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Review on Regulatory Requirements for Approval of Biologics

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ABSTRACT

Biologics is any pharmaceutical product manufacture in, extracted from, or synthesized from a biological source. Biologics are very complicated structurally as compared to drug molecules. These they obtain from living things, several types of biologics which are used for diagnosis, prevention, and treatment also. Biologics show less stability than drug molecules. The regulation of biologics for approval quite similar to a drug molecule, but some regulatory bodies are different. There are several regulatory bodies which are come under the regulation of biologics such as IND, NDA, FDA, PHSA, CBER, CDER, PMA, BLA, 510K. This approval process of biologics takes more time as same as a drug. Several licenses are required for the approval of biologics. Many dosage forms of biologics are available on market. CBER is a center of the FDA is control all approval process of biologics.

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INTRODUCTION

Section 351 of the public health service (PHS) act defined as "Biologics are single or combination of virus, Therapeutic serum, Toxin, Antitoxin, Vaccine, Blood, Blood component or Derivatives, Allergenic product, or Analogues product used for treatment, diagnosis, and prevention of disease condition [1]. The European Union regulation defined Biological Medical products as "A protein as a nucleic acid-based pharmaceutical substance used for therapeutic or In-vivo diagnosis purposes, which is produced by means other than direct extraction from a native (Non-engineered) biological source. Each new biologic is a novel product. Many times, biologics occur in the parenteral formulation. Generally, multi-use vials are used as a container. After administration of biological parenteral preparation into the body then it's difficult to measure the concentration of biologics in the body. Biosimilar is the term used in the European Union for biologics [2,18].

The most important thing is Hormones such as insulin, glucagon, and human growth Harmon are regulated as a drug under the FDA act, not as a biological product. Both FDA's centers such as CDER and CBER are responsible for the regulation of the biological product.[3]

Biologics are also called Biotherapeutics or Biopharmaceutical, these are derived from a living organism. Biologics are differing from small molecule (SM) drugs regarding weight and synthesis also many more. Some biologics are a combination of protein and drug and this has therapeutic activities such as Antibody(protein)- Drug conjugation. The first protein-based biologics, which was made by recombinant technology is insulin and it was approved in the United States in 1982 form that time biologics sector grow rapidly. Presently more than 200 biologics have reached to market [4]. About 1/3th of the market which is made from biologics product. As compared to drugs, biologics have unique therapeutic action. Biologics product having severed limitation also, these products must be administered as an intravenous or subcutaneous injection because the oral route is not comfortable and cost of biologics product are also high. Biologics are unable to pass BBB and cell membrane. [2,16]

Biosimilar is a drug that manufactures from the large-scale operation of a living cell. Biosimilar is very similar to the older drug but not structurally identical.[4] They are isolated from the living source – humans, animals, plants, fungal and microbial. The European medicinal agency uses the terms Advance *therapy medical product* (ATMPs) for medicine for human use that is "based on genes, cell or tissue-engineered", including gene therapy

medicine, somatic cell therapy medicine, tissue-engineered medicine, and combinational therapy. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available. The term "Bio pharmacology" is sometimes used to describe the branch of pharmacology that studies biopharmaceuticals [5,7].

TYPES OF BIOLOGICAL PRODUCT [6,42]

1) Blood Derivatives
2) Whole blood
3) Proteins
4) Vaccines
5) Cellular and gene therapy
6) Allergic extracts
7) Human tissue
8) Xenotransplantation produces

Table No. 1: Difference between Drug and Biologics

Drugs	Biologic
It contains a defined structure. Drug made by chemical synthesis. It is easy to characterize. Drug is relatively stable. Usually taken orally. Generally prescribed by a general practitioner.	Biologics made by living cells. It has a heterogeneous structure. It is difficult to characterize. Variable sensitivity to environmental cond. It is generally taken by injection. Only prescribed by specialist immunogenic

REGULATORY BODIES

1. FDA
2. PHSA

3. CBER AND CDER

These are regulatory bodies play an important role in the approval of biologics. These bodies control all activities of biologics and drug molecules [17,18]

