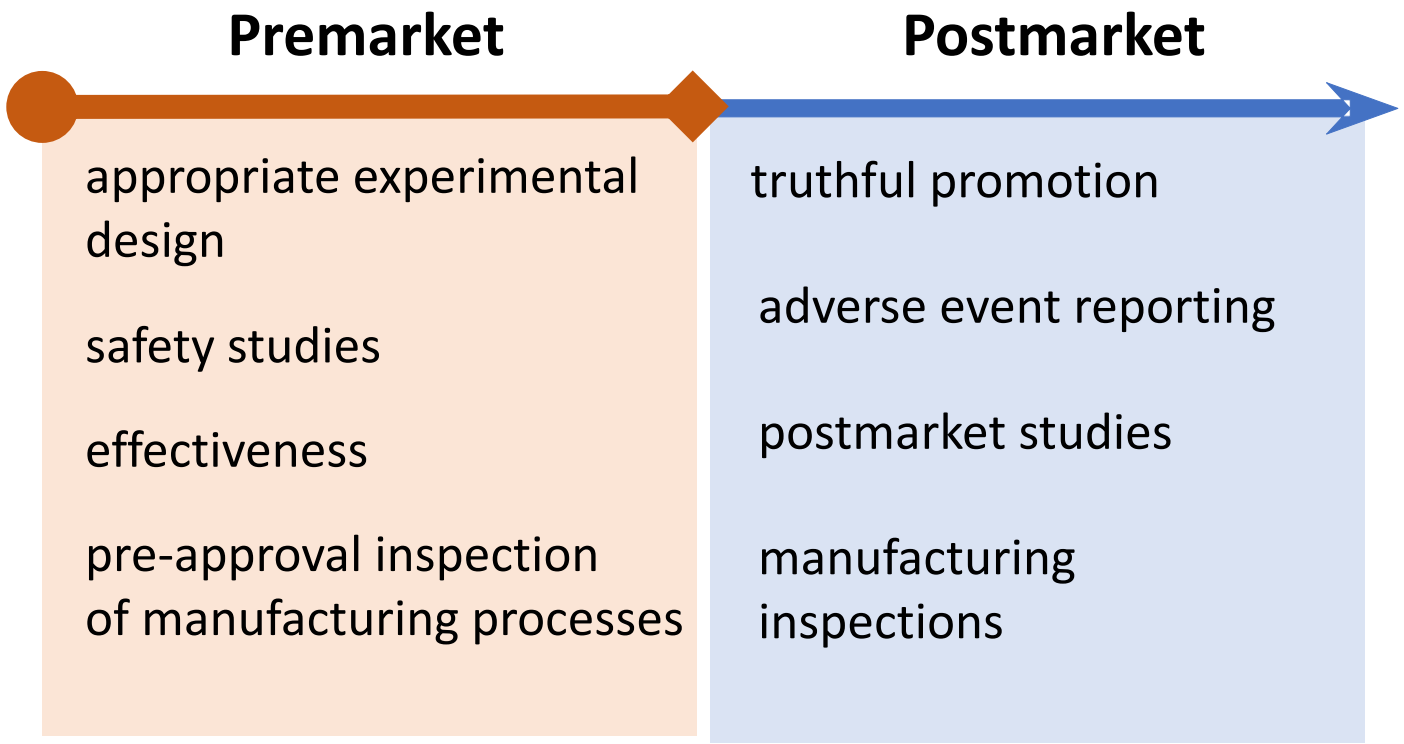


Figure 6.1

Divisions of the FDA

Center for Biologics Evaluation and Research (CBER)

Regulates biological products such as vaccines, biologics, cellular, tissue and gene therapies, blood, blood-derived products, devices, and tests used to safeguard blood from infectious agents, and xeno-transplantation products.

Center for Drug Evaluation and Research (CDER)

Regulates all prescription and over-the-counter drugs (includes biological large molecule drugs like monoclonal antibodies and cytokines, etc.), monitors drug advertising

Center for Devices and Radiological Health (CDRH)

Regulates all devices including those emitting radiation (ultrasound, electronic). Has under this directive the Office of In Vitro Diagnostics, which regulates all aspects of in-home and laboratory diagnostic tests (in vitro diagnostic devices, or IVDs)

- ✓ FDA's goal is to get safe and effective biomedical products to the public.
- ✓ This is conceptually the same goal that the manufacturers have.

Conflicts usually arise due to

Different view of risk versus benefit between the Company/sponsor and the FDA reviewers

The PDUFA (Prescription Drug User Fee Act, 1992)

increased the application fees paid by industry sponsors to the FDA to help fund the review of new drugs; in turn, the FDA has made several performance promises

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) : *charges user fees for device premarket reviews*

Working with the FDA

- ✓ The FDA has also made great efforts in recent years to work with industry on complex new technologies and to give them guidance and clarity on FDA's internal processes and reviews.
- ✓ FDA website : is a handy reference on most policy and process questions

Science rules – most of the time!

- The FDA is an organization driven by the scientific method and scientific principles of analysis
- Statistically valid analysis of the results must be used to support the claim for the indication
- The dialogue with the FDA is a formal and highly specific interaction

International harmonization

- The FDA also works outside U.S. national borders to protect U.S. consumer health
- In recognition of the increasing global trade in medical products and the myriad complex regulations in place in various countries, there is an ongoing effort to harmonize the regulatory regimes in the three largest markets
  I. European Union
  II. Japan
  III. United States

Regulatory pathways for drugs (biologicals or synthetic chemicals)

- The first step is to decide whether the product is regarded as a drug, device, or diagnostic and then further classify it according to perceived risk factors

Definition of drug product

A drug is defined

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.

Source: www.fda.gov/cder/drugsatfda/Glossary.htm)

- ***Biologic drug products*** *are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes*

New drug passes through the FDA : Planning the regulatory path for drugs as follows

- ✓ Define the exact indication and clinical trial endpoints
- ✓ Decide if this is an orphan drug product

There are three main regulatory gateways and paths for a drug product to reach the market:

(1) Approval of an NDA,
(2) Abbreviated pathway with an ANDA, or 505(b)2 submission, and
(3) OTC (over the counter)

Drug product approval pathways

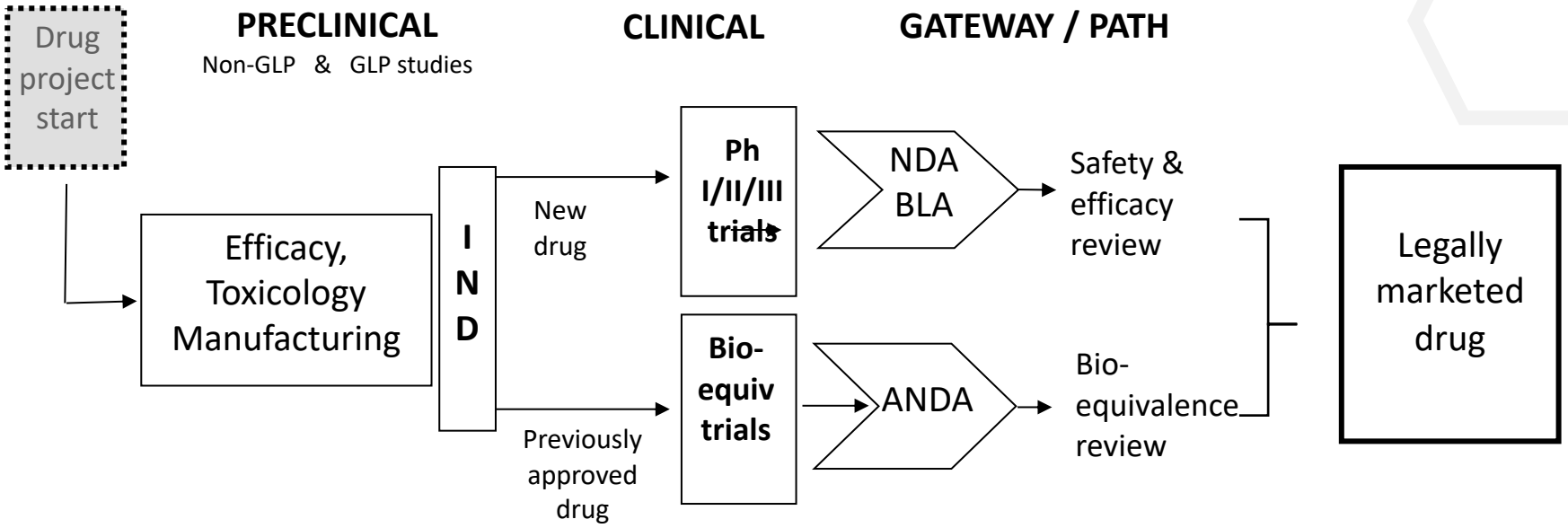


Figure 6.2

There are three types of FDA meetings corresponding to major milestones in drug development

