Policy Number	**ADM1001.028**
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Inside the U.S. Food and Drug Administration (FDA)

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Related Policies (if applicable)
RX503.001 Off-Label Use of Drugs Without a Medical Policy

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

In general, any equipment, drug, device, and/or supply that does not have marketing approval (permission for commercial distribution) from the United States (U.S.) Food and Drug Administration (FDA) **is considered experimental, investigational and/or unproven**.

Any equipment, drug, device, and/or supply that has received marketing approval but the equipment, drug, device and/or supply **is not** being used for the purpose or manner for which it was initially rendered, **is considered experimental, investigational and/or unproven**.

Any equipment, drug, device, and/or supply that **has not** been manufactured according to established FDA standards, regulations and/or procedures, **is considered experimental, investigational and/or unproven.**

In some cases, the off-label use of equipment, drugs, devices, and/or supplies **may be considered eligible for benefit coverage**. *Those instances, along with determination of coverage criteria, are addressed in separate Health Care Services Corporation (HCSC) Medical Policies. When a separate HCSC Medical Policy is not found for the off-label use of a drug, refer to RX503.001: Off-Label Use of Drugs Without a Medical Policy.*

Special Comment: FDA review and approval of devices only addresses safety of the device. The FDA does not address efficacy. Therefore, HCSC does not necessarily recognize benefit coverage for FDA approved devices unless well-designed controlled studies in the peer-reviewed medical literature demonstrate efficacy and improved health outcomes from use of the device.

Policy Guidelines

None.

Description

The following is an overview of several components and processes that the Food and Drug Administration (FDA) regulates, more in-depth information can be located on the FDA website at <https://www.fda.gov>.

What is the U.S. Food and Drug Administration (FDA)? (1)
The FDA is a U.S. (Federal) government agency that regulates the following items:

- Food (human and animal, other than meat and poultry);
- Dietary Supplements (human and animal);
- Drugs (human and animal);
- Cosmetics;
- Medical and/or Occupational Devices, Equipment, Supplies (human and animal);
- Radiation Emitting Products (human and animal);
- Biologics;
- Blood Products; and
- Tobacco Products.

What does the FDA do? (2)
The FDA is responsible for:

- Protecting the public health by assuring that foods (except for meat from livestock, poultry and some egg products which are regulated by the U.S. Department of Agriculture) are safe, wholesome, sanitary and properly labeled; ensuring that human and veterinary drugs, and

vaccines and other biological products and medical devices intended for human use are safe and effective;
- Protecting the public from electronic product radiation;
- Assuring cosmetics and dietary supplements are safe and properly labeled;
- Regulating tobacco products; and
- Advancing the public health by helping to speed product innovations.

The FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions. (3)

The mandate of the FDA is to regulate by approving, labeling, and monitoring the numerous medical products in an expeditious, yet thorough evaluation of the product's safety and effectiveness in meeting the labeling claims. The process is handled by FDA review teams to recommend approval of a product. Following approval, safety teams determine whether the product is hurting an individual. Under current law, the FDA must approve all drugs and devices before they can be marketed. Although the process may be known as the FDA testing program, the FDA does very little of the testing. The developer of a new drug or device uses its own lab or hires another private company to conduct animal tests on the product for safety before proceeding to clinical trials. Generally, these tests are often conducted by a medical school department or consulting firm. When each phase of the testing is completed, the developer submits details of the testing process, evidence of adherence to FDA protocols, and the test results to the FDA.

The FDA requires clinical testing for most products, such as drugs, devices, biologics, and blood products. However, dietary products are not pre-approved for safety and efficacy. Only after the dietary supplement has been marketed, will the FDA monitor for unsafe products. Certain foods, such as infant formulas or medical foods are regulated more strictly than other dietary supplements as they are consumed by highly vulnerable individuals.

Neither the FDA nor the federal government regulates the practice of medicine. Any approved drug or product may be used by a licensed practitioner for uses other than those stated in the product label. The FDA's role is to mandate that products should be labeled with their ingredients, be safe, and be effective. A licensed provider may choose to use an FDA approved product for other indications than those stated on the product label. Off-label use is not illegal. (Refer to Off-Label Use of Drugs Without a Medical Policy for coverage criteria.) There is an obligation by providers to report any adverse events, including events resulting in hospitalization or death of a patient, especially those not previously described on the product label.

In October 2024, the FDA began implementing a reorganization of the agency. The FDA is an agency within the Department of Health and Human Services and consists of nine Center-level organizations: (4)
1. Center for Biologics Evaluation and Research (CBER),
2. Center for Devices and Radiological Health (CDRH),

3. Center for Drug Evaluation and Research (CDER),
4. Center for Tobacco Products,
5. Center for Veterinary Medicine (CVM),
6. Human Foods Program,
7. National Center for Toxicological Research,
8. Office of Inspection and Investigation, and
9. Oncology Center of Excellence.