FDA

FDA team was established in 1997 to gives quality and safety to the biological product. FDA are having several centers for approval of biologics such as CBER and CDER. The biological product comes under two acts as the Public health service act (PHSA) and Food and Drug Administration (FDA). FDA divided [30,46,47].

a) Centre for Drug Evolution and Research (CDER).

b) Centre for Biological Evaluation and Research (CBER).

c) Centre for Device and Radiological Health (CDRH).

d) Centre for Veterinary Medicine (CVM).

e) Office of Regulatory Affair (ORA).

f) Centre for Food Safety and Applied Nutrition (CFSAN).

g) National Centre for Toxicological Research (NCTR).

h) Centre for Tobacco Product (CTP).[1]

FDA is one part of the Food, Drug, and Cosmetic Act. F, D, and C Act present in Title-21 of code federal regulation [7,30].

FDA is a consumer protection agency; these are present in a branch of the US Government under the "Department of Health and Human Service" (DHHS). FDA has lots of responsibility including regulation of drugs, biologics, medical devices, animal drugs, food, and cosmetics. FDA's major activities are: 1) Reviewing new products, 2) Enhancing safe manufacturing and handling, 3) Monitoring for new risks, standards, and regulation, 4) Research, 5) Taking action to protect public health.[2] FDA which regulate the programs: -

a) Food and dilatory supplement

b) Medication

c) Generic drugs

d) Over the counter drugs (OTC)

e) Biological product

f) Cosmetic

g) Veterinary Product

h) Tobacco product

i) Regulation of living organisms.[3]

Regulatory submission refers to the application to provide the data or information to FDA regarding the development, approval, or post-approval report of biologics [34,36,48]. FDA is responsible to gives market approval to biologics in the United States under the authority of the Federal Food, Drug and Cosmetic Act, and section 351 of the Public Health Service Act (PHSA). The review of an application takes place in three major centers of the FDA such as- CDER, CBER, and CDRH [8,13,14,15].

Types of FDA meeting: - The main purpose of conducting the meeting is to solve the problem which occurs during the development of biological products and also to present a proposal and provide an answer [37,38]. There are several types of FDA meeting as follows-

Pre-IND meeting:

In this meeting, a sponsor presents all information such as characterization, manufacturing, Non-clinical test data, and other information and discusses the initial plan and protocol of human clinical trials [16,66].

The goal of the meeting:

To receive the FDA feedback on the proposed studies and to reach an agreement on what information the sponsor needs to submit in IND Application [66].

End of phase-2 meeting:

Most application meetings during the biological development process [19,20].

Special protocol and Ad Hoc technical meeting:

This meeting is taken to discuss and resolve the technical issue that arises during drug development.

Pre-NDA/BLA meeting:

In this meeting sponsor and FDA discusses the upcoming application-How data will be presented and many more [8,9,10].

Advisory committee meeting:

This meeting takes place as a public forum after the submission of NDA and BLA. These meetings are conducted for several products. When FDA want to be advised of academic, medical and another external expert about approvability of an application.[15]

Labeling meeting:

This meeting takes place between the sponsor and FDA regarding the language of the product labeling or prescribing information. These meetings take place after the submission of NDA/BLA. This is the final and critical stage of product development and FDA approval [6,27].

PHSA:

The public health service act which is present in code federal rule (CFR) in title no. 50, from which section no.42. The public health service act was started in 1944 [23,24].

The act established the federal government's quarantine authority for the first time. It gave the United States Public Health Service responsibility for preventing the introduction, transmission, and spread of communicable diseases from foreign countries into the United States. The Public Health Service Act granted the original authority for scientists and special consultants to be appointed "without regard to the civil-service laws", known as a Title 42 appointment. [1,3]

