



JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Regulation of Drug and Medical Device in USA

Shraddha Makwana, Krupa Thula, Dr. Dilip Maheshwari

Department of Quality assurance, L.J. institute of pharmacy, Ahmedabad, Gujarat, India

ABSTRACT:

Developing a new drug required great amount of research work in chemistry, manufacturing, control, preclinical science and clinical trials. Every country has its own regulatory authority which is responsible of evaluating whether the research data support the safety, effectiveness and quality of new drug product and to enforce the guidelines which regulating the marketing of new drug. Similarly, Medical device regulation plays a significant role in the design, development, and commercialization of new medical technologies. A comprehensive understanding of the various regulatory requirements and their practical implementation is thus an essential cornerstone of successful medical device innovation. Medical devices which are used to treat different diseases and which can be used by physician in different surgeries must go through the regulatory process to check its safety and effectiveness before going through clinical trial and marketing. This article focuses on history, mission, statutory requirements, administration and related issues with respect to drugs and medical devices in United State of America (USA).

KEYWORDS: Regulatory process, Regulatory authority, Clinical trial, Medical Device, USA

Article history:

Received 6 Mar 2014

Accepted 14 April 2014

Available online 13 May 2014

INTRODUCTION:

In the present scenario, countries have different regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy^[1].

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, an application to the competent authority of the concerned country for marketing of drug is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect^[2].

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research

For Correspondence:

Ms. Shraddha Makwana

Department of Quality assurance, L.J.

institute of pharmacy, Ahmedabad, Gujarat,

India

Email: shraddha.makwana03@gmail.com

(www.jpsbr.org)

trial and its adverse effects (in particular populations), should also be monitored [3].

Similarly, Medical devices vary greatly in complexity and application. Examples range from simple devices such as tongue depressors, medical thermometers, and disposable gloves to advanced devices such as computers which assist in the conduct of medical testing, implants, and prostheses. The design of medical devices constitutes a major segment of the field of engineering. The global medical device market reached roughly 209 billion US Dollar in 2006. It used for human beings for the purpose of one or more of the followings

- i. diagnosis, prevention, monitoring, treatment or alleviation of disease;
- ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;
- iii. investigation, replacement or modification of the anatomy or of a physiological process;
- iv. control of conception

FDA has several rules and regulation which check the safety and effectiveness of medical devices before marketing.

REGULATION OF DRUG IN USA

Drug approval process in USA:

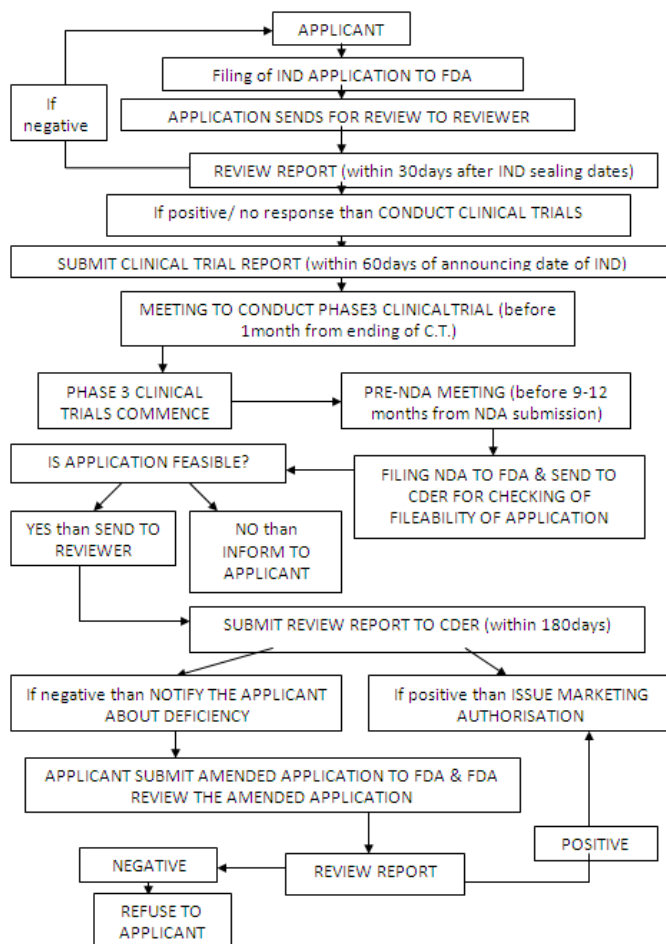
Filing process for IND & NDA in USA:

In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia. In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity [4]. However, in 1937, due to sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing. Further, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labeling). [5,6]

FDA approval process begins only after submission of investigational new drug (IND) application. The next step is phase I clinical trials (1-3 years) on human subjects (~100). The drug's safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II. If evidence of effectiveness is shown in phase II, phase III studies (3-4 years) begins. [7, 8, 9].

