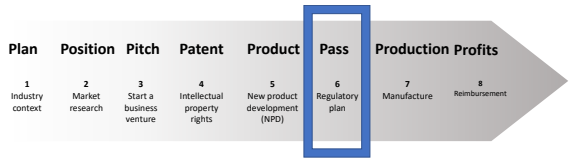
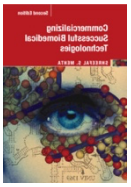


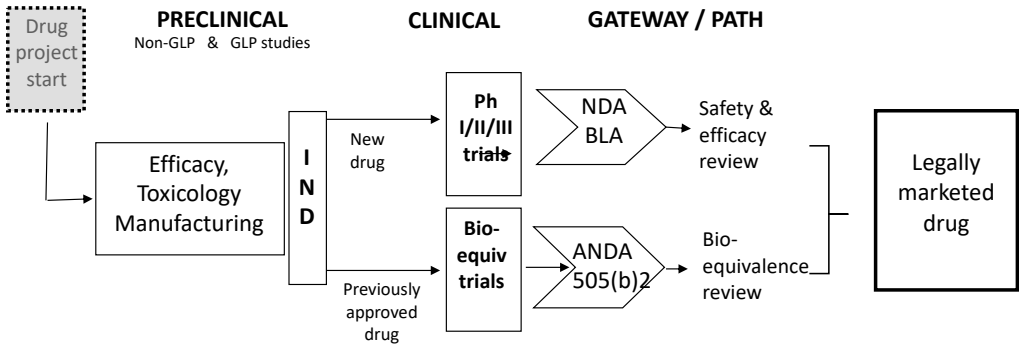


Chapter 6: Practical Tips and Notes on Regulatory Pathways

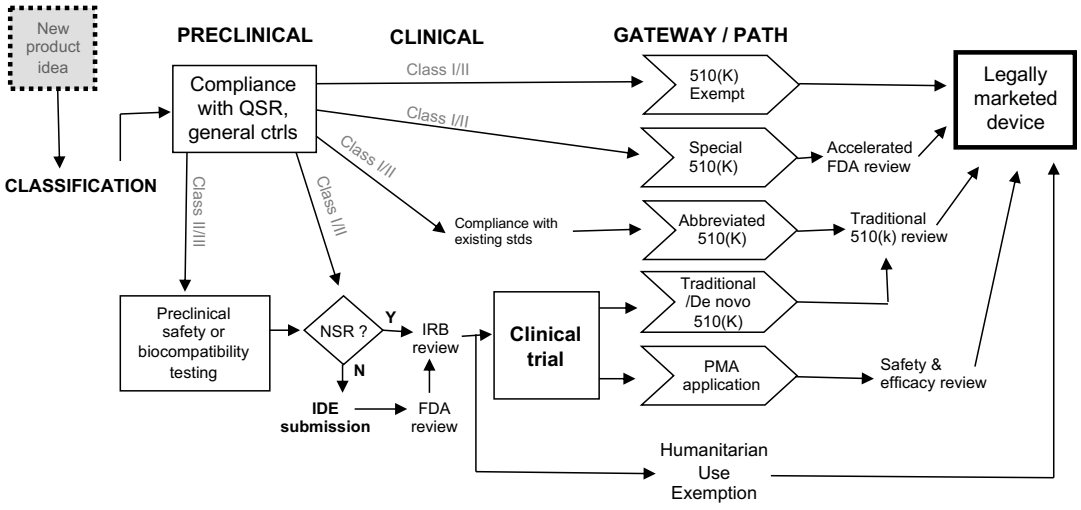
The first step on the regulatory pathway is to decide whether the product is regarded as a drug, device, or diagnostic (or combination product) and then further classify it according to perceived risk factors. These classifications, if agreed to by the FDA reviewers, will dictate the evaluation criteria applied for review of the application.

Note: 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.