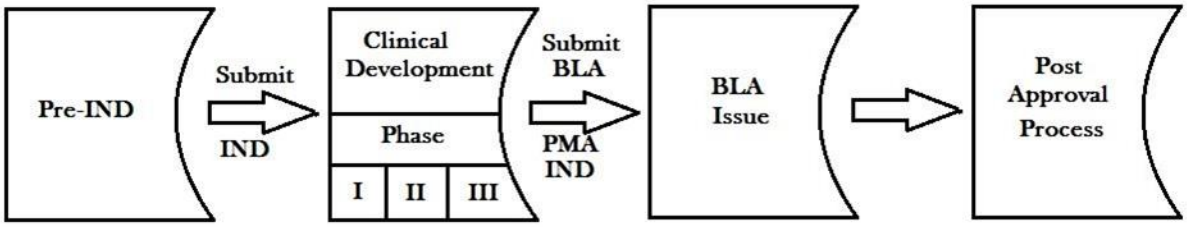

Figure No. 1: Biological product approval cycle

CBER AND CDER

It works under FDA and Public Health Service Act (PHSA). The main objective of CBER is to protect and enhance public health by regulating biological products, vaccines, tissue, and gene therapy product [1,44]. CBER is responsible for assuring the safety, purity, potency, and effectiveness of biologics and related products. Not all biologics are regulated by CBER. Monoclonal antibodies and other therapeutic proteins are regulated by CDER [3,22,25].

1) The following product will be regulated by CBER such as-

a) Gene and gene product.

b) The allergenic extract is used for the diagnosis and treatment of allergies.

c) Venom, antitoxin, and antivenin.

d) Blood, several blood products, and the device used for collection, testing, and processing of blood.

e) Xenotransplant

f) Human cell, tissue or cellular, and tissue base product

2) CDER regulated by certain biologics such as-

a) Immunomodulators (except vaccine or allergenic compound).

b) Hormones

c) Monoclonal antibodies for in vivo use.

d) Most protein for therapeutic use (except those specifically noted as being regulated within CBER) [6,3].

CBER procedure having four main criteria for approval of advertising and promotional materials-1) Material must include proper prescribing information. 2)Material not required false. 3) Material must contain a fair balance. 4) material must be consistent with the approved package insert; also, the generic name of the product must be used in advertising [6,45].

It works under FDA and Public Health Service Act (PHSA).

a) IND Process (CBER)

b) BLA Process (CBER)

c) 510K Process (CBER)

d) Premarket Approval (PMA) Process (CBER)

e) NDA.

CBER Product Jurisdiction Officer:

Food and Drug Administration,
Centre for Biologics Evaluation and Research
10903 New Hampshire Ave
WO71-7240,
Silver Spring, MD 20 993-0002.
Phone: - 240-402-7912
*Email- CBERProductJurisdiction@fda.hs.*gov

All CBER device applications should be address to the above address [3,5].

IND (Investigational New Drug application)

After preclinical investigation when the new biological molecules have been screened for pharmacological activity and acute toxicity potential in animals the sponsor required permission from FDA for its clinical trials in humans. The sponsor applies to the conduct of human clinical trials called IND [28].

According to the food, drug, and cosmetic act sponsor of biologics are must be required to fill IND application form before biologics products may be given to a human. This is to protect the rights and safety of the subject. The sponsor of an IND takes a responsibility for initial clinical trials. The sponsor is maybe an academic institute, government agency, pharmaceutical company, and private or public organization [7]. An IND generally goes into effect 30 days after FDA receives it. FDA is taken 30 days for checking the IND application [17]. FDA receives the IND for safety issues. IND content information of preclinical studies according to preclinical studies sponsor decide clinical study safe or not [8,29,50]. Biologics are the commonly recombinant proteins of human origin, they require less safety information before filling IND [9]. Several meetings are taking place during this time between both sponsor and agency. The clinical investigation phase may take as many as 12 years to complete, only one in five compounds tested may show clinical effectiveness and safety [6,15].

Format and Contents: -

a) Cover sheet (Form FDA 1571).2.

b) A table of contents.

c) Introductory statement and General Investigational plan.

d) Investigator's Brochure.

e) Protocol

f) Chemistry, Manufacturing, and Control information.

g) Pharmacology and Toxicology information.

h) Previous human experience with IP.

i) Additional Information. [7,6,10]

As part of IND, the clinical protocol is must be submitted. The clinical protocol includes-

a. Statement of purpose and objectives of the study.

b. Outline of investigational plan and study design.

c. Identifying some patients to be involved.

d. The basis for subject selection with inclusion and exclusion criteria.

e. Information of design plan, including dose level, routes of administration, and duration of patient exposure.

f. Explanation of the patient observation, measurement, and test to be used.

g. The clinical procedure, Laboratory test, and monitoring to be used in minimizing patient risk.

h. All information such as the name, address, and credentials of the principal investigator and co-investigator.

i. Location and Description of the clinical research facilities to be used.

j. Approval of the authorized IRB [7,39].