1. Pre-IND meeting
2. End-of Phase II meeting
3. Pre-NDA/BLA meetings

Practical tips for successful FDA meetings

1. Understand the purpose of the meeting clearly
2. Have the right people at the table. Sponsors should select representatives who are leading areas of potential queries by the FDA
3. Practice and prepare. The FDA will usually provide (the day before) written responses to the questions sent in by your team when requesting the meeting.
4. Word your discussion and questions in a way to get clarity on issues and to gain binding agreement.
   - ✓ **Pre-IND/Phase I** – Polymorphs, enantiomers, or other unique physico-chemical properties. Reasons for selection of specific form of compound for drug product. Qualification of impurities.
   - ✓ **End-of-Phase II meeting -** Agreement on final drug product synthesis scheme, specifications, impurities, etc.

- *FDA staff are similar to you and your team. Being well prepared, providing adequate briefing information, and keeping to scheduled times are all important to make these FDA meetings successful.*

Preclinical studies regulated by the FDA

- Preclinical studies that are submitted to the FDA should be well described and summarized and the data should be completely transparent with detailed records.
- Specific preclinical studies include : efficacy data establishing the utility of the drug in treating the specific indication
- A pre-IND meeting can be held to discuss the planned GLP toxicology studies and the plans for phase I and II clinical studies.

Preclinical toxicology or safety studies must be carried out under strict GLP guidelines and include the following

- Safety pharmacology studies
- Single and repeat dose toxicology studies in two species of mammals
- Genotoxicity studies
- Reproduction toxicity studies
- Other supplementary studies if safety concerns are identified

- Pharmacology studies
- Pharmacokinetic (PK) studies and an examination of the absorption, distribution metabolism, and excretion (ADME) behavior
- Chemical and manufacturing details
- Detailed description of the drugs' manufacturing process
- The drug must be manufactured in facilities that are following general cGMP
- Specific issues for preclinical testing of biological drugs
- Local tolerance and immunogenicity studies
- Mutagenicity

Specific studies required for safety pharmacology endpoints are determined on a case-by-case basis

FDA and post marketing surveillance

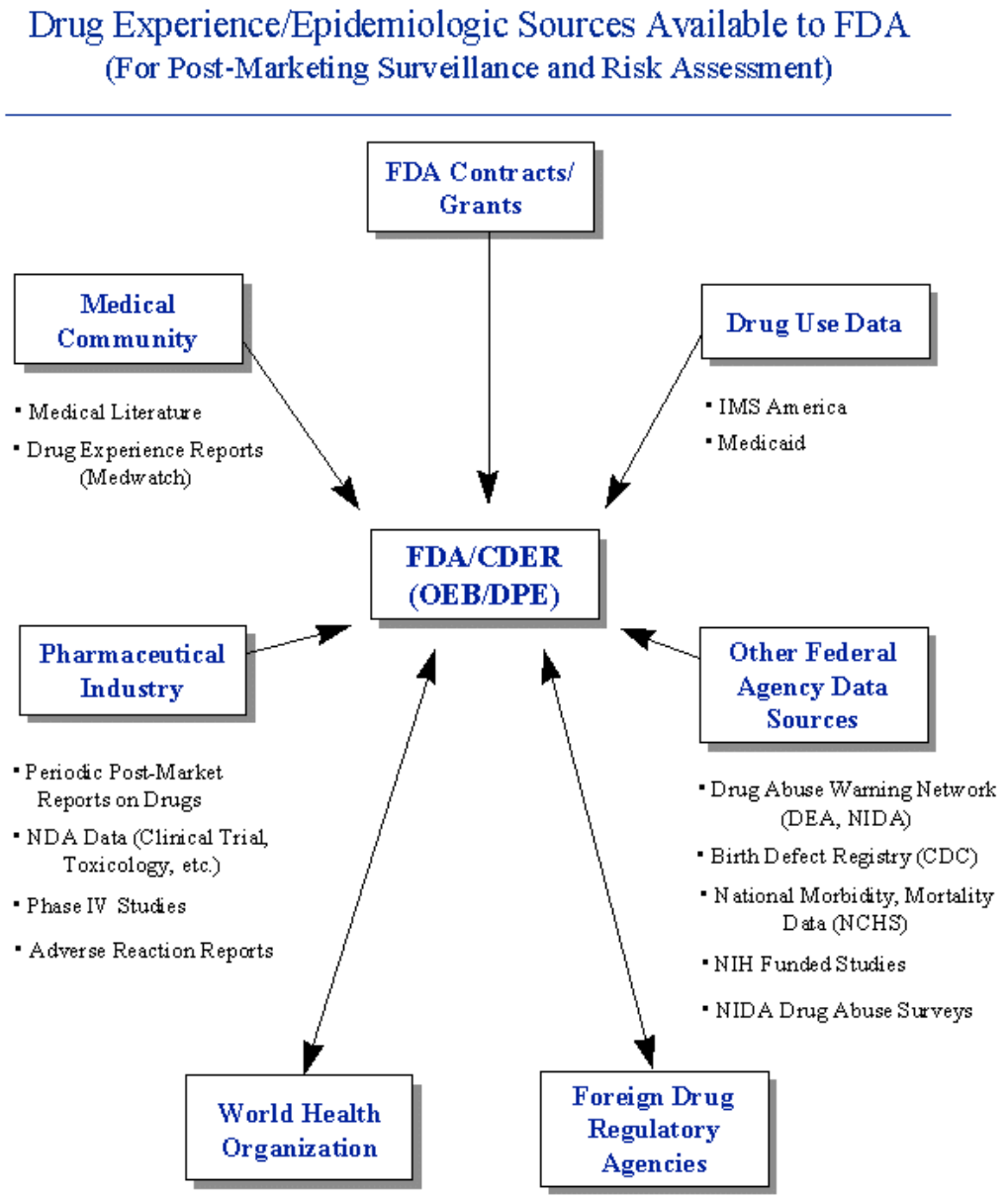


Figure 6.4

Filing an investigational new drug application

IND

- Submitted by a sponsor-investigator, defined as one who initiates and conducts a clinical trial

- **Two types :**
  I. A commercial IND - commercial sponsor
  II. A research IND - academic researcher

Clinical studies can be initiated 30 days after the date of receipt of the IND by FDA, unless the sponsor receives requests for more information by the FDA within those 30 days

IND submission must include the following

- ✓ Introductory statement and general investigational plan
- ✓ Investigator's brochure
- ✓ Clinical protocol
- ✓ Include endpoint measurements and detailed statistical analysis methodology
- ✓ Chemistry manufacturing and controls (CMC) section
- ✓ Pharmacology and toxicology information