A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics, manufacturing and proposed labeling. [10]

The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Center for Drug Evaluation and Research by a team of scientists. Generally approval of an NDA is granted within two Years (on an average), however, this process can be completed from two months to several years [11].



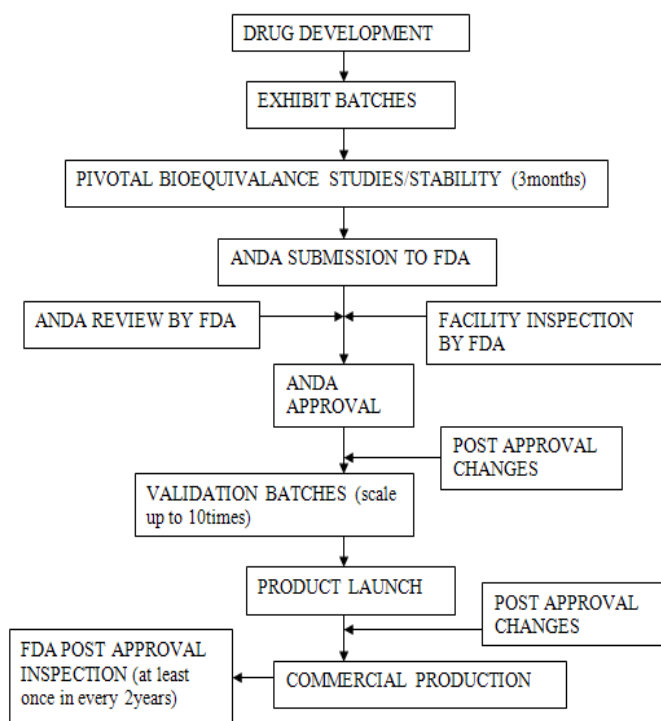
FLOW CHART: 1 FOR FILING PROCESS OF IND & NDA IN USA

Note: IND-Investigational New Drug, FDA-Food and Drug Administration, NDA-New Drug Application, CDER-Centre for Drug Evaluation and Research, C.T- clinical trial.

Filing process for ANDA in USA:

Dossier for generic drug filling shall be submitted in the form of CTD in US. Generic drug is identical--or bioequivalent--to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price.[8]

The patent protects the investment in the drug's development by giving the company the sole right to sell the drug while the patent is in effect. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms. Once approved, the applicant may manufacture and market generic drug product to provide a safe, effective, low cost alternative to American public.[8]



FLOW CHART: 2 REPRESENTS GENERIC PRODUCT REGISTRATION PROCESS IN USA

REGULATION OF MEDICAL DEVICE IN USA

Definition of medical device in USA by the FDA:

A medical device is an instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to diagnose, prevent, or treat disease or other conditions, and does not achieve its purposes through chemical action within or on the

body (which would make it a drug).^[12] Whereas medicinal products (also called pharmaceuticals) achieve their principal action by pharmacological, metabolic or immunological means, medical devices act by other means like physical, mechanical, or thermal means.

Classification of medical device

Class I: General controls

Class I devices are subject to the least regulatory control. Class I devices are subject to "General Controls" as are Class II and Class III devices.^[13,14] General controls include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.^[14]

Most Class I devices are exempt from the premarket notification and a few are also exempted from most good manufacturing practices regulation.^[14] Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.^[14]

Class II: General controls with special controls

Class II devices are those for which general controls alone cannot assure safety and effectiveness, and existing methods are available that provide such assurances.^[13]

In addition to complying with general controls, Class II devices are also subject to special controls. A few Class II devices are exempt from the premarket notification. Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance.^[14]

Devices in Class II are held to a higher level of assurance than Class I devices, and are designed to perform as indicated without causing injury or harm to patient or user.

Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.^[13,14]

Class III: General controls and Premarket approval

A Class III device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices.^[14,15] Such a device needs premarket approval, a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of Class I.^[13,14]

Examples of Class III devices that currently require a premarket notification include implantable pacemaker, pulse generators, HIV diagnostic tests, automated external defibrillators, and end osseous implants.^[14]

All 510(k) applications must include descriptive information, labeling, and may require performance and effectiveness testing depending upon the devices technological characteristics and risk associated with its application.

If the device is determined by FDA to be substantially equivalent then the device may be marketed. If FDA determines the device is not substantially equivalent, the manufacturer may resubmit another 510(k) with new data, file a petition to reclassify the device, or submit a premarket approval (PMA) application

Types of 510(k)

1) Special 510(k)^[15]

- Limited to certain circumstances and must contain a “Declaration of Conformity” with design control requirements
- FDA intends to process special 510(k)s within 30 days of DCO receipt

2) Abbreviated 510(k)^[15]

- Guidance document exist
- A special control has been established
- FDA has recognized a relevant consensus standard

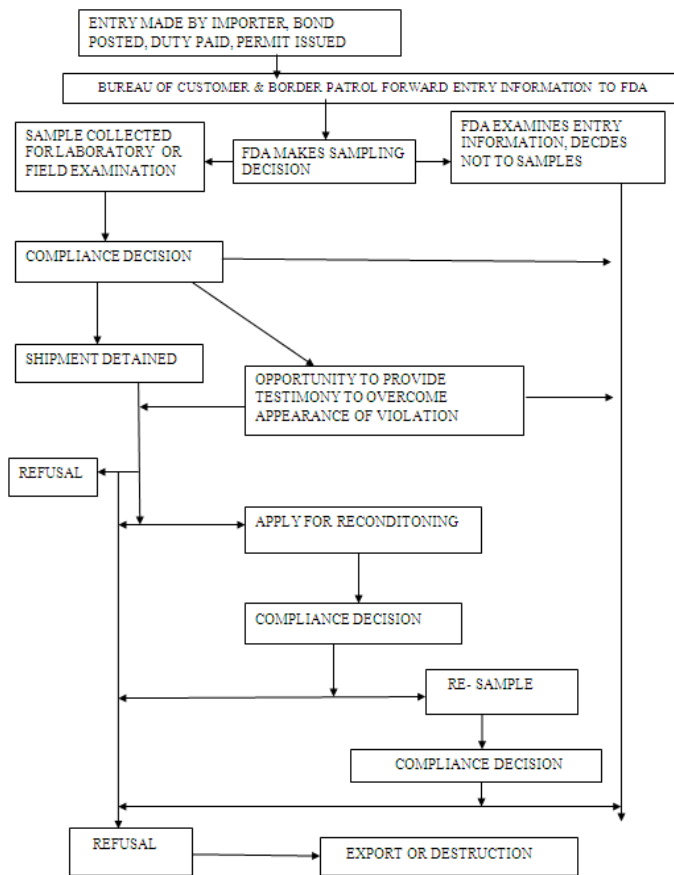
3) Traditional 510(k)^[15]

No specific 510(k) form but there is an FDA suggested format

4) De Novo 510(k)^[16]

The de novo 510(k) is a 510(k) without a predicate device. It is not a commonly

Used path (4 clearances in 2006).



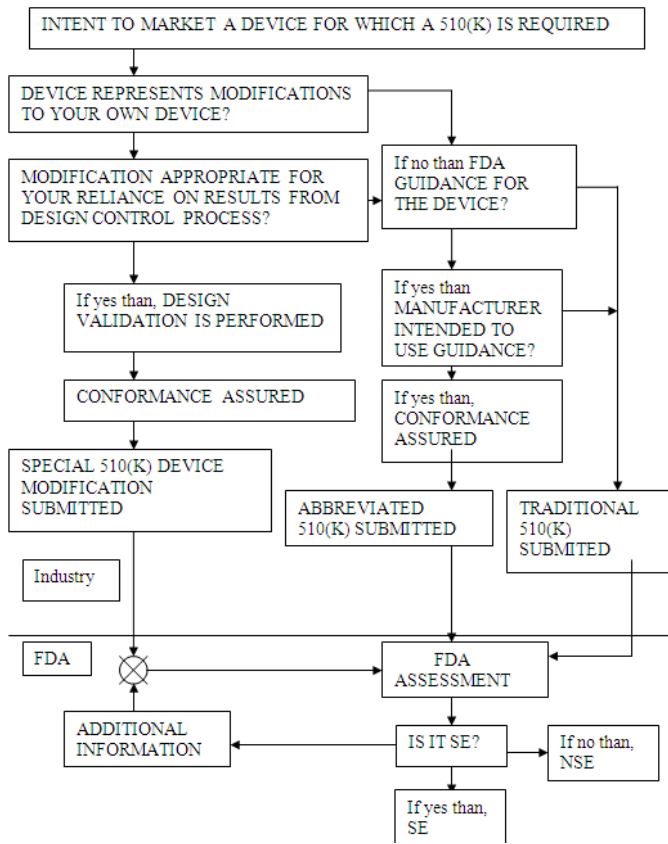
FLOW CHART: 3 REPRESENT IMPORT PROCESS FOR MEDICAL DEVICE IN USA