The application Review process of IND

1)After review by CDER or CBER, CDR, the application is sent to the document control center which is responsible for the review of the application. 2) Then the acknowledgment letter is sent to the applicant and the project manager is assigned to coordinate the NDA review process. 3) The CD is responsible for the distribution of various copies of IND to the different divisions for evaluation. 5) The project manager performs the initial screening of application are refused for feeling.6) If the concern is found, then a deficiency letter is sent to the applicant [10,54,55].

Clinical Trials

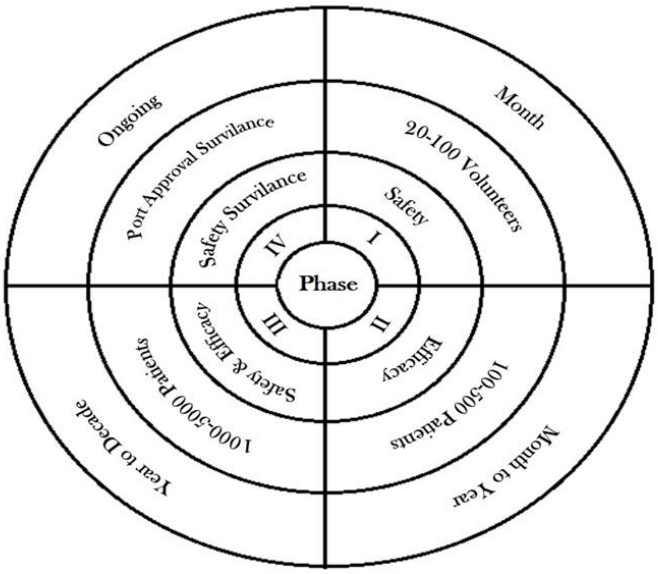

Figure No. 2: Phases of Clinical Trials

NDA (New Drug Application)

NDA and BLA application is required to market a new drug and biologics product. NDA is used by CDER for the market to drug products. BLA is used by CBER for the market to biologics products. Here some confusing condition occurs because some biological product is approved under NDA while other are approved under BLA. The review and approval of NDA are based on safety, efficacy, according to detailed reports of clinical trials [1,5,9,27]. The pre-NDA meeting between the sponsor and FDA to discuss the content and format of the NDA. The purpose and main mission of NDA are to gain permission to market the drug and biologics [7,56,57]. NDA has a specialized review team of highly qualified experts. The review team will decide to approve or disapprove the NDA [6,58].

Classifies new drug applications according to the type of drug being submitted and its intended use:1) New molecular entity 2) New salt of previously approved biologics 3) New formulation of previously approved biologics, 4) New combination of two or more biologics, 5) Already marketed drug product- Duplication (i.e., new manufacturer), 6) New indication (claim) for already marketed drug (includes switching marketing status from prescription to OTC), 7) Already marketed drug product (no previous approved NDA) [4,64,65].

Format and Contents

The application is **r**equired to be submitted in common technical documents format with the following different section: -

a) FDA form 356h

b) User fee cover sheet (FDA form 3397)

c) Cover letter (comprehensive table of contents for modules 1 to 5)

d) Summary

e) Chemistry, Manufacturing, and control.

f) Sample, Method validation package, and labeling.

g) Nonclinical Pharmacology and Toxicology.

h) Human Pharmacokinetic and Bioavailability.

i) Microbiology (for the anti-microbial drug only).

j) Statistical method and analysis of clinical data

k) Safety update report (typically submitted 120 after NDA submission).

l) Statement regarding compliance to IRB and informed consent requirements.

m) Case report tabulation.

n) Case report form.

o) Patient information and certification.

p) Other information. [1,7,8,6,11]

General requirements for filing NDA

The new NDA regulation requires the application to be submitted in 2 copies: A) An archival copy- 1) It is a complete copy of application 2) submission that serves as its permanent record. B) A Review copy- It is divided into 6 technical sections: - 1) Chemistry, manufacturing, and control. 2) Non-clinical pharmacology and Toxicology. 3) Human pharmacokinetics and bioavailability [4,67].