IND review process

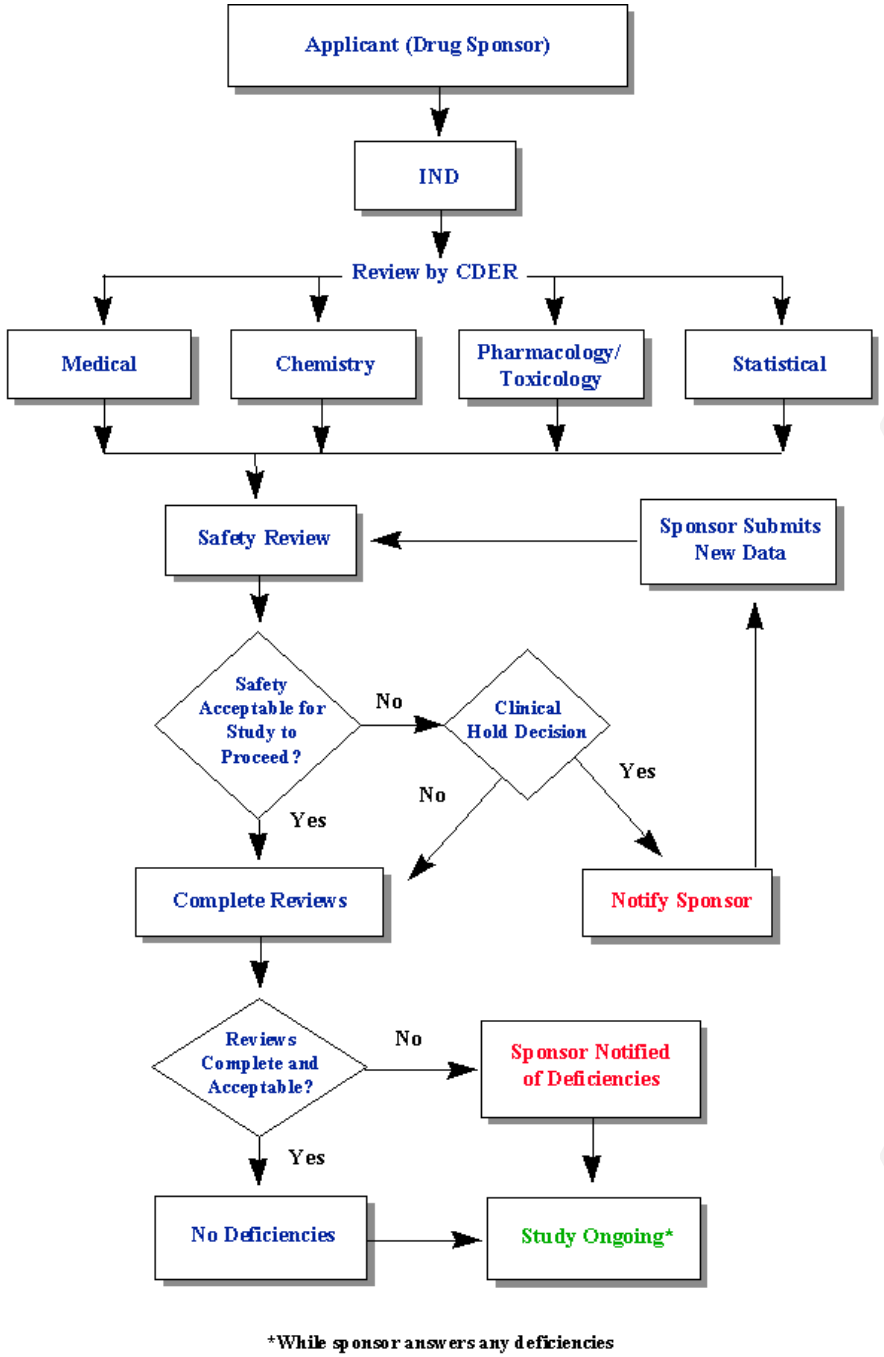


Figure 6.5

New drug application (NDA) submission:

- The submission of the NDA is the key component in the regulatory approval process.
- The NDA has over 20 sections which include the following key sections:
  - ✓ Application summary(50–200 pages)
  - ✓ CMC chemistry, manufacturing, and controls section
  - ✓ Nonclinical pharmacology and toxicology
  - ✓ Human pharmacokinetics and bioavailability
  - ✓ clinical data
  - ✓ Safety update reports

Drug master files

- A drug master file (DMF) is a voluntary submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs
- DMFs are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file.
- For example, an IND or NDA sponsor can refer to a DMF submitted by a contracted manufacturing facility to support their application

NDA review process

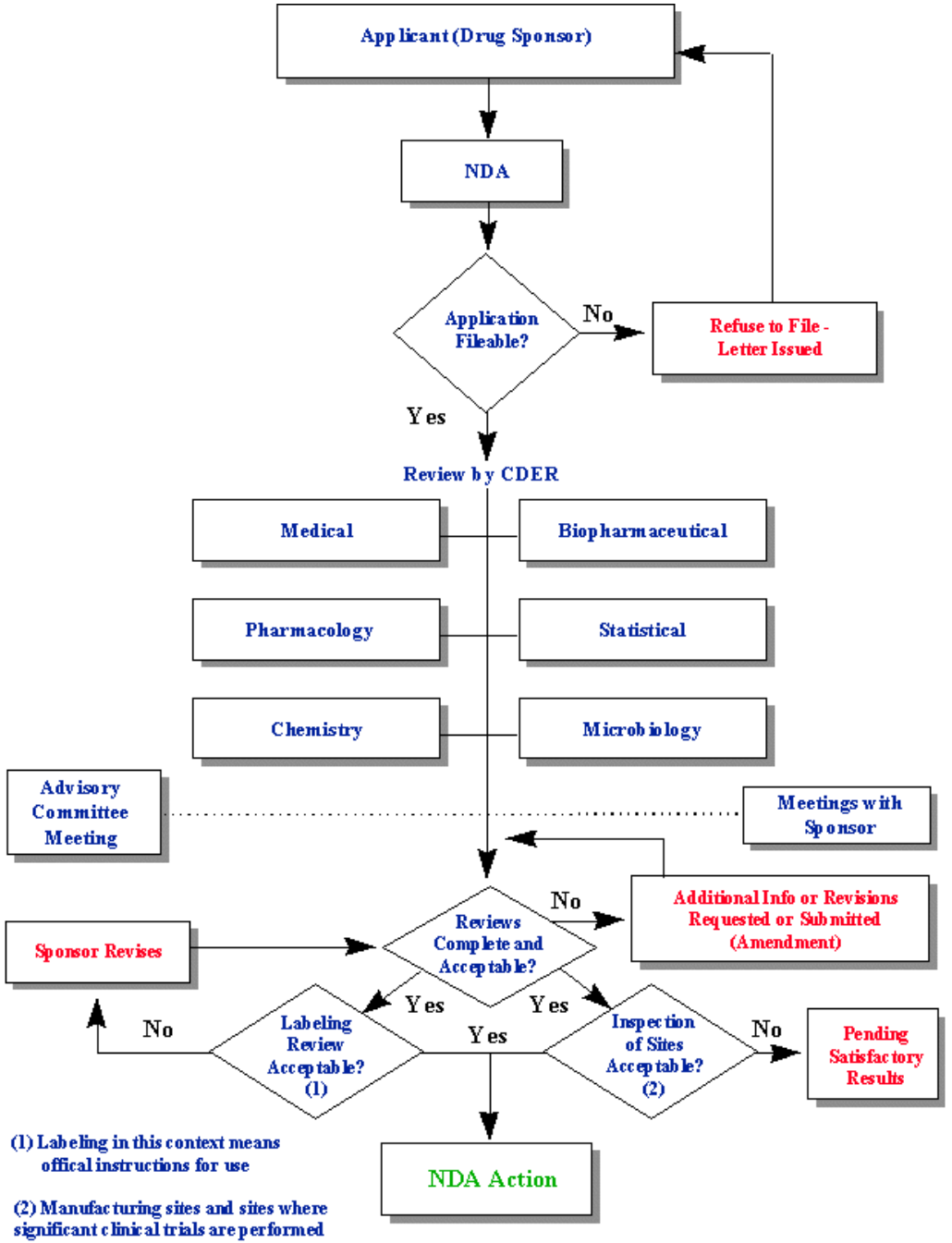


Figure 6.6

Drug regulatory pathways

Abbreviated pathway for duplicate drugs (ANDA)

- **To market a copy of a drug** that has been on the U.S. market after its patent has expired,
- The ANDA must be filed for indications that were already approved for the original drug molecule
- **For biosimilars,** or copies of approved biological products the 351(k) pathway for approval. provides a similar path as the ANDA for small molecule drugs,