Premarket Notification-510(k):^[14]

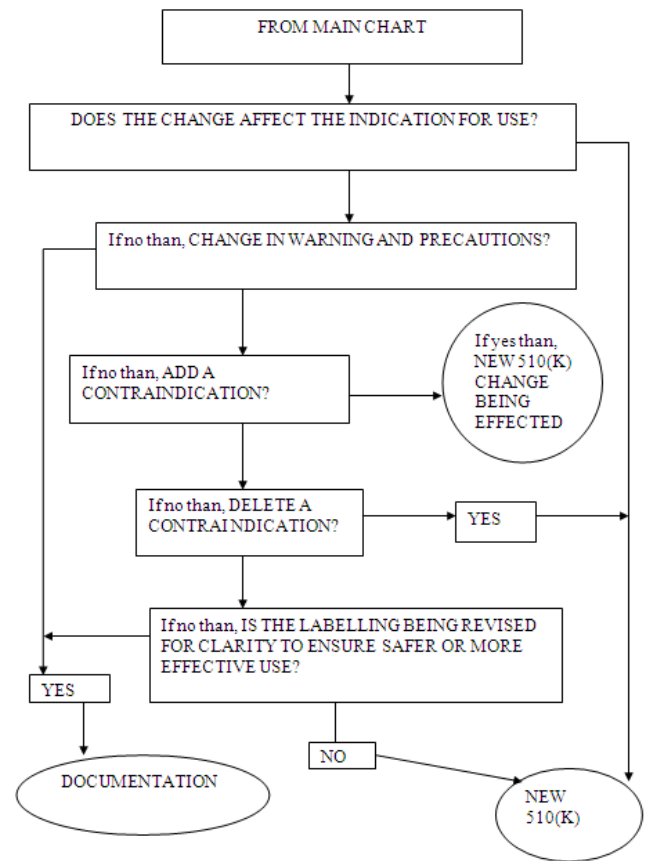
The faster marketing process is premarket notification or 510(k). The 510(k) applicant must demonstrate to FDA that their device is substantially equivalent to a legally marketed device that is, one that was marketed before May 28, 1976 or one that was marketed after that date that was found substantially equivalent through the 510(k) process.

A device is substantially equivalent if, in comparison to a legally marketed device it:

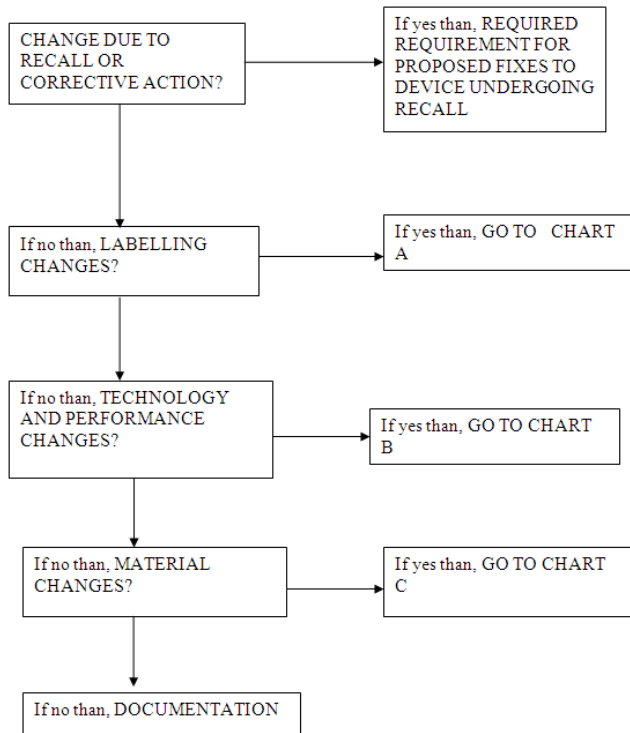
- has the same intended use; and
- has the same technological characteristics as the legally marketed device, or
- has different technological characteristics, and submitted information