NDA Review Process

1) CBER's, Central Document room (CDR) initially handles the administration process of application, including stamp and date [9,49]. 2) Determination of user fees status and user fees cover shit is sent to the regulatory information management staff. 3) The CD is responsible for the distribution of various copies of NDA to the different divisions for evaluation.4) Then the acknowledgment letter is sent to the applicant and the project manager is assigned to coordinate the NDA review process. 5) The project manager performs the initial screening of application are refused for feeling. 6) FDA review team will convene at 45 days meeting to determine the application should be filed or refused [10,41].

BLA (Biological License Approval)

A BLA is "a request for permission to introduce or deliver for introduction biologics product into interstate commerce". The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in the manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards [1,10,62]. Form 356h specifies the requirements for a BLA. This includes:

- Applicant information
- Product/Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling [3]

The main requirement is to submit the BLA to FDA firstly. All information regarding BLA must be submitted to FDA within 30 days of biological product withdrawal from sale. [12,31,32,33]

FDA Review of BLA:

1)The two main agency the BLA such as "Prescription Drug User Fee Act (PDUFA). And FDA Good Review Management Principles and Practices (GRMPs).2) After sponsor submission of BLA, the agency assembles the all-reviewer member and they focus on each content of BLA such as clinical trials and toxicology issues.3) after submission of BLA, within 60 days FDA decide that BLA application file or not.4) Many times FDA refuses to file when BLA did not show satisfactory information. 5) During the filling period, the FDA will also decide whether to choose the BLA as a priority as standard application.6) after the FDA has begun a substantive review of the BLA, reviewers may issue information request (IR) and discipline review (DR) letter to the applicant [2,17,35,40].

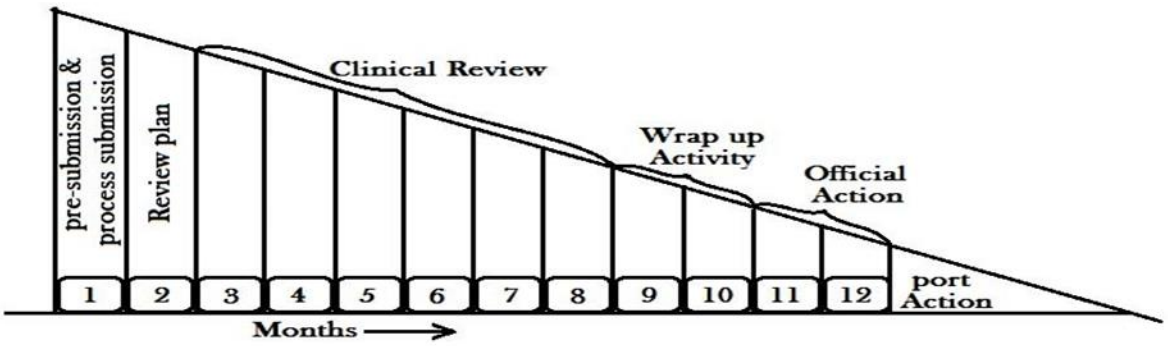

Figure No. 3: BLA Approval Process

Pre-submission meeting between applicant and FDA:

I. Purpose- discussion about contents of BLA.

II. Timing- At least 2 months for plan submission.

III. FDA and applicant may agree if submission of same component delay [52].

Mid-cycle and other communication:

I. If any update is required then the information regarding that is provided to the applicant.

II. If additional information is required then also.

III. If the deficiency is there then also inform the applicant.

IV. Generally, the FDA contact the applicant within 2 weeks of the internal mid-cycle review meeting.

V. For mead cycle communication FDA invite the applicant and told about some changes.

Wrap up- meeting:

I. This concentrates on the safety, efficacy, and quality of the product.

II. About 8 months required for submission of application [43,51,53].

Contents of BLA:

a) A BLA must contain the following information: Form FDA 356h (cover sheet)

b) Applicant information

c) Product/manufacturing information Source material / raw materials

d) Manufacturing process and controls

e) Formulation

f) Facility information

g) Contamination / cross-contamination information

h) Environmental assessment or categorical exclusion

i) Safety, efficacy and use Pre-clinical studies

j) Clinical studies

k) Labeling. [1,8,10]

PMA (Pre-Marketing Approval)

PMA is necessary when a device developer which developed a new innovative device and having wishes to market that device. PMA shows that the device safe and effective or not. The PMA process is more complicated than the 510k process. The review time of PMA is about 1 year [58,59,60].