An abbreviated approval pathway for reformulated versions of drugs 505(b)(2)

- A 505(b)(2) application is an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant
- Usually a path for re-purposed drugs where a change in formulation or method of dosage provides some significant benefit to the patients, usually by reducing side effects or providing a more convenient dosage

Regulatory pathway for over-the-counter drugs

- Over-the-counter (OTC) drug products are those drugs that are available to consumers without a prescription
- The FDA maintains a list of OTC drug monographs. These monographs are a kind of "recipe book" covering acceptable ingredients, doses, formulations, and labeling

Post-market clinical studies (Phase IV) and safety surveillance

- The FDA has an active surveillance program that requires sponsors to report any serious side effects not listed on the label

ANDA (generics) review process

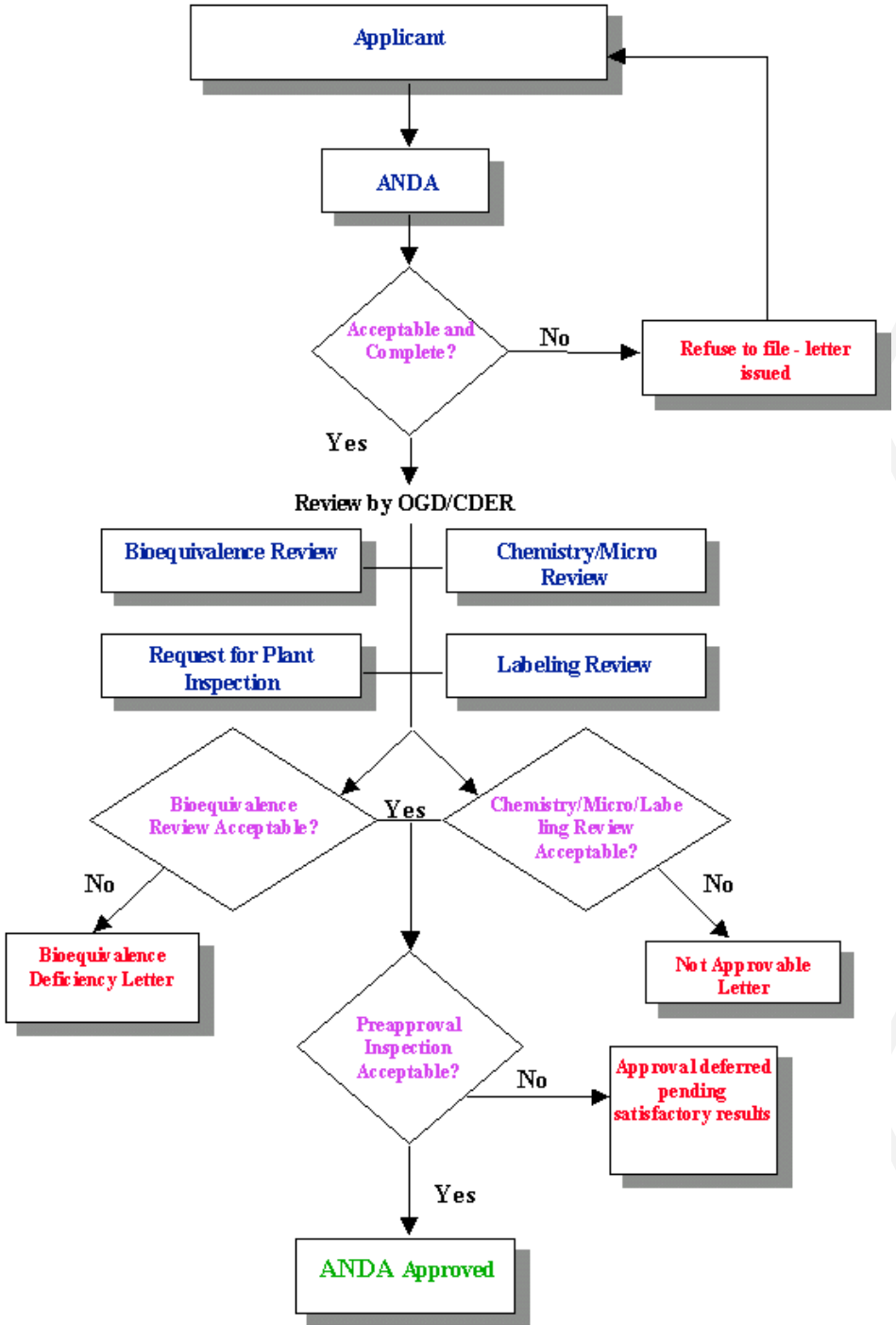


Figure 6.7

Speeding up access to drugs

Fast Track

- The Fast Track Drug Development Program facilitates the development and expedites the review process of drugs intended for the treatment of a serious or life-threatening condition.

Three criteria:

I. The drug must be targeted for use by a person that has a serious or life-threatening Condition

II. The drug must be intended to treat a serious condition, and

III. The drug must have the potential to address unmet medical needs.

A drug that receives Fast Track designation is eligible for some or all of the following:

- Frequent meetings with FDA : to discuss the drug's development plan
- Eligibility for Priority Review or Accelerated Approval, i.e., approval on an effect on a surrogate
- **Eligible for Rolling Review** : a drug company can submit completed sections of its New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed

Accelerated approval

- A Priority Review designation is given to drugs that offer major advances in treatment
- **A Priority Review designation** : the time it takes FDA to review a new drug application is reduced.
- The goal for completing a Priority Review is six months.