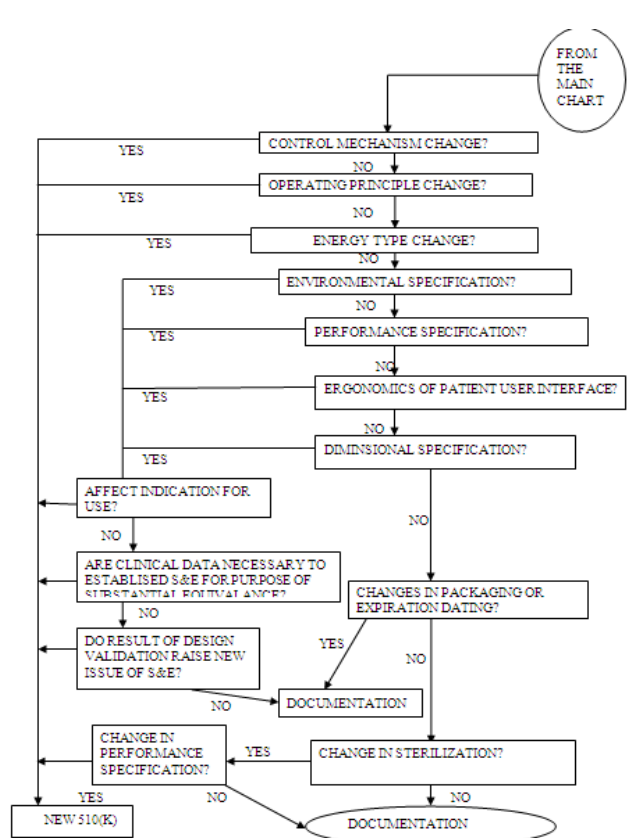
FLOW CHART: 4 THE NEW 510(K) PARADIGM [17]



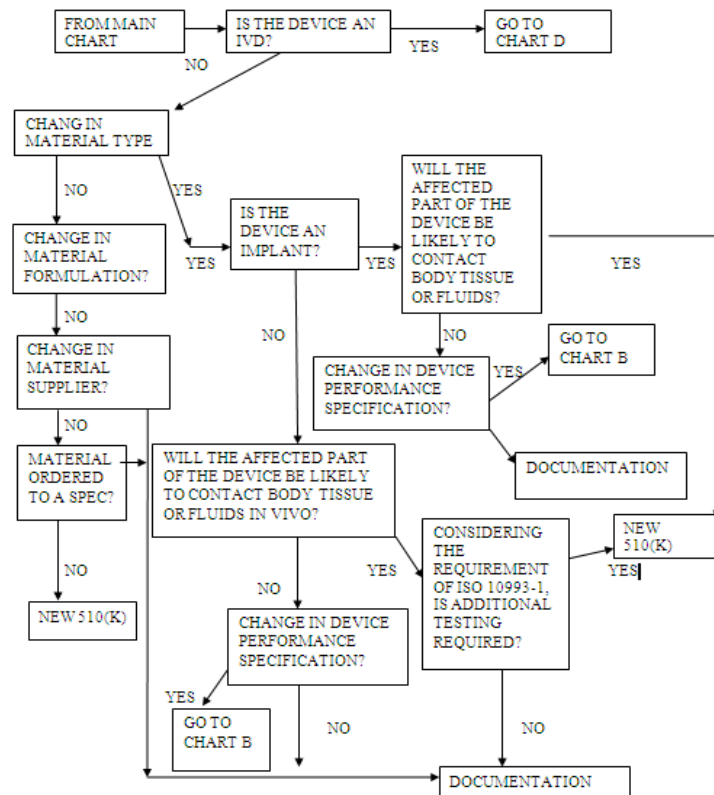
FLOWCHART: A - IS IT A LABELLING CHANGE? [17]