PATHS TO DRUG PRODUCT APPROVAL:

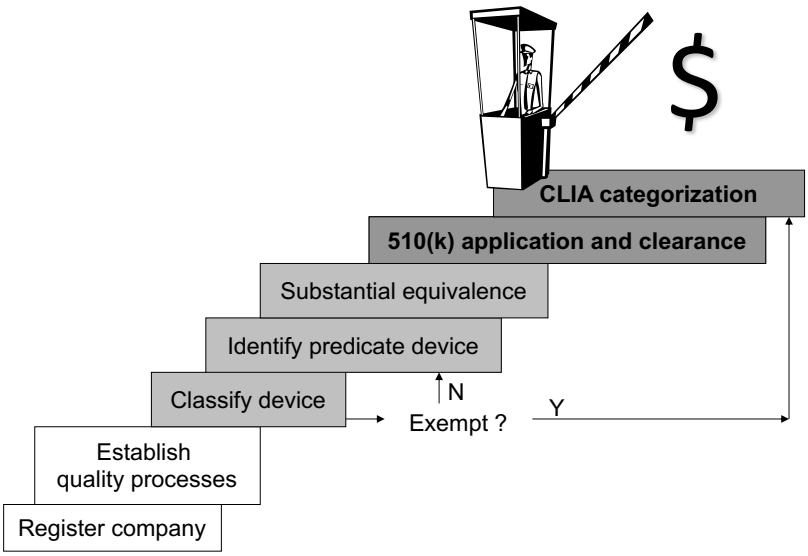


PATHS TO MEDICAL DEVICE PRODUCT APPROVAL:



Some of the above text is excerpted from the book :
Commercializing Successful Biomedical Technologies, (2nd Edition, Cambridge University Press)

PATHS TO IN VITRO DIAGNOSTICS PRODUCT APPROVAL:



Q. How to prepare for an FDA meeting ?

- The FDA is an organization driven by the scientific method and scientific principles of analysis
- The dialogue with the FDA is a formal and highly specific interaction
- The FDA approval or rejection of a company's proposal is based on seeing if statistically valid analysis of the data supports the claim for the indication.

In general the company/sponsor should:

- Understand and state the purpose of the meeting clearly
- Read all relevant guidance documents checking the FDA website frequently for updates
- Consider working with a regulatory consultant or have a team member along who has presented to the FDA successfully before
- Have the right people at the table from the company/sponsor. Sponsors should select representatives who are leading areas of potential queries by the FDA
- 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.

- Word the key questions in a way to get clarity on issues and to gain binding agreement. E.g. instead of asking open ended questions about what to do, propose a specific path, with explanation of the reason for that choice, and then ask if the FDA reviewers agree with the selected path and rationale. This format will keep the discussion and their responses focused on the outcome being sought.

Example topics to prepare to discuss in drug product FDA meetings

- Key FDA meetings are the pre-IND meeting and the pre- and post Phase II meetings.

- Typical issues to be resolved or discussed in a Pre-IND/Phase I meeting – Polymorphs, enantiomers, or other unique physico-chemical properties; Reasons for selection of specific form of compound for drug product; Qualification of impurities.

- The discussion in a pre-IND FDA meeting is focused on data and scientific methodology without any commercial issues being raised with the FDA. The sponsor typically would propose a study design (s) with explanations based on scientific analysis or statistical methodology and seek agreement from the FDA

- End-of-Phase II meeting - Agreement on final drug product synthesis scheme; specifications; impurities; endpoints and analysis methods; etc.

- The end-of-Phase II meeting is a critical meeting in the development process, as the study protocol, endpoints and statistical methodologies of the Phase III studies and other details for a successful NDA (New Drug Application) or BLA (Biologic License Application) are agreed on during this meeting. The sponsor is expected to provide proof of efficacy and other data to support the Phase III design and endpoints and to show that the drug is performing a desired function.

Q. How is software for medical use classified for FDA review ?

- 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).

- Artificial intelligence or Machine Learning Adaptive software is challenging for the FDA to evaluate for safety as its consistency is hard to gauge

- Currently, SaMD products on the market have been approved through the 510k and some through de novo pathway – mostly 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

- For now, the FDA is qualifying adaptive new software products by a broad company-wide 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.

- Check the FDA website for updated guidance for developers of AI software products. This is an aera of active learning and policy development as the regulatory risk assessment is catching up with the technology.

Q. How are Tissue engineering, cell and gene therapy products evaluated by FDA?

Note that 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.

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

- In 2017, the FDA released a new expedited pathway specifically for investigational regenerative medicine therapies

- These therapies are designated regenerative medicine advanced therapies (RMAT) and carry benefits of breakthrough designation and offers other benefits such as accelerated approval.

Note: Chapter 6 in the book contains examples and outlines of typical content of IND, IDE, 510K, NDA, ANDA submissions which can be several thousands of pages. All filings to the FDA are electronic, making it somewhat easier than prior physical filings.