The FDA Development Process for Devices (5)

Essentially, medical equipment, devices, and supplies are subject to general controls, which are the baseline necessary for marketing, proper labeling, and monitoring performance once the product is available to the American public. The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides several mechanisms to achieve this goal, including the classification of devices, establishment of registration, device listing, adherence to Good Manufacturing Practices (GMPs), and extensive control over market introduction of devices. Thus, any individual engaged in the manufacture, preparation, propagation, compounding, assembly, and/or processing of a medical device intended for human use is subject to this regulatory process enforced by the FDA. Medical device regulation is based on the concept of risk. The following steps list the process to medical device approval:

- Step One – Device discovery and concept. The development process begins when researchers see an unmet medical need.
- Step Two – Preclinical research – Prototype. At this stage, the device prototype is not for human use.
- Step Three – Pathway to approval. Device application process. Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness. As device class increases from Class I to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most regulatory control. (6)

  The three classes listed below are based on the degree of control necessary to assure the various types of devices are safe and effective. (7)

  1. Class I – devices of the least risk, under general control, such as enema kits and elastic bandages. Forty-seven percent of medical devices fall under this category and 95% of these are exempt from the regulatory process.
  2. Class II – devices presenting greater concern; therefore, they are subject to special controls in addition to general controls. Examples of class II devices include powered wheelchairs, and some pregnancy test kits. Forty-three percent of medical devices fall under this category.
  3. Class III – devices, under general control and the Premarket Approval (PMA) process, which include many implanted and life-supporting or life-sustaining products that are subject to the most stringent controls and requirements. Examples of Class III devices include implantable pacemakers and breast implants. Ten percent of medical devices fall under this category.

- Step Four – FDA device review. Once there is enough information on a device's safety and effectiveness, medical device developers, can file an application to market the device to the public.
- Step Five – FDA Post-Market Device Safety Monitoring. It is possible that new safety concerns may emerge once the device is on the market. As a result, FDA continues to monitor the device performance after a device has been approved through such mechanisms as manufacturer inspections, reporting problems with programs that allow manufacturers, health professionals, and consumers to report problems associated with approved medical devices, and active surveillance.

Additional Considerations – Device software functions: Device software functions may include "Software as a Medical Device (SaMD)" and "Software in a Medical Device (SiMD)." The FDA notes that the International Medical Device Regulators Forum (IMDRF) defines SaMD as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device to be software as a medical device." In 2013, IMDRF formed the Software as a Medical Device Working Group (WG) to develop guidance supporting innovation and timely access to safe and effective Software as a Medical Device globally. Chaired by the FDA, the Software as a Medical Device WG agreed upon several items including a framework for risk categorization for software as a medical device. (8)

The FDA Drug Development Process (9)

The drug approval process from a laboratory to the market shelves is usually long with varied routes of exploration. Often a drug is developed to target a specific disease, while others are discovered by accident. Most drugs undergo pre-clinical animal laboratory testing or trials, never advancing to human clinical trials or review by the FDA. If a drug does advance to the FDA, a rigorous evaluation begins by scrutinizing the clinical trial design, the severity of adverse effects, the manufacturing conditions, the labeling instructions, and the drug distribution and regulations. Similar to the development process for devices noted above, the following steps are listed in the process to drug development and approval:

- Step One – Discovery and Development,
- Step Two – Preclinical Research,
- Step Three – Clinical Research,
- Step Four – FDA Review, and
- Step Five – FDA Post-Market Safety Monitoring.

The FDA has developed four distinct approaches to making drugs as rapidly available as possible when they are the first treatment for a serious disease or when they have advantages over existing treatments (10):

- Fast Track is a process designed to facilitate the development and advance the review of drugs that treat serious conditions, and fill an unmet medical need, based on promising animal or human data. Fast tracking can get important new drugs to the patient earlier. The drug company must request the Fast Track process.

- Breakthrough Therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy. A drug with Breakthrough Therapy designation is also eligible for the FastTrack process. The drug company must request a Breakthrough Therapy designation.
- Priority Review means the FDA aims to take action on an application within 6 months, compared to 10 months under standard review. A Priority Review designation directs attention and resources to evaluate drugs that would significantly improve the treatment, diagnosis, or prevention of serious conditions.
- Accelerated Approval Allows for earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. (11)

Therapeutic Biological Products (12)

Biological products are a subset of drugs; both are regulated under provisions of the Federal Food, Drug, and Cosmetic Act. However, only biological products are licensed under the Public Health Service (PHS) Act. Biological products are generally derived from living material--human, animal, or microorganism. FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Both the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) have regulatory responsibility for therapeutic biological products, including premarket review and oversight.