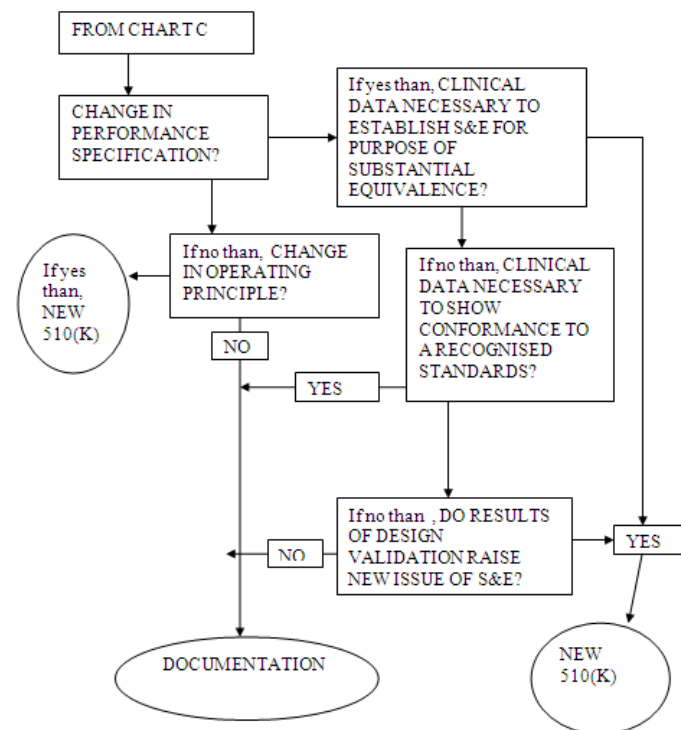
MAIN FLOWCHART: WHEN TO FILE A 510(K) AFTER CHANGE TO A LEGALLY MARKETED DEVICE [17]



FLOW CHART: B- IS IT A TECHNOLOGY OR PERFORMANCE CHANGE? [17]



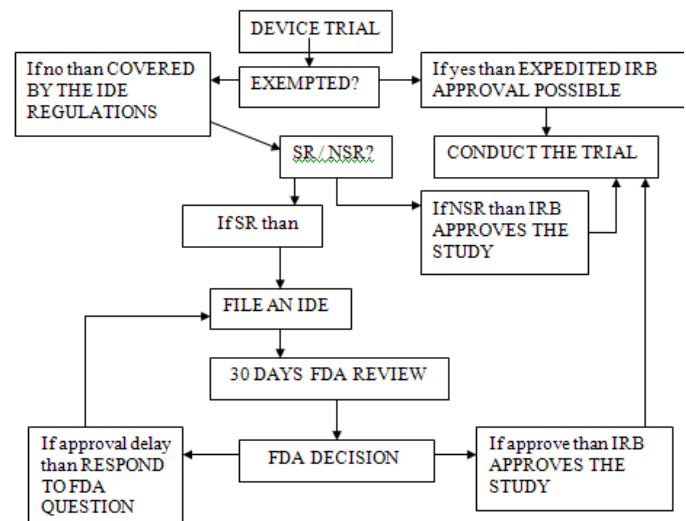
FLOW CHART: C- IS IT A MATERIAL CHANGE? [17]



FLOW CHRT: D – MATERIALS CHANGE [17]

Medical device clinical trials [18]

- (5) Adherence to the principles of good clinical practices (GCPs), including adequate human subject protection (HSP) is universally recognized as a critical requirement to the conduct of research involving human subjects. Many countries have adopted GCP principles as laws and/or regulations.
- (6) The Food and Drug Administration’s (FDA’s) regulations for the conduct of clinical trials, which have been in effect since the 1970s, address both GCP and HSP. These FDA regulations and guidance documents are accessible from this site.
- (7) International GCP guidance documents on which FDA has collaborated and that have been adopted as official FDA guidance are also be found here. Finally, this site includes links to other sites relevant to the conduct of clinical trials, both nationally and internationally.



FLOW CHART: 5 REPRESENTS REGULATORY PATHS FOR MEDICAL DEVICE CLINICAL TRIALS

Where SR- significant risk and NSR- no significant risk

Significant Risk Device (SR)

A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants.

Studies of devices that pose a significant risk require both FDA

and an Institutional Review Board (IRB) approval prior to initiation of a clinical study. FDA approval is obtained by submitting an IDE application to FDA. In order to conduct a significant risk device study, a sponsor must submit *a complete IDE application to FDA for review* and obtain FDA approval of the IDE; submit the investigational plan and report of prior investigations to the IRB at each institution where the investigation is to be conducted for review and approval; and select qualified investigators, provide them with all necessary information on the investigational plan and report of prior investigations, and obtain signed investigator agreements from them.