PMA Process

PMA is a large and very complex document, which contains about 2000 pages. It can require several years to obtain all information regarding Preclinical, clinical, and manufacturing data that is necessary to PMA [63,68,69]. After PMA device approval, an approval letter, a summary of safety and effectiveness, and official labeling are placed on the CDRH website. All documents provide more technical and regulatory detail than a 510k. Once a PMA development plan has been established and reviewed by the ODE, it is time to execute it. Generally, multiple activities are executing such as manufacturing development, validation, preclinical function, and bioavailability testing, and clinical testing processed along parallel. In some cases, it may be clear that during the planning phase that some data such as manufacturing process information or preclinical testing data, may be available long before the clinical trials have ended. In this case, it is advantageous to submit PMA to ODE [73,74,75].

PMA requirements:

The following are required to be submitted within a traditional PMA:

a. Name, address, and table content

b. Description of the device form and function

c. Practice and the procedures-what device is used for

d. Foreign and Domestic market history of the device, if any

e. Detail about the manufacturing process in making the device

f. Summary of clinical and non-clinical studies.

g. Conclusion of studies include safety and effectiveness of the device

h. Reference to any performance standard followed

i. Labeling

j. Result of the non-clinical lab study

k. Result of clinical studies on human patients

l. Financial certification [8,6]

510K

More than 3000 medical devices in the US market every year are approved through the 510k premarket notification process. The 510k process is rapid, flexible, and adaptable to many devices. The main goal of 510k is *"Demonstration of sustained to a device that was on the US market before May 28, 1976, or to a device that has already gone through 510k clearance process".* The device is successfully gone through the 510k process are called "510k cleared". The previously cleared device which is included in 510k for comparison purposes called the "predicted device"[76,77].

Types of 510k: There are four main types of 510k are as follows-

a) Traditional 510k- Traditional 510k filed when sponsor developed a similar device or equivalence to a device that has been cleared through the 510k processor was already in the market before the 1976 medical Device Amendments were sighed on May 26, 1976.

b) Abbreviated 510k: - This 510k is similar to the traditional 510k in function. A sponsor can choose to comply with FDA accepted standards during the testing process. A declaration of conformance included in the 510k, stating that the device meets the specification in the reference standard.

c) Special 510k: - A special 510k is submitted when a sponsor has made some modification in her/his device and has not added a new indication for use.

d) De Novo 510k: - The De Novo 510k is a 510k without a predicate device. It is not a commonly used path, but in some circumstances, it is appropriate [78].

Content of 510k:

a) The cover sheet (FDA form 3514).

b) The cover letters

c) The table of content

d) User fee information

e) Statement of substantial equivalence

f) Labeling

g) Advertising and promotional material.

h) Comparative information. [6,8,78]

Table No. 2: Difference between Regulatory bodies use for Approval of Biologics and Drug

Sr. No.	Regulatory Bodies	Biologics	Drug
1.	FDA	YES	YES
2.	IND	YES	YES
3.	NDA	YES	YES
4.	ANDA	NO	YES
5.	PMA	YES	NO
6.	CBER	YES	NO
7.	CDER	YES	YES
8.	BLA	YES	NO
9	510K	YES	NO
10.	DRUG APPLICATION FOR OTC DRUG	NO	YES

CONCLUSION

The study of biologics is very important because of its biologics and complexity in nature. These biologics are heterogeneous. These are very sensitive to environmental conditions. Biologics are injected into the body. There are several committees are come under the regulatory authority of biologics such as FDA, PHSA, NDA, NDA, CBER, 510K, PMA. The FDA and PHSA are control all approval processes of biologics products. 510k and PMA are having about the same function related to the medical device.

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