FDA interactions in drug development

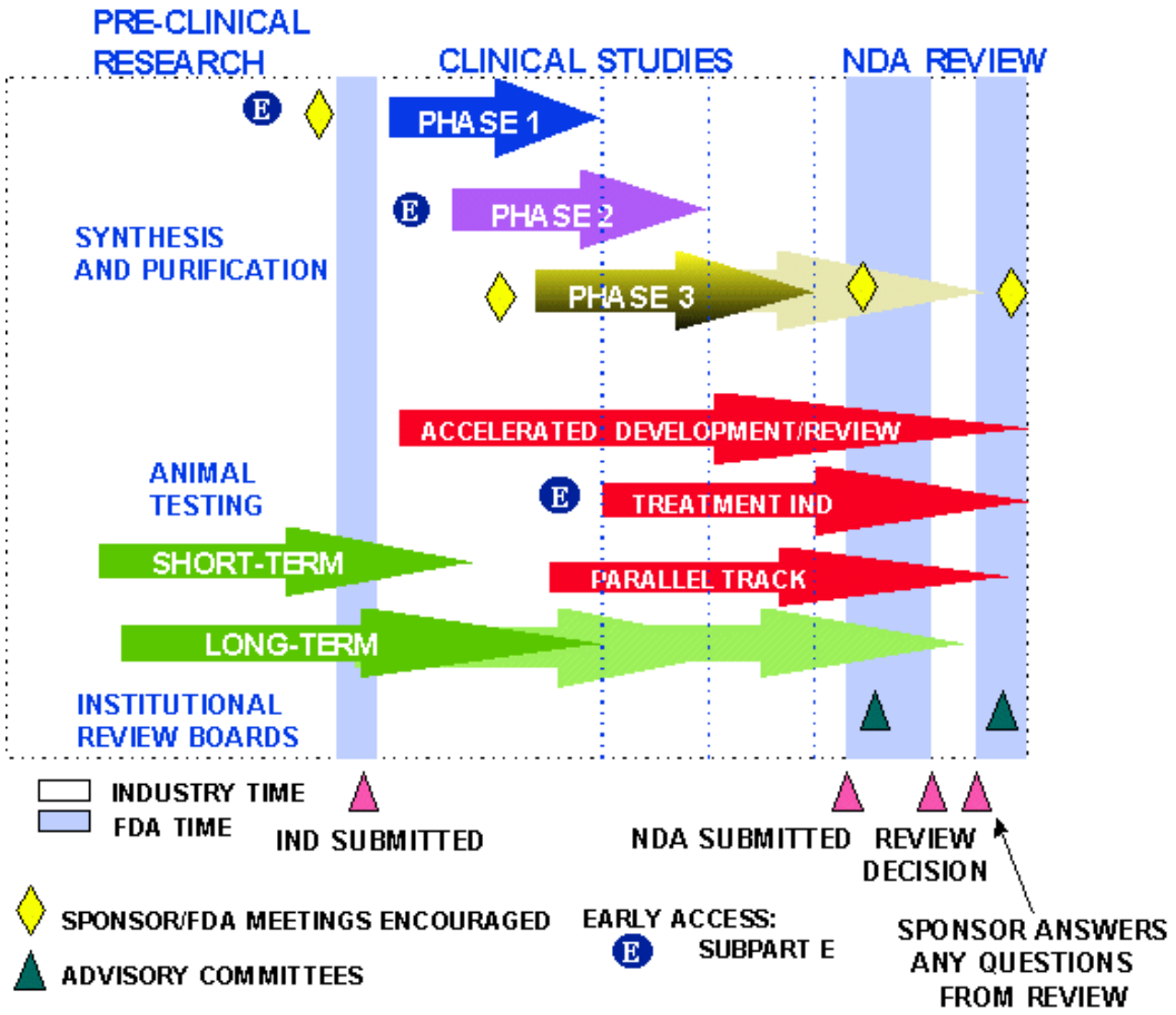


Figure 6.3

Orphan drugs

- **Orphan drugs** : that treat rare diseases affecting U.S. patient populations < 200,000
- The FDA's Office of Orphan Products only designates orphan drugs
- Does not influence the approval and review process of CDER or CBER.
- The Orphan Drug Act (1983) gives 7 years of market exclusivity
- Over 200 orphan drugs were approved from 1983 to the present.
- This Act has provided a commercialization pathway for drug molecules whose patents have expired and had promise to treat these rare diseases but had no financial incentive for entrepreneurs to take risks and invest in development

Devices: regulatory pathways and development considerations

There are four possible regulatory pathways for medical devices and an additional one for diagnostics to get to market :

1) exempt from FDA review
2) 510 (k) clearance process for devices that are similar in action to another approved device
3) De novo process for new to the market devices (without a predicate) whose safety profile and technology is well understood
4) PMA review for new to the market devices deemed high risk.

For diagnostics – if they are exempt from (2) and (3), they have to go through CLIA categorization.

Devices (contd)

Step1:

Determine the jurisdiction of the FDA center – is it a device?

- Medical devices range from simple tongue depressors to complex programmable pacemakers with micro-chip technology, X-ray machines, and include in vitro diagnostic products
- A device is defined by its primary mode of action in the indication specified by the company.

Step2:

Classify the medical device – what controls and regulations apply?

- classify the device by its indication and intended use and the risk it poses to patient/user if it malfunctions or fails.
- Will indicate the type of submission to be made to the FDA to commercialize the device.
- **Class I :** General Controls apply
- Exemptions / Without Exemptions
- **Class II :** General Controls and Special Controls apply
- Exemptions / Without Exemptions
- **Class III :** General Controls apply and Premarket Approval required

Step3:

Determine the specific path and marketing application required to be submitted

- Class I exempt devices do not need to get approval before marketing
- Class I and Class II devices that are not exempt can go through a premarket notification 510(k) submission to get clearance and most Class III devices will go through a premarket approval (PMA) process
- The 510(k) submission is dependent on first locating a substantially equivalent device already on the market and then filing data that demonstrates such equivalence of the new device.
- Substantial equivalence has to be established both,in the technological characteristics and intended use of the new device in comparison to a chosen predicate device.

Medical device regulatory pathways

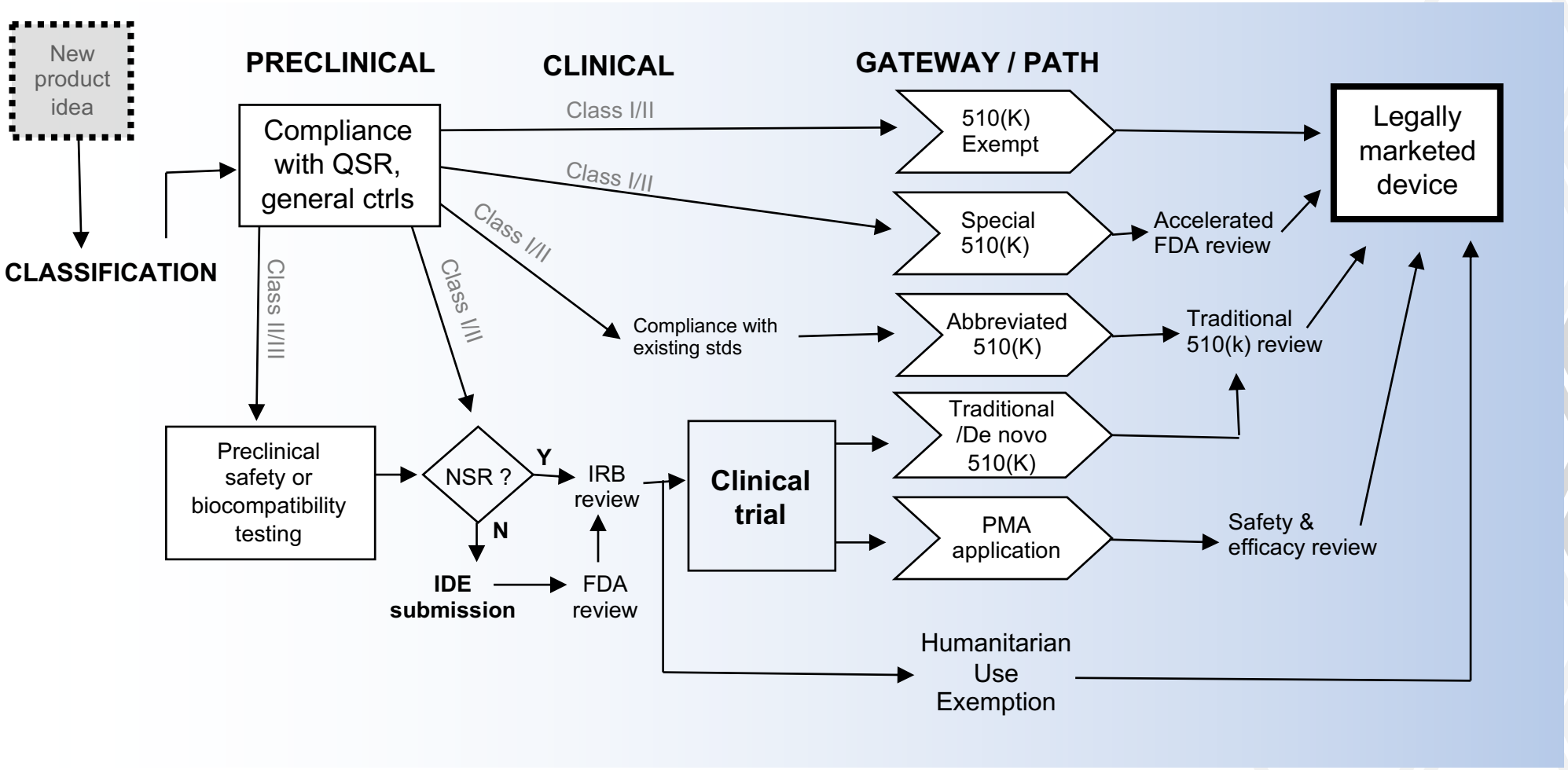


Figure 6.8

- If a clinical trial is needed to demonstrate substantial equivalence, an investigational device exemption (IDE) must be applied for and approval obtained from the FDA before starting such trials.
- The sponsor can also directly submit a De Novo classification request to the FDA
- A premarket application (PMA) process is necessary when the new device is not
- substantially equivalent to any other device that has been cleared through 510(k) process.

The PMA process

- submission and approval of an investigational device exemption (IDE) to allow clinical trials to be conducted
- The clinical trials should ascertain the safety and
- efficacy of the device in its intended use. The data will be analyzed and submitted in a PMA to the FDA.