Once an IDE application is approved, the following requirements must be met in order to conduct the investigation in compliance with the IDE regulation:

Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

Distribution - Investigational devices can only be distributed to qualified investigators

Informed Consent - Each subject must be provided with and sign an informed consent form before being enrolled in the study. Protection of Human Subjects, contains the requirements for obtaining informed consent.

Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols under

Prohibitions - Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited

Records and Reports - Sponsors and investigators are required to maintain specified records and make reports to investigators, IRBs, and FDA *Nonsignificant Risk Device (NSR)*

Nonsignificant risk devices are devices that do not pose a significant risk to the human subjects. Examples include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters.

A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study. Sponsors of studies involving nonsignificant risk devices are not required to submit an IDE application to FDA for approval. Submissions for nonsignificant device investigations are made directly to the IRB of each participating institution.

Sponsors should present an explanation to the IRB where the study will occur of why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to FDA within five working days.

FDA considers an investigation of a nonsignificant risk device to have an approved IDE when IRB concurs with the nonsignificant risk determination and approves the study.

The sponsor also must comply with the abbreviated IDE requirements under

Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.":

IRB Approval – The sponsor must obtain and maintain Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study;

Informed Consent – The sponsor must assure that investigators obtain and document informed consent from each subject according to 21 CFR 50, Protection of Human Subjects, unless documentation is waived by an IRB in accordance with §56.109(c);

Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46). Guidance on monitoring investigations can be found in Guideline for the Monitoring of Clinical Investigations.

Records and Reports - Sponsors are required to maintain specific records and make certain reports as required by the IDE regulation.

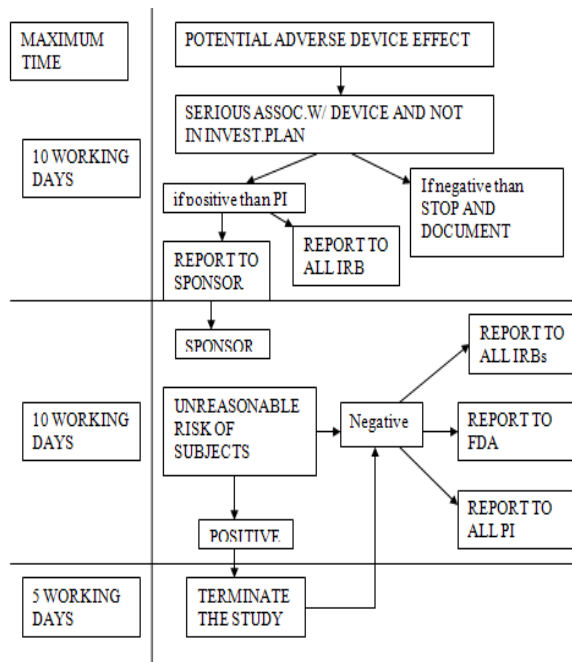
Investigator Records and Reports – The sponsor must assure that participating investigators maintain records and make reports as required (see Responsibilities of Investigators); and

Prohibitions –Commercialization, promotion, test marketing, misrepresentation of an investigational device, and prolongation of the study are prohibited

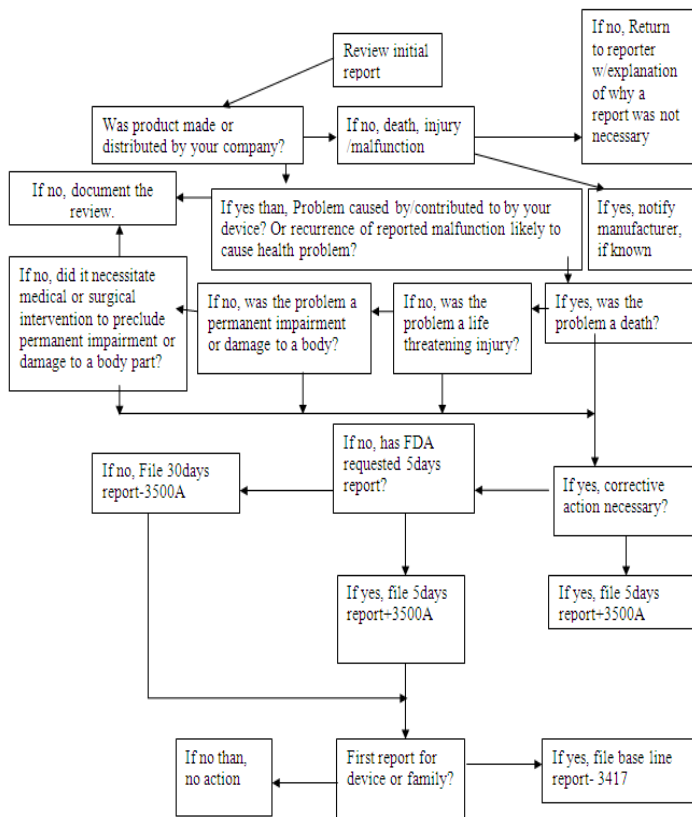
Adverse device effect reporting^[16]