Following initial laboratory and animal testing that show that investigational use in humans is reasonably safe, biological products (like other drugs), can be studied in clinical trials in humans under an investigational new drug application (IND). For drug approvals, a new drug application (NDA) is used, however a biologic license application (BLA) is required for biological products subject to licensure under the PHS Act. FDA approval to market a biologic is granted by issuance of a biologics license.

The 510(k) Clearance Process (13)

From 1976 going forward, any product that was found to be essentially similar to one that was marketed prior to May 28, 1976, was basically "grandfathered in." The Food, Drug and Cosmetic Act requires device manufacturers who must register, to notify the FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification - also called PMN or 510(k). The FDA determines whether the device is equivalent to a device already placed into one of the three classification categories (previously addressed). Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the

first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected.

The 510(k) clearance process involves a comprehensive review of safety and performance data for the device, which may include scientific, non-clinical, and clinical data, as appropriate, to determine if a new device is substantially equivalent to a device that is already on the market (that is, a predicate device). Because there are many types of devices, the content in 510(k) submissions can vary greatly. (14)

Premarket Approval (PMA) Process (15)
Premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence (both non-clinical laboratory studies and clinical investigations) to assure that the device is safe and effective for its intended use(s). (15) Typically, this data is generated through an investigational device exemption (IDE) trial that has been reviewed by the FDA. The manufacturer presents the data to an FDA advisory committee. The committee votes on a recommendation for further action to the FDA. If the advisory committee recommends for approval, the FDA takes the recommendation under advisement and issues their final determination sometime after the advisory committee meeting. The time frame is unpredictable, ranging from a month to over a year. Frequently, there is publicity when the advisory committee recommends approval, but final FDA approval, if given, occurs later. (7, 16)

The FDA De Novo Classification (17)
The Food and Drug Administration Modernization Act of 1997 (FDAMA) added the de novo classification option as an alternate pathway to classify novel devices of low to moderate risk that had automatically been placed in Class III after receiving a “not substantially equivalent” (NSE) determination in response to a premarket notification [510(k)] submission. Section 513(f)(2) of the FD&C Act was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA), on July 9, 2012, to allow a sponsor to submit a de novo classification request to the FDA for novel low to moderate risk devices without first being required to submit a 510(k).

There are 2 options for de novo classification for novel devices of low to moderate risk.

- Option 1: Any person who receives an NSE determination in response to a 510(k) submission may, within 30 days of receipt of the NSE determination, submit a de novo request for the FDA to make a risk-based evaluation for classification of the device into Class I or II.
- Option 2: Any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may submit a de novo request for the FDA to make a risk-based classification of the device into Class I or II, without first submitting a 510(k) and receiving an NSE determination.

Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions.

Special Designations Assigned for FDA Approvals

Humanitarian Device Exemption (HDE) – This exemption applies to devices that would otherwise be subject to the PMA process, but are intended to treat relatively rare diseases, affecting less than 8,000 patients per year. This process recognizes the fact that it may be difficult to recruit adequate numbers of patients to participate in clinical trials, and thus, the FDA requires the manufacturer to submit data regarding the safety of the device and the "probable" benefit. (18, 19)

Orphan Product Designation – The Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States. In addition, the Orphan Drug Act provides financial incentives to attract industry's interest through a seven-year period of market exclusivity for a drug approved to treat an orphan disease. The FDA was authorized to designate drugs and biologics for orphan status (the first step to getting orphan development incentives) provide grants for clinical testing of orphan products and offer assistance in how to frame protocols for investigations. A subsequent amendment defined a rare disease as one affecting under 200,000 people, though a disease with more patients could qualify if the firm could not recover the costs of developing the drug. (20, 21)

Glossary of Terms

- Accelerated Approval – A highly specialized mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses.
- Advisory Committee – A panel of outside experts convened periodically to advise the FDA on safety and efficacy issues about FDA-regulated products. The FDA is not bound to take the committee's recommendations, but usually does.
- Bioequivalence – When 2 products are equal in the rate and extent to which the active pharmaceutical ingredient becomes available at the site(s) of drug action.
- Brand Name Drug (BND) – A drug marketed under a proprietary, trademark-protected name.
- Clinical Studies – Human studies designed to distinguish a drug or device's effect from other influences.
- Cosmetic – Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance of the individual.
- Device – see Medical Device.
- Drug – A substance intended to diagnose, treat, cure, or prevent disease and articles (other than food) as well as intended to affect the structure or any function of human or animal body. A substance recognized by an official pharmacopoeia or formulary.
- Drug Form/Product – The finished dosage form (tablet, capsule, etc.) that contains a drug substance.