Device regulatory pathways in the European Union (EU)

- In the EU, every marketed medical device must carry a Conformité Européenne (CE) mark indicating that it conforms to relevant directives set forth in the (2017) EU Medical Device Regulation (MDR)
- *A device with a CE mark can be marketed in any EU member state*
- *An application can be filed in any EU member state and is then reviewed by a "notified body" (NB) in that state.*
- *These notified bodies are third-party reviewing organizations to assess and assure conformity with requirements of the relevant MDR directives.*

Preclinical considerations – special controls and QSR for Class II and III devices

- Special controls are specific issues that the FDA has identified for a type of device (e.g. all scalpel blades) and would like to see addressed by the sponsor when submitting either a 510(k) or a PMA

- The FDA issues guidance documents detailing these concerns

- The QSR (quality systems regulation) (21 CFR part 820) is the device equivalent of the pharmaceutical good manufacturing process (GMP) regulations
- QSR impacts the preclinical stage significantly as it includes design controls (21 CFR 820.30) which apply to preclinical studies for all class II and III
- Devices as soon as they move beyond initial concept and feasibility testing studies.
- All relevant activities must be documented in the design history file (DHF) which must be regularly updated during the development process and filed with the FDA

- This reliability and consistency established with the help of design and production controls will eventually provide safer products for patients and also save money in the long run for the manufacturer by improving yields and reducing the risk of product returns or lawsuits
- The quality system, when implemented, will usually encompass the entire organizational structure in particular with an emphasis on management responsibilities for review of the quality system outputs.
- Help the company in compliance to regulations

Quality System Records for Medical devices

- The recording requirements of the QSR (DHF, DHR, and DMR) thus regulate the device from concept to development. The goal of the QSR is to create a set of self correcting systems that will reliably produce a high-quality design, with a controlled and predictable production process
- European Medicine Agency (EMA) requires each manufacturer of. medical devices and in vitro diagnostics to establish a quality management system (QMS) and have a corresponding responsible person designated within the company

510(k) submission type and content and CE technical documentation

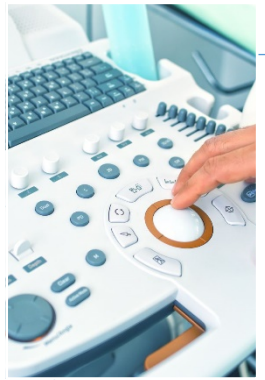
- There is no specific 510(k) form but instead a format for the submission is described in 21 CFR 807 and in multiple guidance documents published by the FDA on their website
- The 510(k) process is much shorter than the PMA route
- Most companies try to qualify their devices into the 510(k) pathway

First step : find a predicate device that is most similar (substantially equivalent) to the device intended for submission through the 510(k) program
Next step: read all guidance documents published on this type of device by the FDA.

Show substantial equivalence to a predicate device

510(k) submissions (contd.)

The four types of 510(k) submissions are



Traditional 510(k)

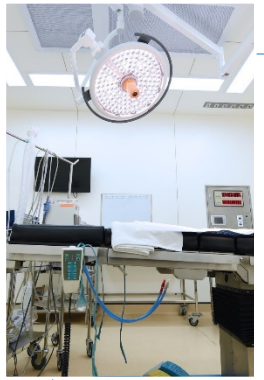
- If the new device is not a modification of one of the sponsor's own previously cleared devices and does not need to conform to any special control or guidance document from the FDA. The FDA has 90 days to review this submission

Special 510(k)

If the sponsor has modified their own 510(k) cleared device, but has not added a new indication or altered fundamental scientific technology of the device. The FDA has 30 days to review this submission.

Abbreviated 510(k)

- If the new device has to conform to a special control or guidance, a declaration of conformance has to be included in this abbreviated 510 (k), stating that the device meets the referenced standards.



De novo 510(k)

if this is a 510(k) without a predicate device, where the sponsor can demonstrate that the device has few risks and that the detailed PMA reviews for safety and effectiveness are not required. This should be confirmed in discussion with the FDA.

510(k) submissions (contd.)

A 510(k) submission typically contains

- **Comparative information :** most important section, containing data with critical choice of comparison parameters
- **Indication for use form:** list of indications for use
- **510(k) summary:** Publicly available information on FDA website

The CE technical documentation *is the equivalent of a 510(k) premarket submission for the EMA CE mark application. I*

PMA submission content includes

- Summary of safety and effectiveness
- Device description, intended use, and manufacturing data
- Performance standards referenced
- Technical data (nonclinical): Nonclinical laboratory studies' section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests
- Technical data (clinical): The Clinical Investigations Section includes study protocols, safety and effectiveness data, adverse reactions and complications, results of statistical analyses
- Labeling and Environmental assessment

Humanitarian use devices (HUDs)

- A humanitarian use device (HUD) treats or diagnoses a disease or condition that affects fewer than 4,000 individuals in the United States per year and can be approved by the FDA under the Humanitarian Device Exemption (HDE)
- The applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

CE Mark technical document equiv 510(k)