If any potential adverse device reported in investigation plan investigation plan than within 10 days if its positive than PI should report to all IRB and sponsor and if its negative than stop and document.

Within 10 working days If any unreasonable risk of subject is positive than terminate the study within 5 working days and if it's negative than report to all IRB, FDA and all PI.



FLOW CHART: 6 REPRESENTS ADVERSE DEVICE EFFECT REPORTING ^[16]



FLOW CHART: 7- MEDICAL DEVICE REGULATION DECISION TREE ^[16]

ACKNOWLEDGEMENT:

The authors are thankful to Dr. K. Pundarikakshudu, Principal of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities to carry out the work.

REFERENCES:

1. Horner A., Comparison of a global submission of new biological entity and a new chemical entity - strategic decisions and criteria for implementation (2005) (<http://www.dra.uni-bonn.de/hoerner>). Accessed 09 March 2014.
2. Ng R., Drugs: from Discovery to Approval (2004) (<http://www.pharmatext.org/2008/06/drugs-from-discovery-to-approval.html>). Accessed 10 March 2014.
3. Lipsky MS, Sharp LK, "From Idea to Market: The Drug Approval Process", J Am Board Fam Pract, 2001;14: 362-367.
4. Stringer S., "What Has Been Happening With Over-the-Counter Drug Regulation" ,Food and Drug Law Journal, 1998; 5: 633-91.
5. CFR: Title 21, Food and Drugs: Chapter I--Food and Drug: PART 312—Investigational New Drug Application (http://www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html). Accessed 09 March 2014.
6. Investigational New Drug Application (IND) (<http://www1.pointcross.com/source/ddg/steps/ind/index.html>). Accessed 10 March 2014.
7. Fernandez D.S., Huie J., Hsu J., "The Interface of Patents with the Regulatory Drug Approval Process and How Resulting Interplay Can Affect Market Entry" Handbook of Best Practices. 2011; 965-971.
8. Generic Drugs Filing Requirements, (pharmatresures.blogspot.com/.../generic-drugs-filing-requirements-us-Vs-europe). Accessed 11 March 2014.
9. Boas VMI, Tharp PC, "The Drug Approval Process in the U.S., Europe, and Japan", J Managed Care Pharm, 1997; 3: 459-465.
10. Marketing Authorization Procedures in USA and Europe, (<http://www.lsnewsr.sgs.com/lsnewsr/lsnewsr-december-issue/marketingau>) Accessed on 13 March 2014.
11. Ghalamkarpour A., Marketing Authorization Procedures in the European Union - Making the Right Choice (2009). (<http://www.lsnewsr.sgs.com/lsnewsr>). Accessed 12 March 2014.
12. Summarised from the FDA's definition as per (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm>). Accessed 10 March 2014.

- 13 "Device Classification and General and Special Controls and General Controls for Medical Devices". Medical Devices. U.S. Food and Drug Administration, Retrieved 2010; 10-15.
- 14 Medical Device Regulations, (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070958.htm#25>) Accessed 13 March 2014.
- 15 Medical Device Regulation in USA, (<http://www.fda.gov/cdrh/devadvice/3143.html>). Accessed 12 March 2014.
- 16 Douglas J, Pisano Mantus, David S. Mantus, "FDA regulatory affairs, a guide for prescription drugs, medical devices, and biologics", Informa health care, New york, 2nd edition, 142-161.
- 17 Premarket Notification 510(k), (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket/submissions/premarketnotification510k/ucm134034.htm>). Accessed 13 March 2014.
- 18 Medical Device Regulation, (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046164.htm>). Accessed 14 March 2014.