- Emergency Use Investigational New Drug (IND) – This allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND application in accordance with 21 CFR (Code of Federal Regulations), Sec. 312.23 or Sec. 312.20.
- FDA Action Date – Date when any FDA regulatory action was taken, such as an original or supplemental approval took place.
- FDA Application Number – This number, also known as new drug application (NDA) number, is assigned by the FDA staff to each application for approval to market a new drug in the U.S. One drug can have more than one application number if it has different forms or routes of administration.
- Generic Drug – The same as a brand name drug in dosage, safety, strength, method of administration, quality, performance, and intended use.
- Investigational Device Exemption (IDE) – This process allows for the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support and complete the marketing approval process.
- Investigational New Drug Application (IND) – An application that a drug sponsor must submit to the FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including structural formula, animal test results, and manufacturing information.
- Label – The official description, approved by the FDA, of a product which includes the indication (what is it used for), who should use or take it, any adverse effects, instructions for use in pregnancy, children, and other populations, and safety information.
- Medical Device Safety Communications – The FDA posts these communications to describe the FDA's analysis of a current issue and provide specific regulatory approaches and clinical recommendations for patient management.
- Marketing Status – Indicates how a product is sold in the U.S., such as prescription, over the counter, discontinued, or none.
- Medical Device – A product that is marketed as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other related articles, component parts, or accessories, and meets specifications noted in 201 (h)(1) of the Food, Drug and Cosmetic Act.
- New Drug Application (NDA) – An application requesting FDA approval to market a new drug for human use in the interstate commerce. The application must contain, among other things, data from specific technical viewpoints for FDA review, including chemistry, pharmacology, medical, biopharmaceutics, statistics, and anti-infective microbiology.
- Over-The-Counter (OTC) – A product that is safe and effective for use by the general public without a physician's prescription.
- Pharmacology – The science that deals with the effect of drugs on a living organism.
- Post-Marketing Surveillance (PMS) – The FDA's ongoing safety monitoring of marketed products and risk assessment programs to identify adverse events that did not appear during the drug approval process.
- Preclinical Studies – Studies that test a drug on animals and other nonhuman test systems. They must comply with the FDA's good laboratory practices. Data about a drug's activities

and effects in animals help establish boundaries for safe use of the drug in subsequent human studies (clinical studies). Also, because animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on offspring.

- Recall – A recall is a method of removing or correcting products that are in violation of laws administered by the Food and Drug Administration (FDA).
- Treatment Investigational New Drug (IND) Application – is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted, and the FDA review takes place.
- User Fees – Fees collected from companies that produce certain products, such as drugs and medical devices, and from some other entities, such as certain accreditation and certification bodies. The FDA uses these fees to supplement the annual funding that Congress provides for the agency.

Rationale

While there may be exceptions, most benefit plans or health contracts specifically exclude coverage for the patient's use of equipment, drug(s), device(s), or supply(s) when used:

- During a clinical trial or study, and/or
- For purposes or in a manner other than the service was intended, and/or
- For cosmetic or not medically necessary indications or conditions, and/or
- In instances considered to be experimental, investigational and/or unproven.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
03/15/2025	Document updated with literature review. Coverage unchanged. The following references were added: 2-3, 5-9, 11-15, and 18-23; some updated; and others removed.
03/15/2024	Reviewed. No changes.
03/15/2023	Document updated with literature review. The following editorial modification was made to Coverage: Changed “that has not received” to “that does not have” in the following sentence: In general, any equipment, drug, device, and/or supply that does not have marketing approval (permission for commercial distribution) from the United States (U.S.) Food and Drug Administration (FDA) is considered experimental, investigational and/or unproven; with no change to intent. References 28-34 were added; others updated, and one removed.
08/15/2022	Reviewed. No changes.
01/15/2022	Document updated with literature review. Coverage unchanged. References 26-28 added; others updated.
08/15/2020	Reviewed. No changes.
10/01/2019	Document updated with literature review. Coverage unchanged. Added reference 25.
07/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. Coverage unchanged.

08/01/2016	Reviewed. No changes.
11/01/2015	Document updated with literature review. Coverage unchanged.
04/15/2014	Document updated with literature review. Coverage unchanged.
03/15/2013	Document updated with literature review. Coverage unchanged.
06/15/2008	Policy reviewed without literature review; new review date only. This policy is no longer scheduled for routine literature review and update.
05/01/2006	New medical document