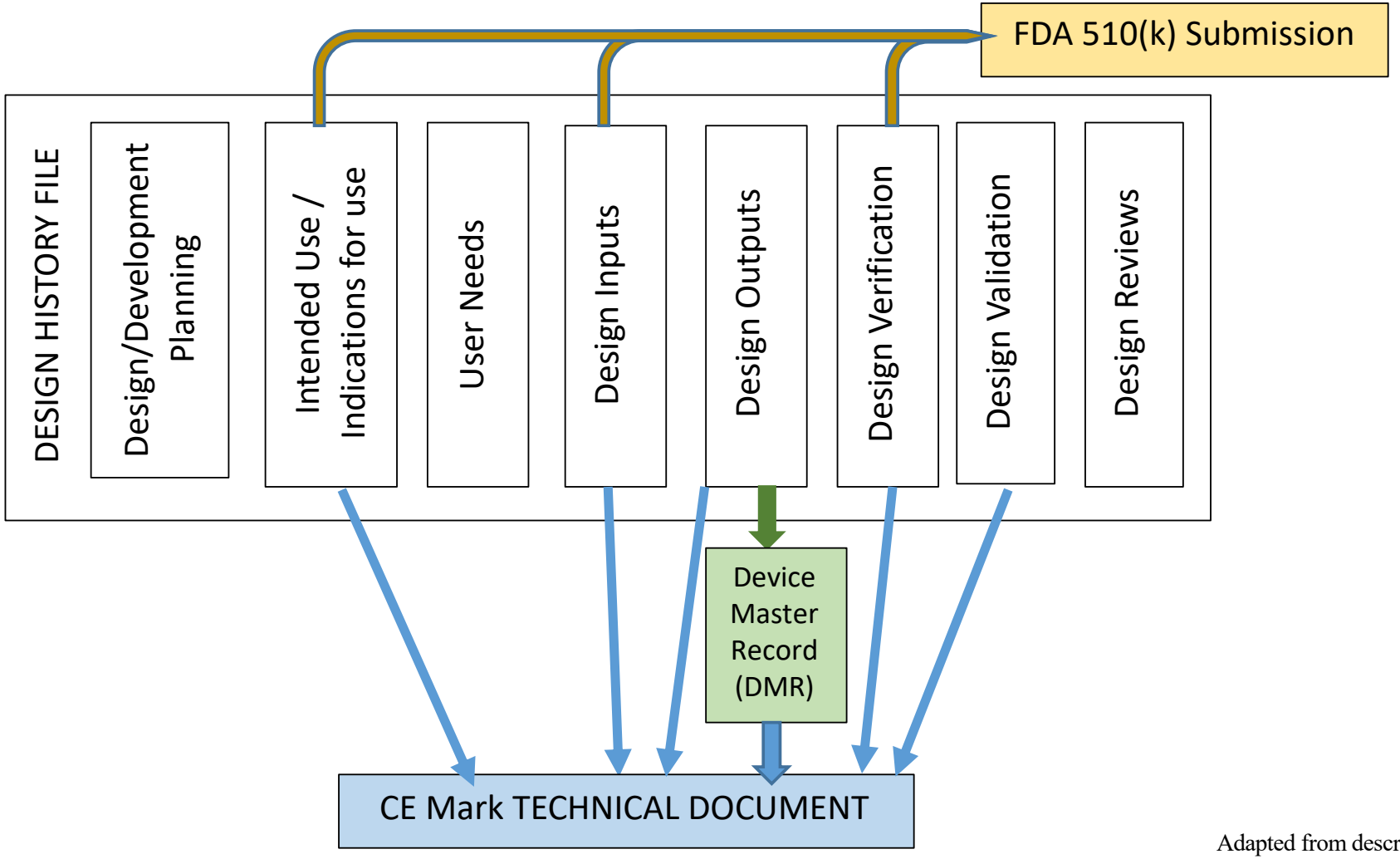


FIGURE 6.9

Adapted from descriptions at http://www.consultys.ch/technical-dossier

Diagnostics: regulatory pathways and NPD considerations

- In vitro devices (IVD) are mostly regulated as medical devices
- The specific office : CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD).
- Three major groupings of diagnostics through their commercial and regulatory practices
  I. Analyte-specific reagent (ASR)
  II. Laboratory developed test (LDT)
  III. In vitro diagnostic (IVD)
- IVDs are also subject to the clinical Laboratory Improvement Amendments (CLIA) of 1988 - established quality standards for laboratory testing and an accreditation program for clinical laboratories
- The regulations established three categories of testing on the basis of the complexity of the testing methodology:
  1. Waived tests
  2. Tests of moderate complexity
  3. Tests of high complexity

IVD – regulatory clearance or approval steps to market:

- IVD products that are exempt from 510(k) or PMA processes, must then go through CLIA categorization and other IVDs that are not exempt must go through the CLIA categorization in addition to the 510K or PMA reviews
- Almost all molecular diagnostic testing today is CLIA-regulated and not under FDA.

Diagnostics FDA regulatory path

- FDA regulatory clearance Class I/II diagnostic device (6-9 months)
  - Register company as medical device manufacturer with FDA
  - Establish quality processes - design, packaging, labeling and manufacturing
  - Classify device – Class I exempt, Class I or Class II.
  - If exempt, apply directly for “CLIA category only”
  - Identify predicate device(s) for application
  - Establish substantial equivalence with approved tests
  - Pre-market notification or 510(k) or CLIA categorization request
  - Post-marketing reporting

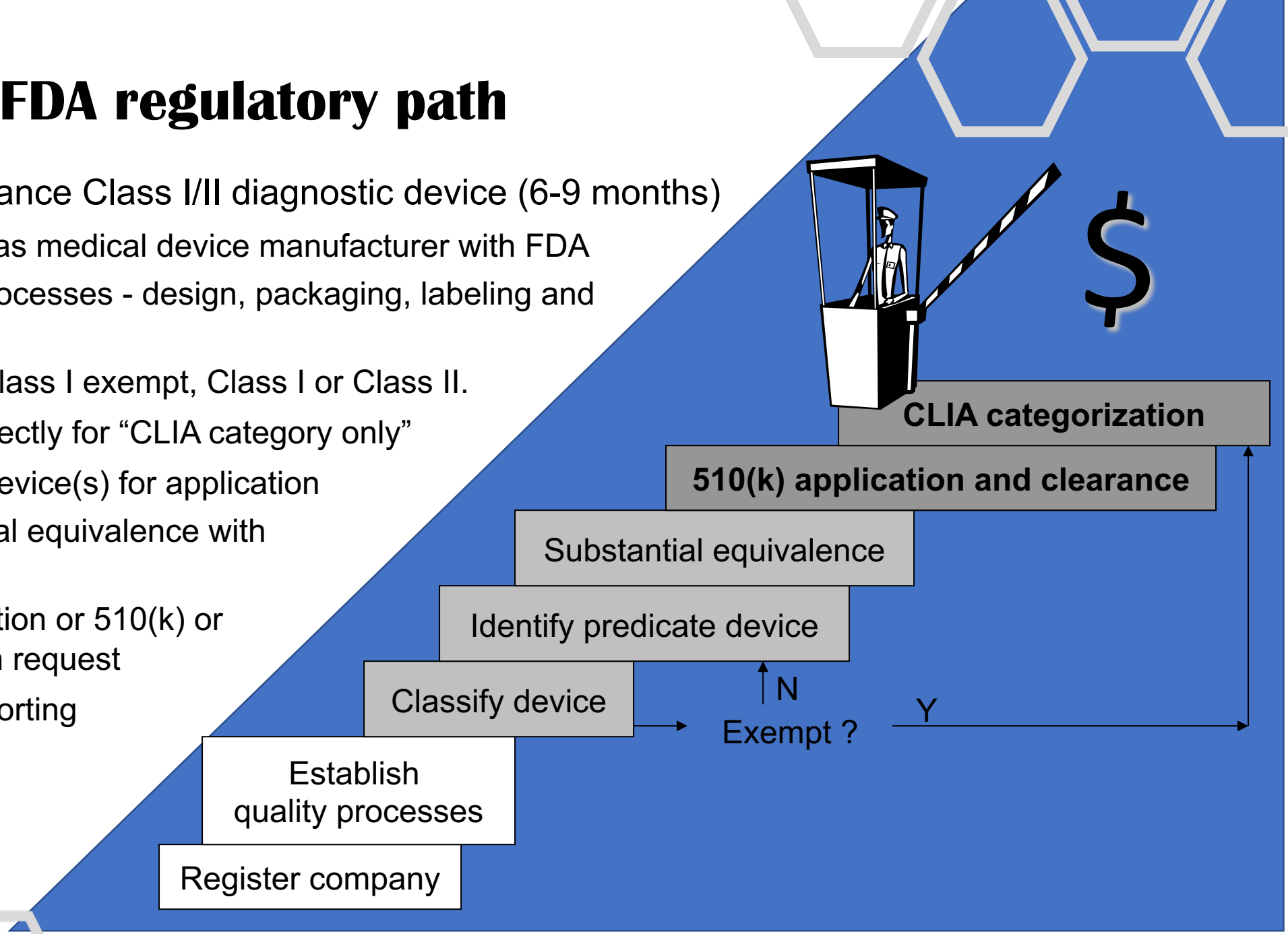


FIGURE 6.10a

Diagnostics (contd.)

CLIA program

- The Centers for Medicare & Medicaid Services (CMS) assumes primary responsibility for financial management operations of the CLIA program, which is self-funded by user fees from regulated labs.
- The CMS pays the FDA for CLIA categorization of commercially marketed tests.
- The FDA CLIA program assigns commercially marketed in vitro diagnostic test systems to one of three CLIA regulatory categories based on their potential risk to public health: waived, moderate complexity or high complexity.

Analyte-specific reagents or “home-brew” tests

- **“ASRs** : ‘antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.’
- FDA classified the building blocks of in-house tests as analyte-specific reagents (ASRs) and began to regulate them, but still puts very few controls on most ASRs
- Both the manufacturers of ASRs as well as the laboratories using them are subject to incremental regulation with controls
- Most molecular diagnostic tests or nucleic acid tests (NATs) or genetic tests fall under the description of ASRs and are restricted devices
- In simple terms an analyte-specific reagent (ASR) is the active ingredient of an in-house test. Most ASRs are classified as Class I devices, exempt from the premarket notification process

Analyte-specific reagents (contd.)

Manufacturers have to

I. Assure the quality of the materials being used to create these tests

II. Assure that laboratories preparing these tests were able to establish and maintain performance and understood their responsibility for accomplishing this

III. Provide appropriate labeling so that healthcare users would understand how these tests were being validated

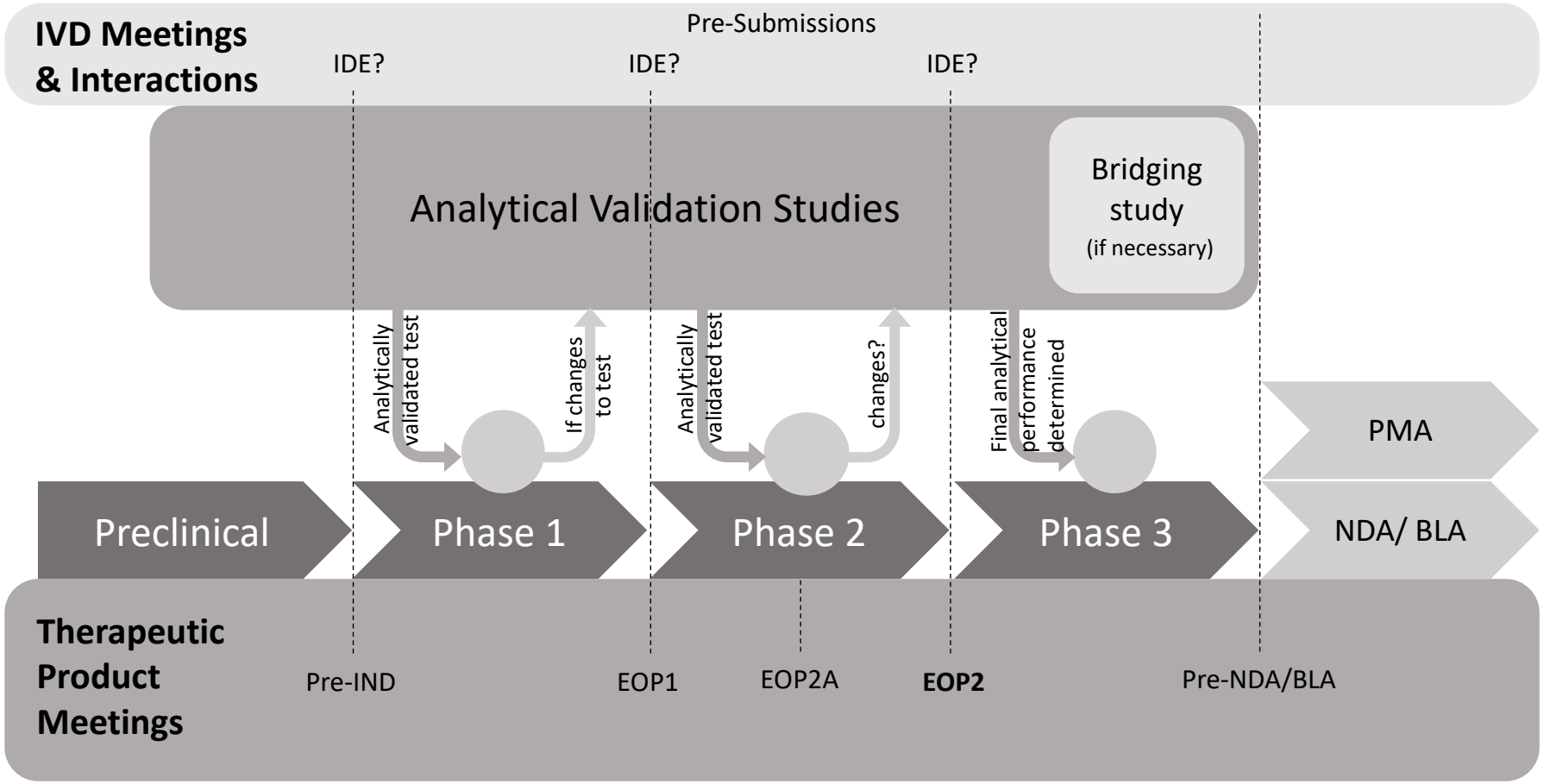
The manufacturer of an ASR has to register and list their establishment with the FDA and can only sell the ASR to:

I. In vitro diagnostic manufacturers
II. Clinical laboratories qualified to perform high complexity testing as regulated under the CLIA
III. Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners

- ✓ Specific ASRs involved in blood screening are classified as either Class III, or in
- ✓ selected cases Class II devices, and require premarket approval. ASRs used to
- ✓ diagnose life-threatening contagious diseases with high public health impact are also
- ✓ classified as Class III products. Examples of these include tests for HIV and tuberculosis

Laboratory developed tests (LDTs), which are run by certified clinical test labs, enable ASRs to be used in diagnostic tests without FDA supervision. Many companies choose this route to commercialize their diagnostics as it is easy to get to revenues quickly

Diagnostics + Drug Co-development – FDA interactions



EOP1 = End of Phase I, EOP2 = End of Phase 2.

FIGURE 6.11

Figure taken from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-codevelopment-vitro-companion-diagnostic-device-therapeutic-product

Combination products, artificial intelligence and software, genetic materials, and tissues

Combination products – drugs and devices bundled together

- Combination product includes
  - ✓ A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity
  - ✓ A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect

The Office of Combination Products at the FDA helps guide manufacturers who are increasingly designing and developing innovative medical products

- Specific combination products remain in one of three product centers
  - ✓ The CDER,
  - ✓ the CBER,
  - ✓ the CDRH

Examples of approved combination products are:

- Bioresorbable hemostat that contains collagen and thrombin
- Transdermal patch containing drug for ADHD
- Dental bone grafting material with growth factor
- Paclitaxel-eluting coronary stent system
- Dermagraft Human fibroblast-derived dermal substitute

Software and artificial intelligence in medical products

Software that is used by itself (i.e. not tied to a device) is treated as a medical device (software as a medical device, SaMD).

- ✓ 29 different software products (mostly through 510k some through de novo pathway) were on software that had algorithms locked – i.e. the analysis done by the software was fixed at the time of application and thus could be reproduced reliably
- ✓ **Challenge :** the adaptive learning nature makes their consistency difficult to gauge
- ✓ **Pre-certification process :** FDA will assess the culture of quality and organizational excellence of the sponsor software company and have reasonable assurance of the high quality of their software development, testing, and performance monitoring of their products.

- The MDR introduces a new classification rule for software such that programs intended to merely "monitor physiological processes" will be classified Class II a or higher. Most machine learning software based medical devices will be classified as Class II a or Class Iib
- *devices are regulated by the Member States who can designate independent accredited "notified bodies" to conduct the required conformity assessments.*
- *In most other countries such China, India, Brazil, or Japan, the regulatory bodies are following the U.S. or EMA framework, which are being harmonized by International Medical Device Regulators Forum*
- *ISO standards for medical devices*
  - ✓ *e.g. ISO 13485*

Cellular, tissue, and gene therapies

- The Office of Cellular, Tissue, and Gene Therapies was formed in 2002 in CBER

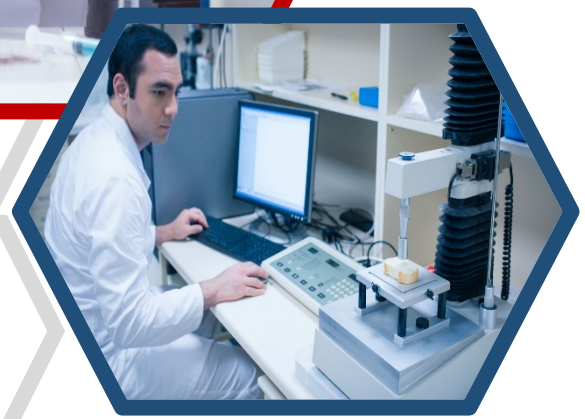
  Product types:
  - Cellular and TISSUE-based products
  - Gene therapies
  - Xenotransplantation
  - Combination products containing living cells/tissues
  - Unique assisted reproduction (ooplasm transfer)

- Responsible for assuring the safety, identity, purity, and potency of all products

- Cell, tissue or gene therapy products do not need premarket approval if there is:
  - Minimal manipulation
  - Homologous use
  - Not combined with drug or device
  - Exerts NO systemic, or
  - Exerts systemic effect, but is Autologous OR
  - Allogeneic in first- or second-degree relative OR
  - For reproductive use

- **Tissue engineered products are treated as combination products**
- The primary center is decided by Office of Combination Products based on the primary mode of action of the combination product.
- In 2017, the FDA released a new expedited pathway specifically for investigational regenerative medicine therapies
- These therapies are designated regenerative medicine advanced therapies (RMAT)
- RMAT designation requires early clinical proof of efficacy

Companies with novel products have to work not only in product and technology development, but equally diligently work on educating regulatory bodies and payers to ensure smooth passage of regulatory and reimbursement issues



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